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Review

ARTIFICIAL INTELLIGENCE IN DIAGNOSIS AND TREATMENT OF INFERTILITY

ВЕШТАЧКА ИНТЕЛИГЕНЦИЈА ВО ДИЈАГНОСТИКА И ТРЕТМАН НА ИНФЕРТИЛИТЕТ

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Abstract

Before the emergence of artificial intelligence (AI), infertility care relied heavily on manual, clinician-dependent, and often subjective approaches. Although these methods laid the foundation of modern reproductive medicine, they were inherently limited in accuracy, reproducibility, and predictive capacity.

In the **diagnostic evaluation of the infertile couple**, semen analysis was traditionally performed manually by technicians or embryologists. Key parameters - including sperm concentration, motility, and morphology-were assessed under light microscopy, resulting in considerable inter- and intra-laboratory variability. Female evaluation similarly depended on hormone assays (FSH, LH, estradiol) and transvaginal ultrasound measurement of antral follicle count (AFC), both of which were subject to operator bias and offered only moderate predictive value. Conditions such as endometriosis or tubal pathology often required expert interpretation of imaging or invasive laparoscopic assessment.

In **assisted reproductive technologies (ART)**, embryo selection was historically based on morphological grading under light microscopy. Embryologists assessed blastomere symmetry, fragmentation, and overall morphology, yet the process remained subjective and inconsistent across observers. Sperm selection for intracytoplasmic sperm injection (ICSI) was similarly manual, relying on visual identification of motile, morphologically normal sperm - an approach that was labor-intensive and imprecise.

Personalization of ovarian stimulation was also limited before AI. Gonadotropin dosing was determined largely by clinical experience, age, and body habitus, often leading to suboptimal responses, including poor stimulation, excessive follicular development, or risk of ovarian hyperstimulation syndrome (OHSS). Predicting the number of retrievable oocytes was challenging, and dose adjustments were frequently reactive rather than anticipatory.

In summary, infertility diagnostics and treatment prior to AI were grounded in human expertise, direct observation, and clinical judgment. While these practices established the core principles of ART, they suffered from variability, limited reproducibility, and restricted predictive accuracy. The introduction of AI represents a transformative shift - from subjective, experience-dependent evaluation to standardized, data-driven, and personalized reproductive care.

Keywords: Artificial intelligence, infertility, assisted reproductive technologies (ART), in vitro fertilization (IVF), embryo selection; semen analysis, ovarian stimulation, reproductive medicine, ICSI, personalized medicine

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Апстракт

Пред појавата на вештачката интелигенција (ВИ), третманот на инфертилитетот во голема мера се потпираше на рачни, клиничар-зависни и често субјективни пристапи. Иако овие методи ги поставија темелите на современата репродуктивна медицина, тие беа инхерентно ограничени во однос на точноста, репродуцибилноста и предиктивната моќ.

Во дијагностичката евалуација на инфертилниот пар, анализата на спермата традиционално се изведуваше рачно од лабораториски техничари или ембриолози. Клучните параметри-вклучувајќи концентрација на сперматозоиди, подвижност и морфологија-се проценуваа со светлосна микроскопија, што резултираше со значајна интер- и интралабораториска варијабилност. Евалуацијата на жената исто така зависеше од хормонски анализи (FSH, LH, естрадиол) и трансвагинален ултразвук за мерење на антралниот фоликуларен број (AFC), кои беа подложни на операторска пристрасност и нудеа само умерена предиктивна вредност. Состојби како ендометриоза или тубарна патологија често бараа експертска интерпретација на сликовни методи или инвазивна лапароскопска проценка.

Во асистираните репродуктивни технологии (АРТ), селекцијата на ембриони историски се базираше на морфолошко оценување под светлосен микроскоп. Ембриолозите ја проценуваа симетријата на бластомерите, фрагментацијата и целокупната морфологија, но процесот остануваше субјективен и

неконзистентен меѓу различни набљудувачи. Селекцијата на сперматозоиди за интрацитоплазматска инјекција на сперматозоид (ICSI) исто така беше рачна, заснована на визуелна идентификација на подвижни и морфолошки нормални сперматозоиди-пристап кој беше трудоинтензивен и непрецизен.
Персонализацијата на оваријалната стимулација исто така беше ограничена пред ВИ. Дозирањето на гонадотропини главно се определуваше врз основа на клиничко искуство, возраст и телесна конституција, што често доведуваше до субоптимални одговори, вклучувајќи слаб одговор на стимулација, прекумерен фоликуларен развој или ризик од оваријален хиперстимулациски синдром (OHSS). Предвидувањето на бројот на добиени ооцити беше отежнато, а корекциите на дозата најчесто беа реактивни, наместо предиктивни.
Како заклучок, дијагностиката и третманот на инфертилитетот пред ВИ беа засновани на човечка експертиза, директно набљудување и клиничка проценка. Иако овие практики ги воспоставија основните принципи на АРТ, тие се карактеризираа со варијабилност, ограничена репродуцибилност и намалена предиктивна точност. Воведувањето на вештачката интелигенција претставува трансформативен пресврт -од субјективна, искуствено зависна проценка кон стандардизирана, податоциводена и персонализирана репродуктивна грижа.

Клучни зборови: вештачка интелигенција, инфертилитет, асистирани репродуктивни технологии (АРТ), ин витро фертилизација (IVF), селекција на ембриони; анализа на сперма, оваријална стимулација, репродуктивна медицина, ICSI, персонализирана медицина

Introduction

Infertility affects approximately 10-15% of couples of reproductive age worldwide and represents one of the most prevalent chronic reproductive disorders, carrying substantial medical, psychological, and socioeconomic consequences. Despite significant advances in assisted reproductive technologies (ART)-including *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), and cryopreservation-global pregnancy rates per ART cycle remain modest, averaging 30-40% even in optimal clinical conditions. Conventional infertility diagnostics, such as hormonal testing, semen analysis, ultrasound evaluation, and laparoscopy, have long served as the clinical foundation of reproductive medicine. However, these approaches are frequently limited by subjectivity, operator dependency, and restricted predictive capacity, which can impede precise diagnosis and individualized treatment planning.

Prior to the integration of artificial intelligence (AI), infertility assessment relied heavily on clinician experience and manual interpretation. Semen analysis, for instance, was performed under light microscopy to evaluate concentration, motility, and morphology, yet results often varied across observers and laboratories. Female infertility evaluations based on anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and antral follicle count (AFC) were similarly affected by inter-operator variability and provided only moderate predictive insight into ovarian responsiveness. In ART laboratories, embryologists traditionally graded embryos by assessing blastomere symmetry, fragmentation, and overall morphology-a process inherently subjective and inconsistent.
The emergence of AI technologies has introduced a paradigm shift in infertility management by enabling standardized, data-driven, and personalized reproductive care. Machine learning (ML) and deep learning (DL) systems can analyze large, multidimensional datasets including clinical, hormonal, laboratory, and imaging parameters, to identify complex patterns associated with reproductive outcomes. In male infertility, DL algorithms now automate sperm morphology and motility assessments with greater accuracy and reproducibility than manual or conventional computer-assisted systems [2,5]. In female infertility, AI models integrate clinical and hormonal data to predict ovarian stimulation response, thereby supporting individualized gonadotropin dosing and reducing the risks of both poor and excessive ovarian response [1,6].
AI has also transformed embryo evaluation and selection. Deep learning models trained on time-lapse imaging can extract morphological and morphokinetic features associated with implantation potential, outperforming traditional subjective grading systems [4]. These tools enable consistent embryo ranking and may improve pregnancy outcomes while reducing the need for multiple embryo transfers. In reproductive imaging, AI-based diagnostic systems have demonstrated improved sensitivity for the detection of endometriosis and subtle pelvic pathologies on ultrasound and MRI, while reducing operator-dependent variability [3].
Beyond enhancing diagnostic precision, AI supports clinical decision-making and introduces new ethical dimensions to reproductive care. Predictive models assist in estimating live birth probabilities, guiding treatment sequencing, and improving patient counseling. As AI systems expand in complexity and clinical relevance, ethical and regulatory challenges-including concerns regarding data privacy, algorithmic bias, transparency, and explainability-have become increasingly important. Professional and regulatory bodies, such as the European Society of Human Reproduction and Embryology (ESHRE) and the U.S. Food and Drug Administration (FDA), have introduced guidelines to ensure safe, equitable, and evidence-ba-

sed deployment of AI-enabled reproductive technologies [7-9].

In summary, artificial intelligence is redefining infertility diagnosis and treatment by reducing human subjectivity, improving diagnostic accuracy, and enabling personalized therapeutic strategies. This review provides a comprehensive evaluation of current and emerging AI applications across infertility diagnostics, ART procedures, and clinical decision support, while addressing the ethical and regulatory frameworks required for their responsible integration into reproductive medicine. The transition from conventional infertility care toward AI-assisted reproductive medicine is summarized in Table 1.

Table 1. Traditional vs. AI-based approaches in infertility care

Aspect	Traditional Method	AI-Based Innovation	Key Benefit
Semen Analysis	Manual microscopic evaluation	Deep learning-based morphology and motility detection	Objective, reproducible results
Ovarian Response Prediction	Based on age, FSH, AMH	ML models using multivariable data	Personalized dosing, fewer OHSS cases
Embryo Selection	Morphological grading under microscope	CNN-based time-lapse image analysis	Predictive embryo ranking
Endometriosis Detection	2D ultrasound, MRI interpretation	AI image segmentation and pattern recognition	Early, non-invasive diagnosis
Stimulation Protocols	Empirical, physician-dependent	Reinforcement learning and predictive dosing	Optimized outcomes, cost reduction
Outcome Counseling	Population averages	AI-based individualized success prediction	Better patient guidance

I. Diagnostic Evaluation of the Infertile Couple

1. Male Factor

Male infertility contributes to approximately 40–50% of infertility cases and encompasses a broad spectrum of etiologies, including genetic, hormonal, environmental, and idiopathic factors. Historically, semen analysis has been the cornerstone of male fertility evaluation. Embryologists manually assessed sperm concentration, motility, and morphology under light microscopy-methods that, while foundational, are limited by subjectivity, intra-observer variation, and reduced reproducibility. Even with the introduction of computer-assisted sperm analysis (CASA) systems, significant inter-laboratory variability persists [2,5].

The integration of artificial intelligence (AI) into andrology has markedly enhanced diagnostic precision. Comparative diagnostic accuracy between manual, CASA, and AI-based methods is demonstrated in Figure 2.

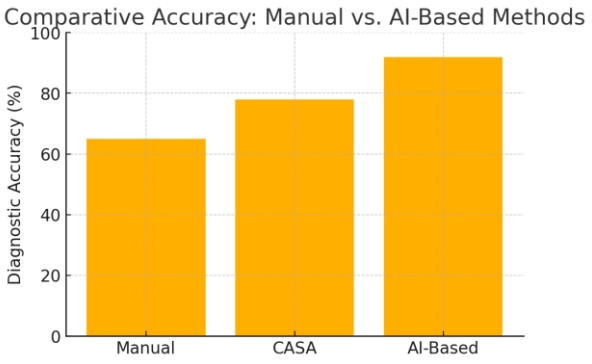

Fig. 2. Comparative accuracy of diagnostic methods

Deep learning algorithms trained on high-resolution microscopy images and video data can automatically quantify sperm motility and classify morphological abnormalities with exceptional consistency. Lee *et al.* [2] demonstrated that AI-based sperm morphology classification surpasses manual scoring in speed, accuracy, and inter-operator reliability. Convolutional neural network (CNN)-based systems have also been applied to dynamic motility pattern recognition, identifying subtle motility phenotypes correlated with fertilization potential [10].

AI innovations extend beyond diagnostic analysis to real-time sperm selection for intracytoplasmic sperm injection (ICSI). Automated imaging platforms now employ deep neural networks to detect viable, morphologically normal sperm within seconds-an advancement particularly beneficial for patients with severe oligozoospermia or non-obstructive azoospermia [5,11]. Emerging AI-integrated microfluidic technologies further combine image-based recognition with biophysical sorting, enabling the selection of sperm based on motility, DNA integrity, capacitation status, and other functional parameters. These platforms improve fertilization efficiency while reducing operator dependency and procedure time.

Machine learning approaches are also being developed to incorporate endocrine and genetic biomarkers into male infertility assessment. Predictive models trained on hormonal parameters (FSH, LH, testosterone) and genetic datasets can differentiate obstructive from non-obstructive azoospermia and estimate the likelihood of successful testicular sperm retrieval [10]. Collectively, these advancements mark the transition from descriptive, operator-dependent evaluation to predictive, stan-

dardized, and data-driven diagnostics in male reproductive medicine.

2. Female Factor

Female infertility results from diverse etiologies, including ovulatory disorders, tubal pathology, uterine anomalies, and endometriosis. Traditional diagnostic approaches, such as hormone assays, pelvic ultrasound, and laparoscopy, are essential yet limited by variability in interpretation and modest predictive accuracy. AI technologies provide advanced analytical capabilities that integrate hormonal, imaging, and clinical data, thereby enhancing diagnostic reliability and efficiency.

AI in Ovarian Reserve and Ovarian Response Prediction

AI-driven models have demonstrated strong performance in predicting ovarian reserve and response to controlled ovarian stimulation. By integrating parameters such as age, AMH, FSH, LH, estradiol, and antral follicle count (AFC), machine learning algorithms including gradient boosting, random forests, and neural networks, can forecast ovarian responsiveness with high precision [1,6]. Alsaad *et al.* [1] showed that ML-based dosing models can individualize gonadotropin regimens, minimizing risks of suboptimal response or ovarian hyperstimulation syndrome (OHSS). Such models are increasingly embedded within IVF cycle planning platforms to optimize dosing strategies and improve oocyte yield.

AI in Imaging and Endometriosis Detection

In reproductive imaging, AI-enhanced ultrasound and MRI systems have significantly improved the detection of endometriosis and uterine pathologies. Smith *et al.* [3] demonstrated that CNN-based segmentation algorithms can identify subtle endometriotic implants, characterize lesion depth, and decrease inter-operator variability compared to standard imaging interpretation. Automated ovarian follicle segmentation using deep learning further standardizes AFC measurement, reducing the subjectivity inherent to manual ultrasound assessment [12].
Radiomic AI models capable of extracting thousands of quantitative imaging features enable non-invasive phenotyping of endometriosis and other pelvic disorders. These tools reduce reliance on diagnostic laparoscopy and support earlier identification, risk stratification, and personalized treatment planning.

AI in Endometrial and Tubal Evaluation

AI applications are also advancing assessment of endometrial receptivity and tubal patency. Machine learning models that integrate time-lapse imaging, Doppler flow patterns, and clinical data can evaluate endometrial thickness, volume, vascularity, and predict optimal implantation windows [13]. In hysterosalpingography (HSG) and sonohysterography, AI-assisted interpretation enhances detection of tubal occlusion and intrauterine abnormalities, providing a faster, more consistent, and standardized approach to female factor infertility evaluation.

3. Multimodal Risk Stratification

Infertility frequently involves overlapping male and female factors, highlighting the need for integrated and holistic diagnostic approaches. Multimodal artificial intelligence (AI) models address this complexity by combining clinical, hormonal, imaging, and, increasingly genetic and molecular data to generate individualized diagnostic profiles. These systems can classify infertility etiologies, such as ovulatory dysfunction, tubal disease, endometrial pathology, or unexplained infertility, and predict the probability of natural conception or success with assisted reproductive technologies (ART).
Recent work utilizing ensemble learning and federated AI frameworks has demonstrated enhanced diagnostic robustness by aggregating data from multiple clinical centers while preserving patient privacy [14]. Federated models overcome the limitations of single-institution datasets, reducing the risk of overfitting and improving generalizability across diverse populations. These integrated AI platforms are now being incurporated into clinical decision-support systems, providing fertility specialists with real-time predictions, risk assessments, and personalized treatment recommenddations.

II. Assisted Reproduction (ART)

Assisted reproductive technologies (ART) constitute the cornerstone of infertility treatment, encompassing procedures such as *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), and embryo transfer (ET). Despite their transformative impact, ART success rates have plateaued over the past decade, largely due to persistent inter-observer variability in embryo grading, empirical ovarian stimulation strategies, and inconsistent sperm selection methods. The advent of artificial intelligence (AI) has redefined these workflows by promoting automation, standardization, and predictive optimization across every stage of the reproductive cycle.

1. Embryo Assessment and Selection

Embryo quality evaluation remains one of the most critical determinants of ART success. Traditionally, embryos have been graded manually under a light microscope based on parameters such as blastomere number, fragmentation, and symmetry. While widely practiced, this process is inherently subjective and often inconsistent between embryologists and across IVF centers. AI-driven time-lapse imaging and deep learning systems have now revolutionized embryo assessment by providing reproducible, quantitative, and predictive evaluation tools.

Convolutional neural networks (CNNs) trained on time-lapse image sequences can automatically extract morphokinetic parameters-such as cleavage timing, cell symmetry, compaction, and blastocyst expansion-and convert these into implantation probability scores [4,15]. The workflow of AI-assisted embryo selection is illustrated in Figure 1. These algorithms outperform traditional manual grading by identifying subtle developmental signatures that are imperceptible to the human eye. Boucret *et al*. [4] demonstrated that deep learning–based embryo evaluation models achieved significantly higher predictive accuracy for clinical pregnancy and live birth compared to morphology-based selection alone.

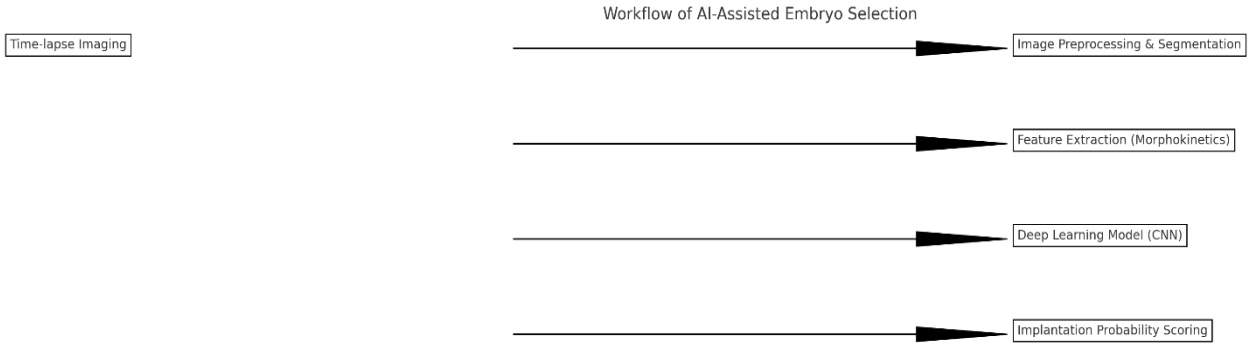

Fig. 1. Workflow of AI-assisted embryo selection

Recent multimodal approaches integrate metabolomic, proteomic, and even genetic data with morphokinetic features to further enhance prediction reliability [16]. Such multi-omics embryo selection systems may reduce the need for invasive preimplantation genetic testing (PGT), supporting the move toward fully non-invasive embryo viability assessment. However, persistent challenges remain, including limited dataset diversity, inconsistencies in annotation standards, and the need for rigorous external validation across IVF centers worldwide [17].

2. Sperm Selection for ICSI

Sperm selection for ICSI has traditionally relied on embryologist judgment to identify morphologically normal, motile sperm under high magnification. This manual process is time-consuming, subjective, and dependent on operator expertise. AI-assisted sperm selection tools now provide automated detection, tracking, and classification capabilities that significantly enhance both efficiency and objectivity.

Deep learning systems can identify viable spermatozoa from microscopy images and microfluidic video data in real time, classifying them on the basis of motility patterns, head morphology, acrosomal status, and structural integrity [2,5,11,18]. AI-guided sperm selection has proven especially valuable in cases of severe male-factor infertility or non-obstructive azoospermia, where motile sperm are difficult to locate manually. Integration of AI with advanced microfluidic platforms has enabled sperm sorting based on motility trajectories, capacitation markers, and DNA fragmentation indices, improving fertilization potential while reducing oxidative and mechanical stress during handling [18,19].

Moreover, novel prototypes of AI-assisted micromanipulators have been developed to autonomously capture, position, and inject selected sperm during ICSI while remaining under embryologist supervision [20]. Although these technologies are currently in early experimental phases, they represent a major step toward semi-automated fertilization workflows designed to reduce operator variation and improve consistency across IVF laboratories.

3. Personalization of Ovarian Stimulation

Controlled ovarian stimulation (COS) aims to recruit multiple mature oocytes, but determining the optimal gonadotropin dose remains one of the most challenging components of IVF cycle management. Traditionally, dosing has been based on clinician experience, patient age, baseline hormone levels, and antral follicle count, often leading to variable responses and risks such as ovarian hyperstimulation syndrome (OHSS). AI has emerged as a transformative tool for

predicting ovarian response and tailoring stimulation protocols.

Machine learning models integrate a broad array of variables including age, AMH, FSH, BMI, AFC, estradiol dynamics, and prior cycle characteristics, to forecast the expected number of retrievable oocytes and recommend individualized gonadotropin doses [1,6, 21]. Patel *et al.* [6] demonstrated that AI-guided stimulation protocols significantly reduced medication requirements and decreased OHSS incidence without compromising oocyte yield or clinical pregnancy rates. More advanced reinforcement learning models dynamically adjust gonadotropin dosing in real time as follicular development progresses, providing fully adaptive stimulation strategies tailored to each patient's cycle-specific response [21].

These data-driven approaches signal a shift from empirical, heuristic dosing toward precision-controlled ovarian stimulation. Integration of AI models with electronic medical records and ultrasound monitoring platforms enables real-time clinical alerts, cycle forecasting, and decision support during stimulation.

4. Outcome Prediction and Counseling

Beyond diagnosis and treatment optimization, AI plays an increasingly critical role in predictive counseling and patient communication. AI-based predictive models estimate probabilities of fertilization, blastocyst formation, implantation, clinical pregnancy, and live birth by incorporating clinical data, embryologic parameters, laboratory metrics, and sometimes genetic or metabolic markers [16,22]. These tools support patient-centered decision-making by enabling realistic expectation-setting and facilitating informed choices regarding fresh *versus* frozen embryo transfer, cycle continuation, or donor gamete options.

Modern outcome prediction platforms frequently integrate explainable AI (XAI) frameworks that highlight which variables (such as embryo morphology, endometrial characteristics, patient age, or ovarian reserve markers) most influence the predicted outcome. This transparency enhances clinician trust, supports ethical use, and strengthens communication with patients.

Clinical integration of these systems has already demonstrated improvements in patient satisfaction, decision-making efficiency, and treatment adherence [23]. However, widespread adoption still requires rigorous external validation, standardized reporting metrics, regulatory oversight, and structured implementation guidelines to ensure safe and equitable clinical deployment.

III. Emerging and Frontier Uses

The scope of artificial intelligence (AI) in reproductive medicine is rapidly expanding beyond traditional diagnostics and assisted reproduction. Novel frontiers now include genomic prediction, microrobotics for gamete manipulation, AI-assisted fertility surgery, and digital health applications for patient interaction. These advancements illustrate the convergence of computational science, bioengineering, and clinical fertility care, signaling a transition toward precision, automation-driven reproductive medicine. The major domains and clinical applications of artificial intelligence in infertility medicine are summarized in Table 2.

Table 2. AI applications by domain in infertility medicine

Domain	Example Application	AI Model / Technique	Output / Advantage
Male Factor	Sperm detection, motility analysis	CNN, object detection	Objective sperm scoring
Female Factor	Ovarian reserve prediction	Regression, ensemble learning	Personalized stimulation plans
Embryology	Time-lapse embryo grading	Deep CNN	Embryo viability score
Genomics	Non-invasive aneuploidy detection	Multi-omics deep learning	Genetic risk prediction
Surgery	Endometriosis detection	Computer vision (segmentation)	Intraoperative guidance
Telehealth	AI chatbots, patient counseling	NLP models	Better access and education

1. AI Integration in Reproductive Genomics

The incorporation of AI into genomic and multi-omics analysis represents a major advance toward individualized reproductive care. Traditional preimplantation genetic testing (PGT) requires embryo biopsy and invasive analysis. Recent breakthroughs in AI-driven genomics allow for non-invasive prediction of ploidy status using time-lapse imaging and spent culture medium metabolomics [24,25].

Deep learning algorithms trained on embryo imaging and metabolomic signatures can detect molecular patterns associated with chromosomal abnormalities, reducing dependence on invasive biopsy techniques. Khosravi *et al*. [16] demonstrated that integrating imaging, transcriptomic, and metabolomic features allows for highly precise prediction of embryo viability. Similarly, genomic prediction models have been applied to polygenic risk scoring (PRS) in embryos, estimating the likelihood of complex disorders and inherited diseases [26].

While the potential of genomic AI is substantial, it introduces profound ethical considerations, including risks of misuse for non-medical selection, trait optimization, or eugenic applications. Ethical frameworks emphasize that genomic AI must prioritize disease prevention, reproductive autonomy, and clinical justi-

fication, avoiding enhancement-oriented or socially discriminatory uses [7,26,27].

2. Microrobotics and AI-Assisted Fertility Procedures

AI-powered microrobotics is emerging as one of the most transformative technological innovations in reproductive medicine. Microrobots equipped with computer vision, magnetic navigation, and AI-based control systems can autonomously transport sperm toward the oocyte, offering new possibilities for severe male-factor infertility or impaired tubal physiology [28].
Fernandez *et al.* [20] reported early experimental success using AI-guided micromanipulators capable of autonomously performing key steps of ICSI, including sperm capture, positioning, and microinjection. These devices employ reinforcement learning algorithms to navigate microscopic environments, recognize oocytes, and execute microinjection maneuvers under embryologist supervision. Other experimental systems combine AI-controlled magnetic microrobots with real-time imaging feedback to deliver sperm directly to the target site, minimizing manual manipulation time and reducing mechanical trauma to gametes [28,29].
Although still in preclinical development, these technologies represent a future direction for semi-autonomous reproductive microsurgery, in which AI augments rather than replaces embryologist and surgical expertise.

3. Real-Time Surgical Video Analysis

In reproductive surgery, particularly laparoscopy and hysteroscopy, AI is being applied to enhance intraoperative visualization, anatomical recognition, and surgical precision. Deep learning-based computer vision models can identify pelvic structures, endometriotic lesions, adhesions, and vascular networks in real-time video streams, providing surgeons with continuous visual guidance during complex fertility-preserving procedures [3,30].
AI-assisted image segmentation tools allow quantitative mapping of lesion size, vascularity, and organ boundaries, improving diagnostic accuracy and reducing operative risk. Early developments in augmented reality (AR) integration enable the overlay of critical structures-such as ureters, ovarian vessels, and bowel loops-onto the surgical field, potentially decreasing iatrogenic injury during difficult dissections [30,31].
Additionally, AI systems analyzing post-operative surgical videos can perform automated skill assessment, identifying instrument trajectories, gesture patterns, and tissue handling quality. Such feedback provides objective metrics for surgical training, contributing to standardized education and continuous improvement in minimally invasive reproductive surgery [31].

4. Patient-Facing AI and Digital Fertility Support

Beyond laboratory and surgical applications, AI technologies are increasingly integrated into patient-facing fertility platforms. Natural language processing (NLP)-based chatbots and mobile health applications assist patients with cycle tracking, hormonal monitoring, medication adherence, and lifestyle optimization, while also providing evidence-based responses to fertility-related questions [32,33].
Moussa *et al*. [23] demonstrated that AI-enhanced counseling tools improve patient satisfaction, engagement, and understanding by offering personalized insights and empathetic interactions. Digital platforms can triage infertility complaints, guide patients through preliminary assessments, and facilitate referrals to reproductive specialists, potentially expanding access to fertility care in underserved populations.
However, reliance on patient-generated data introduces challenges related to data accuracy, privacy, and cybersecurity. Regulatory authorities, including the FDA and ESHRE, stress that patient-facing AI systems must comply with strict data protection standards and function exclusively as decision-support tools rather than replacements for professional medical care [8,9,33].

IV. Limitations, Ethics, and Regulation

While artificial intelligence (AI) is transforming infertility diagnosis and treatment, its integration into routine

Table 3. Ethical and regulatory considerations in reproductive AI

Ethical / Legal Aspect	Example	Clinical Relevance
Bias & Fairness	Training data may not represent all populations	May affect diagnostic accuracy and fairness
Transparency & Explainability	AI models limit interpretability	Reduces clinician trust and patient understanding
Data Privacy & Security	Compliance with GDPR and HIPAA standards	Ensures confidentiality of sensitive reproductive data
Validation & Clinical Safety	FDA/ESHRE guidelines for AI-enabled devices	Protects patient safety and promotes reliability
Accountability & Oversight	Human-AI decision-sharing in clinical practice	Maintains ethical responsibility and professional control

clinical practice remains constrained by fundamental challenges related to data quality, algorithmic transparency, ethical governance, and regulatory compliance. For AI to progress from proof-of-concept studies to widespread clinical adoption, these limitations must be addressed through rigorous validation and multidisciplinary oversight. Key ethical and regulatory considerations associated with reproductive AI are presented in Table 3.

1. Data Quality and Generalizability

A major limitation in reproductive AI research is the lack of standardized, diverse, and high-quality datasets. The majority of existing models are trained on retrospective, single-center data that lack demographic and geographic diversity, thereby limiting generalizebility and external validity [10,17,34]. Variations in laboratory workflows, imaging equipment, and clinical documentation also contribute to inconsistencies in algorithm performance across fertility centers.

Federated learning has emerged as a promising solution. This approach allows AI models to be trained collaboratively on decentralized datasets while maintaining privacy and avoiding data transfer [14,35]. Lin *et al.* [14] demonstrated that federated models trained across multiple fertility clinics achieved predictive performance comparable to centralized datasets. Collaborative initiatives such as the Reproductive AI Network (RAIN) have been proposed to harmonize data labeling, curation, and benchmarking standards [35].

Ensuring transparency and reproducibility requires adherence to standardized reporting frameworks. Journals and institutions increasingly mandate compliance with TRIPOD-AI and CONSORT-AI guidelines, which provide structured requirements for reporting diagnostic and interventional AI trials [36].

2. Algorithmic Bias and Explainability

AI systems are inherently vulnerable to algorithmic bias, as their performance depends on the characterristics of the datasets used for training. Underrepresentation of specific populations, whether based on ethnicity, socioeconomic status, or geographic region, can result in biased predictions and widen disparities in infertility care [7,26,37]. For example, models trained predominantly on data from high-income countries may perform poorly when applied to patients from underrepresented ethnic groups or regions with different clinical profiles.

Explainability further complicates the issue. Many deep learning systems function as “black boxes,” generating predictions without interpretable reasoning, which undermines clinician trust and poses challenges for regulatory approval [13,37].

Recent advances in Explainable AI (XAI) address these concerns. XAI methods provide interpretable outputs such as:

- **heatmaps** highlighting image regions influencing embryo classification,
- **feature-importance analyses** revealing which hormonal, clinical, or imaging variables drive predictions,
- **counterfactual explanations** illustrating how small changes in input data alter outcomes [14,37,38].

These tools enhance transparency, help clinicians validate model reasoning, and support accountable use in patient care. However, their integration into clinical-grade systems remains in early development stages.

3. Data Privacy and Cybersecurity

Infertility care involves exceptionally sensitive personal, reproductive, and genetic information such as gamete characteristics, embryo videos, and detailed reproductive histories. Breaches of such data could lead to significant ethical, psychological, and legal conseqquences.

While regulatory frameworks like the General Data Protection Regulation (GDPR) in the EU and HIPAA in the United States set foundational data protection standards, AI introduces additional risks through cloud-based analytics, decentralized computation, and automated decision-making pipelines [8,9,39].

Emerging privacy-preserving solutions include:

- **Federated learning** to avoid centralizing data
- **Blockchain-based audit trails** ensuring data integrity and traceability [40]
- **Advanced encryption protocols** for secure model training across networks [39,40].

Clinicians and institutions must verify that commercial AI vendors meet institutional security standards and obtain specific patient consent for AI-assisted data processing.

Novel privacy-preserving AI architectures are being developed to enable real-time analytics within secure clinical networks without exposing raw patient data, balancing innovation with confidentiality.

4. Regulatory Oversight and Clinical Validation

Regulatory classification of AI-based reproductive systems remains a significant barrier to clinical deployment. Unlike static medical devices, AI models evolve as they learn from new data, complicating approval pathways and post-market surveillance.

The U.S. Food and Drug Administration (FDA) has introduced a regulatory framework for AI/ML-based Software as a Medical Device (SaMD), emphasizing transparency, change-control plans, and real-world performance monitoring [8,41]. Similarly, the European

Society of Human Reproduction and Embryology (ESHRE) requires robust validation and clinical trials prior to clinical integration [9,42].

Despite these regulatory advances, few reproductive AI tools have obtained clearance due to:

- limited multicenter trials,
- heterogeneous outcome metrics,
- lack of standardized benchmarks.

Establishing harmonized performance metrics-such as AUC thresholds, calibration indices, and clinically meaningful endpoints-is critical for ensuring comparability, reproducibility, and patient safety [42,43].

5. Ethical Governance and Human Oversight

Ethical governance is central to responsible implementation of AI in reproductive medicine. The principle of **AI-augmented care,** where AI provides recommenddations but clinicians retain full responsibility for clinical decisions, remains the most ethically defensible model [7,9,27].

Core ethical principles include:

- **Beneficence:** AI should enhance patient outcomes.
- **Non-maleficence:** Algorithms must not introduce harm through bias or inaccuracy.
- **Autonomy:** AI tools should support informed decision-making, not limit reproductive choice.
- **Justice:** AI systems must promote equitable access and avoid exacerbating disparities.

Rolfes *et al.* [7] and Harris *et al.* [27] emphasize the moral implications of embryo selection algorithms, noting that AI should support, not constrain, reproductive autonomy. Transparent reporting of algorithm design, performance, and limitations is essential for maintaining patient trust.

Institutions are increasingly encouraged to establish **AI Ethics Committees** to oversee deployment, manage conflicts of interest, and ensure continuous auditing. With the introduction of the **EU Artificial Intelligence Act (2024)**, legal accountability now extends to AI developers, distributors, and healthcare institutions, underscoring the importance of compliance with international ethical and regulatory standards [44].

Conclusion

Artificial intelligence (AI) has emerged as a transformative force in the diagnosis and treatment of infertility, driving a paradigm shift from subjective, experience-based medicine toward objective, data-driven, and personalized reproductive care. Its integration across diagnostic evaluation, assisted reproduction, and clinical decision support has already begun to redefine standards of precision, efficiency, and equity in fertility medicine.

In diagnostic evaluation, AI-based algorithms have enhanced the accuracy and reproducibility of semen analysis, ovarian reserve estimation, and imaging-based detection of pelvic pathologies. By automating interpretation and integrating multimodal data-including hormonal, clinical, and imaging inputs-these systems enable earlier and more reliable identification of both male and female infertility factors. Machine learning models further allow prediction of ovarian stimulation outcomes, empowering clinicians to individualize gonadotropin dosing and minimize risks such as ovarian hyperstimulation syndrome (OHSS).

Within assisted reproduction, deep learning has revolutionized embryo and sperm selection, offering objective and reproducible alternatives to manual grading. AI-assisted time-lapse imaging systems can now predict embryo implantation potential with high precision, while AI-guided sperm selection technologies improve ICSI outcomes, particularly in severe male-factor infertility. Machine learning models for ovarian stimulation and treatment personalization are moving ART toward true precision reproductive medicine, improving both clinical efficiency and patient satisfaction.

Emerging and frontier applications, such as genomic prediction, microrobotics for sperm delivery, and AI-assisted reproductive surgery, illustrate the expanding interdisciplinary potential of AI in fertility care. These innovations are pushing the field toward automation and non-invasive assessment, creating opportunities for safer, more accessible, and more personalized interventions. Likewise, patient-facing AI platforms are empowering individuals to engage actively in their reproductive health, enhancing counseling, adherence, and education.

However, these advances are accompanied by signifycant challenges. Data heterogeneity, algorithmic bias, limited generalizability, and regulatory uncertainty continue to restrict the widespread clinical adoption of AI. Ethical concerns regarding transparency, privacy, and equitable access remain central to responsible implementation. Ensuring rigorous validation, explainability, and clinician oversight is essential to maintain trust and uphold medical integrity.

Looking ahead, the future of infertility care will likely be shaped by collaborative intelligence, a partnership between clinicians and algorithms in which AI serves as an extension of human expertise rather than its replacement. As technology continues to evolve, the overarching goal remains constant: to enhance reproductive outcomes while preserving the ethical foundations of compassion, autonomy, and patient-centered care. With sustained innovation, robust regulation, and interdisciplinary collaboration, AI has the potential to transform infertility treatment into a model of truly personalized, predictive, and equitable reproductive medicine.

Conflict of interests: None declared.

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MMP

Original article

ROLE OF INHERITED THROMBOPHILIA IN WOMEN WITH INFERTILITY: A CASE-CONTROL ANALYSIS

УЛОГА НА НАСЛЕДНА ТРОМБОФИЛИЈА КАЈ ЖЕНИ СО ИНФЕРТИЛИТЕТ: АНАЛИЗА НА СТУДИЈА НА СЛУЧАЈ И КОНТРОЛА

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Abstract

Introduction. Inherited thrombophilia has been associated with adverse reproductive outcomes, but its role in infertility remains insufficiently clarified.
Methods. A case-control study including women with infertility (n=38) and a control group (n=36) was conducted at the Institute for Transfusion Medicine- Skopje (ITM-Skopje). Genetic testing for Factor V Leiden G1691A, Prothrombin G20210A and MTHFR C677T mutations was performed in the Laboratory for molecular testing in ITM-Skopje. Statistical significance was set at $p<0.05$.
Results. The absence of thrombophilic mutations was significantly lower in infertile women compared to controls. MTHFR C677T homozygosity was markedly more frequent in the infertility group (39.5%) compared to controls (5.5%) ($p<0.001$). Factor V Leiden mutation was more prevalent in infertile women (10.5%) compared to controls (2.8%), although without strong statistical significance. Prothrombin G20210A mutation was also more frequent in the infertility group (13.2%) compared to controls (5.5%). Combined mutations were observed more frequently in infertile women (21.1%) compared to controls (5.6%).
Conclusion. Inherited thrombophilia, particularly MTHFR C677T homozygosity and combined mutations, may contribute to female infertility.

Keywords: infertility, thrombophilia, Factor V Leiden, prothrombin, MTHFR

Апстракт

Вовед. Наследната тромбофилија е поврзана со негативни репродуктивни исходи, но нејзината улога во инфертилитетот останува недоволно појаснета.
Методи. Направена е студија на случај и контрола, која вклучува жени со инфертилитет (n=38) и контрола група (n=36) во Институтот за трансфузиона медицина-Скопје. Во лабораторијата за молекуларно тестирање е извршено генетско тестирање за мутации на Factor V Leiden G1691A, Prothrombin G20210A и MTHFR C677T. Статистичката значајност е поставена на $p<0.05$.
Резултати. Отсуството на тромбофилни мутации беше значително помало кај жените со инфертилитет во споредба со контролите. Хомозиготната мутација на MTHFR C677T беше забележливо почеста во групата со инфертилитет (39.5%) во споредба со контролите (5.5%) ($p<0.001$). Мутацијата на Factor V Leiden беше почеста кај жените со инфертилитет (10.5%) во споредба со контролите (2.8%), иако без силна статистичка значајност. Мутацијата Prothrombin G20210A исто така беше почеста во групата со инфертилитет (13.2%) во споредба со контролите (5.5%). Комбинирани мутации се регистрираа почесто кај жени со инфертилитет (21.1%) во споредба со контролите (5.6%).
Заклучок. Наследната тромбофилија, особено MTHFR C677T хомозиготната мутација и комбинираните мутации, може да придонесе за женскиот инфертилитет.

Клучни зборови: инфертилитет, тромбофилија, Фактор V Leiden, протромбин, MTHFR

Introduction

Thrombophilia arises from a disruption in the normal balance of the coagulation system, leading to an increased tendency for thromboembolic events. It may be inherited, representing a genetic predisposition to venous or arterial thrombosis, often occurring at a younger age and characterized by a tendency for recu-

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rrence [1]. Although not a disease per se, thrombophilia is a laboratory-defined condition that may be associated with various clinical states, including malignancy, medication use, or pregnancy [2]. Importantly, most individuals with thrombophilia do not develop thrombosis, and its clinical significance depends on the presence of additional risk factors [3].
Thrombophilia has been implicated in a range of clinical manifestations, most commonly venous thromboembolism, but also in adverse pregnancy outcomes such as recurrent pregnancy loss, stillbirth, and placental complications [4,5]. However, the role of thrombophilia testing remains controversial and is generally recommended only when results are expected to influence clinical management [6].
Infertility is a multifactorial condition affecting a significant proportion of women of reproductive age. While hormonal, anatomical, and immunological factors are well established, increasing attention has been directed toward the potential contribution of hemostatic disorders [7]. Inherited thrombophilia, characterized by genetic mutations such as Factor V Leiden, Prothrombin G20210A, and MTHFR polymorphisms, may contribute to infertility through microvascular disturbances, impaired uterine perfusion, and altered endometrial receptivity [8,9].
The role of inherited thrombophilia in pregnancy loss and vascular complications has been extensively studied; however, findings remain inconsistent. While some studies have demonstrated an association between thrombophilia and adverse reproductive outcomes, others have failed to confirm these relationships [10].
The relationship between inherited thrombophilia and infertility remains controversial. Some studies have suggested that a prothrombotic tendency may be associated with unexplained infertility [11], whereas others have not confirmed this association [12]. Current evidence does not support a consistent link between inherited thrombophilia and infertility, except possibly in cases of recurrent implantation failure.
A systematic review and meta-analysis by Di Nisio *et al.* demonstrated a significant association only for Factor V Leiden mutation, which was linked to an increased risk of implantation failure (OR 3.08; 95% CI 1.77-5.36), while no consistent association was found for other thrombophilic mutations [13].
The aim of this study was to evaluate the prevalence of inherited thrombophilia in women with infertility compared to a healthy control group and to investigate its possible role as a contributing factor.

Materials and methods

The case-control study was conducted at the Institute for Transfusion Medicine-Skopje (ITM-Skopje). The study included 74 women, divided in two groups. The data from the performed examinations and analyses in the outpatient clinic at ITM-Skopje were processed for the women with diagnoses according to the inclusion criteria.
Inclusion criteria:
- Women aged 18-45,
- Women with diagnosed primary and secondary infertility according to the criteria of the World Health Organization (WHO).

Exclusion criteria:
- Women who had a previous history of venous thromboembolism,
- Women with pre-existing causes of secondary thrombophilia: autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis), positive antiphospholipid antibodies (APA), positive lupus anticoagulant (LA), extreme obesity, dyslipidemia, nephrotic syndrome,
- Women who refused to participate in the study or gave up at some point in the study.

In the study group, 38 women with diagnosed primary and secondary infertility according to the WHO criteria were included.
The control group included 36 women, age-matched, who gave birth to at least one healthy child without obstetric complications. Presence of gene mutations for factor II Prothrombin G20210A, factor V Leiden G1691A and methylenetetrahydrofolate reductase (MTHFR C677T) was examined in both groups. Sociodemographic data, along with data on personal, family and obstetric history were collected with a standardized questionnaire. Blood samples from the included women were examined in the Molecular Biology Laboratory at ITM-Skopje, with previously given informed consent before taking blood samples and using the results in the preparation of the study, approved by the Ethics Committee at the Faculty of Medicine in Skopje. The method used to examine factor II factor G20210A, factor V Leiden G1691A and MTHFR C677T was molecular detection of point mutations using the Operon kit. A total of 2 ml of venous blood was collected in a vacutainer K2EDTA. Statistical analysis was performed with the statistical package STATISTICA 7.1; SPSS 13.0. Numerical series were analyzed with measures of central tendency and measures of dispersion of data. The Student's t-test (t) was used for testing the significance of difference between groups. A p-value less than 0.05 was considered statistically significant.

Results

The distribution of nationality was homogeneous between the study and control groups and was broadly consistent with the national demographic structure of the Republic of North Macedonia. Macedonians comprised 78.9% of the study group (n=30) and 69.5% of the control group (n=25). Albanians accounted for 7.9%

of the study group and 19.4% of the controls, while participants of other ethnicities represented 13.2% and 11.1% of the study and control groups, respectively. No statistically significant differences were observed between the groups with respect to baseline sociodemographic characteristics (Table 1).

Table 1. Ethnicity

Ethnicity/ Group	Infertility		Control group	
	N	%		%
Macedonians	30	78.9	25	69.5
Albanians	3	7.9	7	19.4
Other	5	13.2	4	11.1
Total	38	100.0	36	100.0

The average age of the study group was lower than that of the control group (mean 33.8, range 24-45 *versus* mean 32.8, range 23-44 respectively), but the difference did not reach statistical significance (p>0.05). The 38 women in the infertility group had a total of 39 pregnancies (mean 1.2±0.9), whereas the 36 women in the control group had a total of 77 pregnancies (mean 2.1±0.5), and this difference was statistically significant (p<0.05). The mean number of spontaneous abortions was higher in the infertility group (0.5±0.88) compared to the control group (0.1±0.23); however, this difference did not reach statistical significance (p>0.05) (Table 2).

Table 2. Clinical characteristics of women with infertility and controls

Variable	Group	Mean	N	Std. Dev.	p-value
Age (years)	Infertility	30.5	38	4.62	>0.05
	Control	32.8	36	4.67	
Number of pregnancies	Infertility	1.2	38	0.94	<0.05
	Control	2.1	36	0.48	
Number of spontaneous abortions	Infertility	0.5	38	0.88	>0.05
	Control	0.1	36	0.23	

Significant differences were observed between women with infertility and controls. A significantly lower proportion of women without thrombophilic mutations was found in the infertility group compared to controls (6/38, 15.8% *vs*. 13/36, 36.1%; p=0.04).

With respect to individual mutations, the prevalence of MTHFR C677T homozygous mutation was markedly higher in infertile women, detected in 15 out of 38 patients (39.5%), compared to 2 out of 36 controls (5.5%), representing a statistically significant difference (p<0.001).

In contrast, the MTHFR C677T heterozygous mutation was observed in 15 infertile women (39.5%) and 20 controls (55.6%), with no statistically significant difference between groups (p=0.16). Factor V Leiden heterozygous mutation was identified in 4 women in the infertility group (10.5%) and in 1 control subject (2.8%) (p=0.36). Similarly, Prothrombin G20210A heterozygous mutation was present in 5 infertile women (13.2%) compared to 2 controls (5.5%), without statistical significance (p=0.43).

The homozygous Prothrombin (F II G20210A) mutation was detected in only one patient in the infertility group (2.6%) and in none of the controls, with no statistically significant difference between groups (p=1.00). Due to the very low frequency of this mutation, this result should be interpreted with caution (Table 3).

Table 3. Prevalence of thrombophilic mutations in women with infertility and controls

Thrombophilic mutations	Infertility		Control		p-value
	N	%	N	%	
Without mutation	6	15.8	13	36.1	<0.05
F II G20210A heterozygous	5	13.2	2	5.5	>0.05
FV Leiden heterozygous	4	10.5	1	2.8	>0.05
MTHFR C677T heterozygous	15	39.5	20	55.6	>0.05
F II G20210A homozygous	1	2.6	0	0.0	1.00
MTHFR C677T homozygous	15	39.5	2	5.5	<0.05
Total	38	100.0	36	100.0	

Combined thrombophilic mutations were more frequently observed in women with infertility compared to controls (8/38, 21.1% *vs*. 2/36, 5.6%), demonstrating a borderline association that did not reach statistical significance (p=0.06). The most common combination in the infertility group was Prothrombin G20210A heterozygous with MTHFR C677T heterozygous mutation (10.5%), which was not detected in the control group. Other combined mutation patterns, including Prothrombin G20210A heterozygous with MTHFR homozygous mutation and Factor V Leiden combined with MTHFR variants, were observed at low frequent-

cies in both groups, without statistically significant differences. Overall, individual combined mutation patterns were rare and did not show significant associations with infertility (Table 4).

Table 4. Combined thrombophilic mutations in women with infertility and controls

Combined mutations	Infertility		Control		p-value
	N	%	N	%	
Prothrombin G20210A heterozygous + MTHFR C677T heterozygous	4	10.5	0	0.0	>0.05
Prothrombin G20210A heterozygous + MTHFR C677T homozygous	1	2.6	1	2.8	1.00
Factor V Leiden heterozygous + MTHFR C677T heterozygous	2	4.3	1	2.8	1.00
Factor V Leiden heterozygous + MTHFR C677T homozygous	1	2.6	0	0.0	1.00
Any combined mutation	8	21.1	2	5.6	0.06
Total	38	100.0	36	100.0	

The analysis demonstrated that MTHFR C677T homozygosity was strongly associated with infertility, with an approximately 11-fold increased odds compared to controls (OR=11.1; 95% CI: 2.3-53.5; p<0.001). This was the only mutation showing a statistically significant association. Prothrombin G20210A and Factor V Leiden mutations were more frequent in women with infertility, with odds ratios of 2.6 and 4.1, respectively; however, these associations did not reach statistical significance, as indicated by wide confidence intervals crossing unity (p>0.05). Combined thrombophilic mutations were also more prevalent in the infertility group (OR=4.5; 95% CI: 0.9-22.4), showing a trend toward increased risk, although this did not achieve statistical significance (p=0.06).

Overall, these findings suggest that while inherited thrombophilia may contribute to infertility, particularly through MTHFR homozygosity, the role of other mutations remains inconclusive and may be limited by sample size.

Table 5. Association between inherited thrombophilic mutations and infertility

Mutation	Infertility (%)	Control (%)	OR	95% CI	p-value
Prothrombin G20210A	13.2	5.5	2.6	0.5-13.5	>0.05
Factor V Leiden	10.5	2.8	4.1	0.4-39.6	>0.05
MTHFR homozygous	39.5	5.5	11.1	2.3-53.5	<0.001
Combined mutations	21.1	5.6	4.5	0.9-22.4	0.06

Discussion

In the present study, the distribution of ethnicity and baseline sociodemographic characteristics was comparable between women with infertility and control group, reflecting the general population structure of the Republic of North Macedonia. The absence of statistically significant differences between groups suggests that the observed associations are unlikely to be influenced by confounding demographic factors.

The analysis of clinical characteristics demonstrated that women with infertility had a significantly lower number of pregnancies compared to controls, which is expected given the nature of the condition. Although the mean number of spontaneous abortions was higher in the infertility group, this difference did not reach statistical significance, indicating that pregnancy loss was not the dominant reproductive issue in this cohort. These findings are consistent with previous reports suggesting that infertility and recurrent pregnancy loss represent distinct, although partially overlapping, clinical conditions [4,7].

The most important finding of this study is the strong association between MTHFR C677T homozygosity and infertility. Women carrying this mutation had a significantly higher prevalence and an approximately 11-fold increased odds of infertility compared to controls. This supports the hypothesis that disturbances in folate metabolism and hyperhomocysteinemia may lead to endothelial dysfunction, impaired uterine microcirculation, and reduced endometrial receptivity [8,9]. Similar associations have been reported in recent studies, although the clinical relevance of MTHFR polymorphisms remains a subject of debate [14-16].

The role of MTHFR mutations in reproductive disorders is controversial. While some authors suggest a significant association with infertility and implantation failure, others emphasize that MTHFR polymerphisms alone may not be clinically meaningful in the absence of elevated homocysteine levels or additional risk factors [3,14]. Recent meta-analyses also highlight considerable heterogeneity among studies, contributing to inconsistent findings [15,16].

In contrast, Factor V Leiden and Prothrombin G20210A mutations were more frequent in the infertility group but did not reach statistical significance. These findings are consistent with existing literature suggesting that these classical thrombophilic mutations

are more strongly associated with recurrent pregnancy loss and thromboembolic complications rather than infertility itself [1,10]. A systematic review by Di Nisio *et al.* demonstrated a significant association between Factor V Leiden and implantation failure, but not with infertility in general [13].

The analysis of combined thrombophilic mutations revealed a higher prevalence in women with infertility, with borderline statistical significance. This finding supports the hypothesis of a possible cumulative or synergistic effect of multiple prothrombotic factors on reproductive function. Similar observations have been reported in recent studies, suggesting that combined mutations may confer a higher risk than single mutations alone [19]. However, due to the low frequency of individual combinations and the limited sample size, these results should be interpreted with caution.

Importantly, a significantly lower proportion of women without any thrombophilic mutations was observed in the infertility group, further supporting the potential contribution of prothrombotic predisposition to infertility. The underlying mechanisms may involve impaired uteroplacental circulation, endothelial dysfunction, and altered implantation processes [2,5].

Despite these findings, the clinical utility of thrombophilia screening in infertile women remains controversial. Current guidelines do not recommend routine testing in the absence of a personal or family history of thrombosis or pregnancy complications, as there is insufficient evidence that such testing improves reproductive outcomes [6,18,20]. A more individualized approach, focusing on selected high-risk patients, has been suggested in recent recommendations [18,20].

This study has several limitations. The relatively small sample size is reflected in the wide confidence intervals and limited statistical power, particularly for rare mutations and combined genotypes. Additionally, homocysteine levels were not assessed, which may be important for interpreting the clinical impact of MTHFR polymorphisms. Larger, well-designed prospective studies are needed to further elucidate the role of inherited thrombophilia in infertility and its clinical implications.

Conclusion

The findings of this study suggest that inherited thrombophilia may contribute to infertility, particularly through a strong association with MTHFR C677T homozygosity. In contrast, Factor V Leiden and Prothrombin G20210A mutations were more frequent in infertile women but did not demonstrate statistically significant associations. Combined thrombophilic mutations showed a trend toward increased risk, although this did not reach statistical significance. Overall, these results indicate that the role of inherited thrombophilia in infertility is complex and not uniform across different genetic variants. Routine screening for thrombophilia in infertile women cannot be universally recommended; however, a selective approach may be considered in specific clinical contexts. Further large-scale, prospective studies are required to clarify the clinical relevance of thrombophilia in infertility and to determine its potential implications for diagnosis and management.

Conflict of interests: None declared.

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MMP

Original article

LABORATORY DIAGNOSIS AND DISTRIBUTION OF TOXIGENIC CLOSTRIDIOIDES DIFFICILE IN ADULTS AND CHILDREN: A ONE-YEAR STUDY

ЛАБОРАТОРИСКА ДИЈАГНОЗА И ДИСТРИБУЦИЈА НА ТОКСИГЕН CLOSTRIDIOIDES DIFICILE КАЈ ВОЗРАСНИ И ДЕЦА: ЕДНОГОДИШНА СТУДИЈА

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Abstract

Clostridioides difficile is a major cause of antibiotic-associated diarrhea, with increasing clinical importance in pediatric and adult populations where asymptomatic colonization is common. This study evaluated the laboratory detection of **Clostridioides difficile** in pediatric and adult patients using a multistep diagnostic algorithm and analyzed the distribution of toxigenic and non-toxigenic strains across healthcare institutions.
During a one-year period (January-December 2024), 767 stool samples from public and private healthcare facilities were analyzed at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje. Diagnostic testing included enzyme immunoassays for glutamate dehydrogenase (GDH) and toxins A and B, with polymerase chain reaction (PCR) testing performed in cases of discordant results.
C. difficile was not detected in 85.5% of samples. Toxigenic strains were identified in 8.07% of samples, while non-toxigenic strains were detected in 5.07%. Among pediatric patients (n=165), toxigenic **C. difficile** was detected in 6.06%, in comparison with 8.64% in adults (n=602). Higher detection rates were observed in nephrology, surgical, and gastroenterology clinics, with public healthcare institutions accounting for the majority of positive cases.
These findings emphasize the importance of a multistep diagnostic approach and careful clinical correlation, particularly in pediatric patients, to differentiate active infection from asymptomatic colonization and to ensure appropriate management of **Clostridioides difficile** infection.

Keywords: Clostridioides difficile infection (CDI), antibiotic-associated diarrhea, laboratory diagnosis, multistep diagnostic algorithm

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Апстракт

Clostridioides difficile претставува значаен причинител на антибиотик-асоцирана дијареја, со сè поголемо клиничко значење кај педијатриската и возрасната популација, каде што асимптоматската колонизација е честа појава. Оваа студија ја евалуираше лабораториската детекција на *Clostridioides difficile* кај педијатриски и возрасни пациенти со примена на мултистепен дијагностички алгоритам и ја анализираше распределбата на токсигените и нетоксигените соеви во различни здравствени установи.
Во текот на едногодишен период (јануари–декември 2024), беа анализирани 767 примероци фецес од јавни и приватни здравствени установи во Институтот за микробиологија и паразитологија при Медицинскиот факултет во Скопје. Дијагностичкото тестирање вклучуваше ензимски имуноанализи за глутамат дехидрогеназа (GDH) и токсини A и B, додека PCR тестирање беше спроведено кај случаи со дискрепантни резултати.
C. difficile не беше детектиран кај 85.5% од примероците. Токсигени соеви беа идентификувани кај 8.07% од примероците, додека нетоксигени соеви беа детектирани кај 5.07%. Кај педијатриските пациенти (n=165), токсиген *C. difficile* беше детектиран кај 6.06%, во споредба со 8.64% кај возрасните пациенти (n=602). Повисоки стапки на детекција беа забележани во нефролошките, хируршките и гастроентеролошките клиники, при што најголем дел од позитивните случаи потекнуваа од јавните здравствени установи.
Овие наоди ја нагласуваат важноста на мултистепениот дијагностички пристап и внимателната клиничка корелација, особено кај педијатриските пациенти, со цел разликување на активна инфекција од асимптоматска колонизација и обезбедување соодветен третман на инфекцијата со *Clostridioides difficile*.

Клучни зборови: инфекција со *Clostridioides difficile* (CDI), антибиотик-асоцирана дијареја,

лабораториска дијагностика, токсигени соеви, мултистепен дијагностички алгоритам.

Introduction

Clostridioides difficile (*C. difficile*) is an anaerobic [1], Gram-positive, spore-forming bacterium capable of producing potent toxins that are a leading cause of antibiotic-associated diarrhea. Although *C. difficile* infection (CDI) predominantly affects adult populations, its incidence among pediatric patients has been increasing in recent years, particularly in hospital environments and among children with underlying medical conditions or compromised immune systems. The clinical presentation of CDI ranges from mild, self-limiting diarrhea to severe, life-threatening complications, including toxic megacolon and sepsis.

In pediatric patients, CDI presents unique diagnostic challenges, as colonization with *C. difficile* is frequently asymptomatic, especially in neonates and young children. Numerous studies have demonstrated that newborns and infants commonly harbor *C. difficile* without exhibiting clinical signs of infection. This phenomenon is attributed to the immaturity or absence of functional toxin-binding receptors in the intestinal epithelium of children under two years of age, which limits the pathogenic effects of the toxins.

Consequently, the interpretation of laboratory findings in pediatric cases requires particular caution. As emphasized in the National Clinical Guidelines of NHS Scotland (2022) [2], the mere detection of *C. difficile* or its toxins does not necessarily confirm active infection in children, underscoring the importance of correlating laboratory results with clinical presentation.

Materials and methods

A total of 767 stool samples were collected between January and December 2024 from public and private healthcare institutions and analyzed at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje. Routine diagnostics included enzyme immunoassays (EIA) for glutamate dehydrogenase (GDH) and toxins A and B [3], followed by polymerase chain reaction (PCR) testing (Amplex method) in cases of discordant results.

Accurate laboratory diagnosis of *Clostridioides difficile* infection (CDI) is essential for appropriate patient management and effective infection control, particularly in the pediatric population. Diagnostic assays are designed to detect the presence of *C. difficile*, its toxins, or toxin-encoding genes in stool samples, thereby aiding in the differentiation between active infection and asymptomatic colonization. However, laboratory results must always be interpreted in conjunction with the clinical presentation.

Glutamate Dehydrogenase (GDH) Test: The glutamate dehydrogenase (GDH) test is a highly sensitive screening assay used to detect the presence of *C. difficile* through identification of a specific enzyme produced by both toxigenic and non-toxigenic strains. Although the test is valuable as an initial step in diagnostic algorithms, it lacks specificity for active infection, as it cannot distinguish between colonization and toxin-mediated disease. Consequently, GDH positivity requires confirmatory testing.

Enzyme Immunoassay (EIA) for Toxins A and B: Enzyme immunoassays (EIA) are among the most commonly employed methods for the detection of *C. difficile* toxins A and B [4,5]. These assays are rapid, cost-effective, and widely available; however, they demonstrate only moderate sensitivity, which may result in false-negative results and underdiagnosis of CDI when used as a standalone test.

Polymerase Chain Reaction (PCR): Polymerase chain reaction-based assays detect genes encoding GDH and major toxins, including *tcdA* and *tcdB*. These molecular methods offer high sensitivity and specificity and have become increasingly integrated into routine diagnostic workflows. Nevertheless, as PCR detects toxin genes rather than active toxin production, positive results must be carefully interpreted, particularly in pediatric patients where colonization is common.

Diagnostic Algorithm for *Clostridioides difficile* Infection

Clinicians should suspect CDI in patients with acute diarrhea (≥3 loose stools in 24h) without an alternative explanation such as laxative use or tube feeds. CDI should particularly be suspected in the setting of relevant risk factors: recent systemic antibiotic use, hospitalization, advanced age, or use of proton pump inhibitors. At the Institute of Microbiology and Parasitology, a combination glutamate dehydrogenase (GDH) plus toxin assay is used, arbitrated by a nucleic acid amplification test (NAAT) which assists in determining colonization *versus* infection (Figure 1). Test of cure is not recommended as *C. difficile* may still be detectable after a course of appropriate therapy and does not indicate persistent disease.

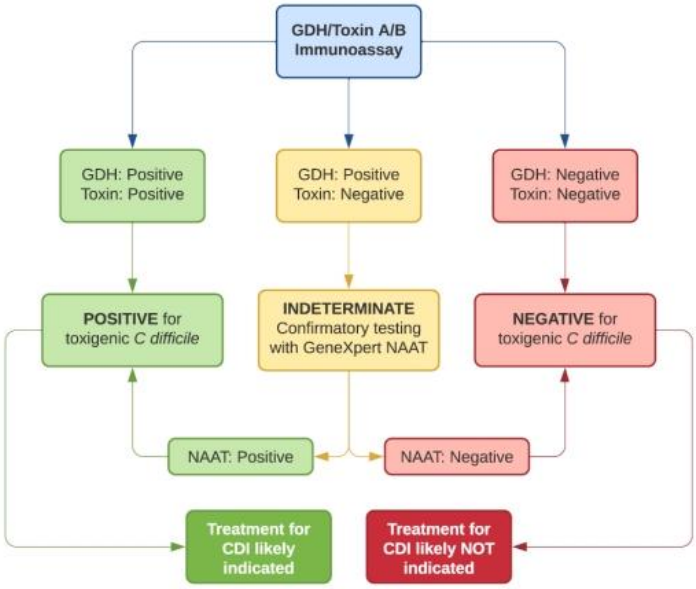

Fig. 1. Diagnostic algorithm for *Clostridioides difficile* infection

Results

Figure 2 shows all tested samples for the presence of **C. difficile** during 2024. In 657(85.5%) out of 767 samples, **C. difficile** was not detected; in 62(8.07%) out of 767 samples, toxic **C. difficile** was detected; in 39 (5.07%) out of 767 samples, non-toxic **C. difficile** was detected. In 4(0.52%) samples, the toxin was detected but not the bacteria (GDH was negative); therefore, a new sample was requested to repeat the analysis. In 5(0.65%) out of 767 samples, further testing with the Amplex test was needed to detect the genes encoding GDH and toxins A and B.

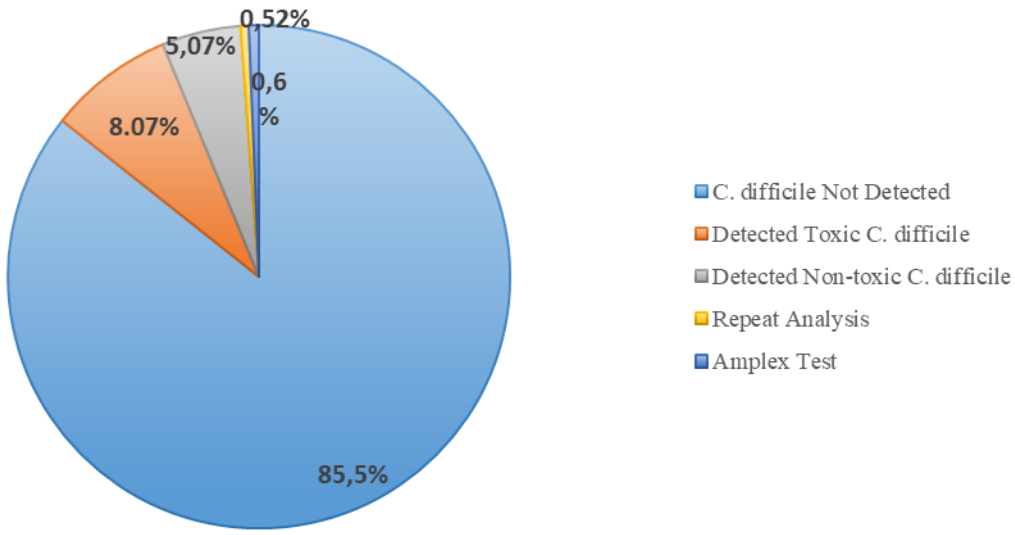

Fig. 2. Display of all tested samples

A total of 45 samples obtained from the University Clinic for Nephrology were analyzed, of which **C. difficile** was not detected in 35 samples, toxic **C. difficile** was detected in 7 samples, and non-toxic **C. difficile** was detected in 3 samples. From a total of 165 samples obtained from the University Clinic for Pediatric Diseases (UCPD) and the Institute for Pulmonary Diseases Kozle, **C. difficile** was not detected in 146 samples, toxic **C. difficile** was detected in 10 samples, and non-toxic **C. difficile** was detected in 9 samples. From a total of 165 samples obtained from the University Clinic for Infectious Diseases, **C. difficile** was not detected in 141 samples, toxic **C. difficile** was detected in 13 samples, and non-toxic **C. difficile** was detected in 7 samples. In 3 samples, the analysis needed to be repeated, and in one sample,

further testing with the Amplex test was required to detect genes encoding GDH and toxins A and B.

At the University Clinic for Gastroenterohepatology, a total of 144 samples were processed, with **C. difficile** not detected in 122 samples, toxic **C. difficile** detected in 14 samples, and non-toxic **C. difficile** detected in 4 samples. For one sample, the analysis needed to be repeated, and in 3 samples, testing was continued with the Amplex test. A total of 114 samples obtained from other clinics were analyzed, and **C. difficile** was not detected in 93 samples, toxic **C. difficile** was detected in 14 samples, and non-toxic **C. difficile** was detected in 7 samples. A total of 120 samples obtained from private health institutions were processed, and **C. difficile** was not detected in 120 samples, toxic **C. difficile** was detected in 4 samples, non-toxic **C. difficile** was detected in 9 samples, and in one sample, further testing with the Amplex test was performed to detect genes encoding GDH and toxins A and B.

Table 1. Distribution of samples obtained from various institutions

Institution	*C. difficile* Not Detected	Detected Toxic *C. difficile*	Detected Non-toxic *C. difficile*	Repeat Analysis	Amplex Test	Total Samples (n, %)
	#	%	#	%	#	%
Infectious Diseases	141	85.5	13	7.87	7	4.24
Pediatric Clinic and Kozle	146	88.5	10	6.06	9	5.45
Gastroenterohepatology	122	84.7	14	9.72	4	2.77
Surgical Clinics	93	81.6	14	12.3	7	6.14
Nephrology	35	77.7	7	15.5	3	6.66
Private Health Institutions	120	89.6	4	2.98	9	6.71

Table 2 shows the number of analyzed samples for **C. difficile** from private health institutions (PHI) compared to the number of samples obtained from other clinics. Out of a total of 767 samples, 134(17.4%) were from PHI, while 633 (82.5%) samples were from other clinics. In 120(89.5%) samples from PHI and 537(84.8%) samples from other clinics, **C. difficile** was not detected. Non-toxic **C. difficile** was detected in 9 (6.7%) out of 134 samples from PHI and in 30(4.7%) out of 633 samples from other clinics. Toxic **C. difficile** was detected in 58 (9.16%) out of 633 samples and 4(2.98%) out of 134 samples from other clinics and PHI, respectively.

Table 2. Display of *C. difficile* samples from PHI compared to *C. difficile* samples from other clinics

Institution	*C. difficile* Not Detected	Detected Toxic *C. difficile*	Detected Non-toxic *C. difficile*	Repeat Analysis	Amplex Test	Total Samples
	#	%	#	%	#	%
PHI	120	89.55	4	2.98	9	6.71
Other Clinics	537	84.83	58	9.16	30	4.73

Discussion

Clostridioides difficile infection (CDI) in the pediatric population represents a significant clinical and public health concern, particularly in hospital settings where exposure risk is increased among hospitalized and immunocompromised patients. Accurate diagnosis of CDI is highly dependent on appropriate specimen collection, with liquid stool being the recommended sample type. Diagnostic testing should be performed in accordance with established protocols in cases of nosocomial diarrhea, as well as in suspected infectious diarrhea after exclusion of other common enteric pathogens.

Current standard diagnostic practice relies on a multistep algorithm. The initial step includes testing for glutamate dehydrogenase (GDH) and toxins A and B, followed by nucleic acid amplification testing to detect genes encoding GDH and the toxins in cases of discordant results. Importantly, laboratory findings must always be interpreted in conjunction with clinical symptoms and patient evaluation. This combined diagnostic approach enables timely and accurate identification of CDI and contributes significantly to improved patient management and clinical outcomes. Although *C. difficile* frequently colonizes the intestinal tract[6] of neonates and young children without causing clinical disease, its pathogenic potential-mediated through toxin production and spore formation-renders it a serious pathogen when active infection develops. Risk factors such as prior antibiotic exposure and disruption of the normal gut microbiota further increase susceptibility to CDI, highlighting the critical role of antimicrobial stewardship in both pediatric and adult populations [7].

Advances in diagnostic methodologies, including toxin detection assays and molecular techniques, have enhanced the precision of CDI diagnosis. Nevertheless, these tools are not sufficient in isolation and must be interpreted within the broader clinical context [8]. Therapeutic strategies, such as treatment with metronidazole or vancomycin and, in selected cases, fecal

microbiota transplantation, have demonstrated effectiveness [9,10]. However, preventive measures remain the cornerstone of long-term CDI control.

Prevention strategies, including strict adherence to hand hygiene, environmental disinfection, patient isolation, and rational antibiotic use, are essential for reducing the incidence of CDI. Furthermore, education of healthcare professionals and caregivers plays a pivotal role in the effective implementation of infection control measures.

In the present study, the high proportion of samples in which *C. difficile* was not detected (85.5%) suggests that specimens were collected from a broadly unselected patient population. Of the samples originating from clinics within the University Clinical Center "Mother Teresa" (82.5% of all samples), *C. difficile* was detected in 9.16%. In contrast, among samples obtained from private health institutions (17.4%), only 2.98% tested positive. Notably, both the number of samples and the number of detected toxigenic *C. difficile* strains from public clinics were approximately four times higher than those from private institutions, likely reflecting differences in patient profiles, hospitalization rates, and underlying risk factors.

When stratified by clinical specialty, the distribution of detected toxigenic *C. difficile* strains revealed the highest prevalence in nephrology (15.5%), followed by surgical clinics (12.3%), gastroenterology and hepatology (9.72%), and infectious diseases (7.87%). However, the elevated percentage observed in nephrology should be interpreted with caution due to the relatively small sample size (n=45). Overall, the findings underscore the importance of an integrated approach combining accurate diagnosis, appropriate therapy, and robust preventive strategies to reduce the burden of CDI, particularly in the pediatric population, and to improve health outcomes across all age groups.

Conflict of interests: None declared.

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MMP

Original article

BLADDER TUMOR MORPHOLOGY AS A PREDICTOR OF RECURRENCE

МОРФОЛОГИЈА НА ТУМОРИТЕ НА МОЧНИОТ МЕУР КАКО ПРЕДИКТОР НА РЕЦИДИВ

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Abstract

Introduction. Bladder cancer is one of the most common urological malignancies worldwide and is characterized by high rates of recurrence and progression. These two fundamental phenomena make the evaluation and management of this disease particularly challenging for the urologist. Identification of reliable prognostic factors is therefore essential for optimizing treatment strategies and follow-up protocols. Among the potential prognostic determinants, the morphological characteristics of bladder tumors may influence the risk of recurrence and progression; however, their precise prognostic value remains incompletely defined.
Aim. To evaluate the association between morphological parameters of bladder tumors, particularly tumor size and focality, and tumor recurrence in patients with low-risk non-muscle-invasive bladder cancer (NMIBC).
Methods. A total of 72 patients with primary bladder tumors classified as low risk according to EORTC criteria were included in this study. The follow-up period was one year. Tumor size was primarily assessed by CT urography, while cystoscopic evaluation was used as a complementary method when precise measurement was not feasible. Tumor focality was assessed during diagnostic cystoscopy and confirmed intraoperatively during transurethral resection of bladder tumor (TURBT). Tumors were classified as unifocal or multifocal. Tumor recurrence during follow-up was recorded as present or absent.
Results. Tumor recurrence was observed in 14 of 72 patients (19.4%) during the one-year follow-up. Tumor size showed no statistically significant association with recurrence, with similar recurrence rates in tumors ≤3 cm and >3 cm. In contrast, tumor focality was signifycantly associated with recurrence, with a markedly higher recurrence rate in patients with multifocal tumors compared to those with unifocal tumors.
Conclusion. In patients with low-risk NMIBC, tumor size did not significantly influence recurrence risk, whereas tumor focality emerged as a strong predictor of recurrence. These findings underline the prognostic importance of tumor focality and support closer surveillance in patients with multifocal bladder tumors.

Keywords: bladder cancer, non-muscle-invasive bladder cancer, tumor focality, tumor size, recurrence

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Апстракт

Вовед. Карциномот на мочниот меур е еден од најчестите уролошки малигнитети во светот и се карактеризира со високи стапки на рецидив и прогресија. Овие две фундаментални појави ја прават евалуацијата и менаџментот на оваа болест особено предизвикувачки за урологот. Идентификацијата на сигурни прогностички фактори е од суштинско значење за оптимизирање на терапевтските стратегии и протоколите за следење. Меѓу потенцијалните прогностички детерминанти, морфолошките карактеристики на туморите на мочниот меур можат да влијаат врз ризикот од рецидив и прогресија; сепак, нивната прецизна прогностичка вредност сè уште не е целосно дефинирана.
Цел. Да се евалуира поврзаноста помеѓу морфолошките параметри на туморите на мочниот меур, особено големината и фокалноста на туморот, и рецидивот кај пациенти со нискоризичен немускулно-инвазивен карцином на мочниот меур (NMIBC).
Методи. Во оваа студија беа вклучени вкупно 72 пациенти со примарни тумори на мочниот меур класифицирани како нискоризични според EORTC критериумите. Периодот на следење изнесуваше една година. Големината на туморот примарно беше проценета со КТ урографија, додека цистоскопската евалуација се користеше како комплементарна метода кога прецизното мерење не беше возможно. Фокалноста на туморот беше проценета при дијагностичка цистоскопија и потврдена интраопе-

ративно при трансуретрална ресекција на тумор на мочниот меур (TURBT). Туморите беа класифицирани како унифокални или мултифокални. Рецидивот за време на следењето беше евидентиран како присутен или отсутен.

Резултати. Рецидив беше забележан кај 14 од 72 пациенти (19,4%) во текот на едногодишното следење. Големината на туморот не покажа статистички значајна поврзаност со рецидивот, со слични стапки на рецидив кај тумори ≤3 cm и >3 cm. Спротивно на тоа, фокалноста на туморот беше значајно поврзана со рецидивот, при што значително повисока стапка на рецидив беше забележана кај пациенти со мултифокални тумори во споредба со унифокалните.

Заклучок. Кај пациенти со нискоризичен NMIBC, големината на туморот не влијаеше значајно врз ризикот од рецидив, додека фокалноста на туморот се покажа како силен предиктор за рецидив. Овие наоди ја нагласуваат прогностичката важност на фокалноста и поддржуваат потреба од поинтензивно следење кај пациенти со мултифокални тумори на мочниот меур.

Клучни зборови: карцином на мочен меур, немускулно-инвазивен карцином на мочен меур, фокалност на тумор, големина на тумор, рецидив

Introduction

Bladder cancer (BC) remains a significant global health concern. With an estimated 614,298 new cases BC was the ninth most commonly diagnosed cancer worldwide in 2022 [1]. In the same year, bladder cancer ranked 13th in mortality worldwide, caused over 220,000 deaths, reflecting its prevalence and clinical impact [1]. Bladder cancer not only poses a substantial burden on health-care systems, but is also associated with high economic costs; for example, in the European Union the total health care expenditure related to bladder cancer was estimated at €2.9 billion in 2012 [2]. Bladder cancer is a malignancy with a significant propensity for high rates of recurrence and the potential for progression to more aggressive disease [3].

Recurrence is defined as the reappearance of bladder cancer at the same site or elsewhere in the bladder after initial treatment, even following complete resection of all visually detectable tumors [4]. Bladder cancer progression is defined as the development of muscle-invasive disease (≥T2), the occurrence of regional or distant metastases, or an increase in tumor grade to high-grade disease during follow-up [5-7].

Recurrence and progression are two pivotal phenomena in bladder cancer, profoundly influencing patient evaluation, the selection of therapeutic strategies, and prognosis. Accurate prediction of recurrence and progression is essential for optimizing clinical management, surveillance, and patient outcomes. Several models and tools have been developed to estimate individual patient risk based on clinical, pathological, and, in some cases, molecular factors.

The European Organization for Research and Treatment of Cancer (EORTC) Risk Tables are a widely used clinical tool developed to predict the risk of recurrence and progression in patients with non–muscle-invasive bladder cancer (NMIBC). They were derived from a large multicenter dataset including over 2,500 patients, integrating key tumor and patient characteristics [8]. The tables provide quantitative estimates of recurrence and progression at 1, 5, and 10 years, allowing clinicians to stratify patients into low-, intermediate-, and high-risk groups based on key variables -including tumor number, tumor size, prior recurrence rate, T stage, histological grade, and the presence of concomitant carcinoma *in situ* (CIS)-and serve as a standard reference in both clinical practice and research.

The aim of our study was to analyze the correlation between the morphological parameters of bladder tumors, particularly tumor size and number of tumors, and tumor recurrence and progression.

Materials and methods

This study comprised 72 patients with primary bladder tumors treated at the University Clinic for Urology in Skopje between January 2021 and December 2023. They were classified according to the EORTC low-risk criteria for recurrence and progression. Muscle-invasive tumors, high-grade pT1 tumors treated with intravesical Bacillus Calmette–Guérin (BCG), as well as patients with carcinoma *in situ* (CIS) were excluded from the study. The follow-up period was one year.

The mean age of patients was 65.85 years (range 41-86 years). The study population was predominantly male, comprising 59 men (81.94%) and 13 women (18.06%).

All patients underwent preoperative ultrasonography (USG) and CT urography prior to transurethral resection of bladder tumor (TURBT). Our observation was that in a considerable number of cases, USG was not performed according to standardized bladder imaging protocols. Therefore, due to the substantial number of examinations lacking valid and adequately documented findings, this method was excluded from the analysis.

Tumor size assessment was primarily based on CT urography measurements. In cases where accurate tumor size measurement was not feasible on CT urography, tumor size was determined cystoscopically as a complementary method, particularly for small or flat lesions and in situations where the tumor could not be clearly delineated due to technical limitations of CT urography.

Tumor focality was assessed during diagnostic cystoscopy and confirmed intraoperatively during TURBT. Based on cystoscopic findings, patients were classified as having unifocal or multifocal tumors. Unifocal tumors were defined as a single visible lesion, whereas multifocal tumors were defined as the presence of two or more synchronous tumors, irrespective of their exact number. Cystoscopy was considered the gold standard for the initial assessment of tumor focality.
Tumor recurrence was evaluated during the one-year follow-up period and recorded as present or absent.
Associations between tumor focality and recurrence were analyzed using the chi-square test. Due to the small number of cases in some categories, Fisher's exact test was additionally applied. A p value <0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software.

Results

During the one-year follow-up period, tumor recurrence was documented in 14 of 72 patients (19.4%) and was significantly associated with tumor focality (*chi-square test* p=0.0066, *Fisher's exact test* p=0.016).

Table 1. Relationship Between Tumor Size and Recurrence During Follow-up

Tumor size	No recurrence	Recurrence	Total	p value
≤3 cm	22	5	27	
>3 cm	37	9	46	0.92

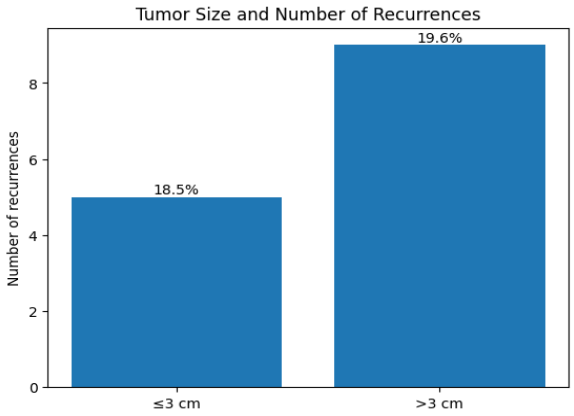

Fig. 1. Tumor size and number of recurrences ne ja gledam vo tekstot
Bar chart illustrating the absolute number of recurrences according to tumor size; percentages indicate recurrence rates within each size category.

Analysis of tumor size demonstrated similar recurrence rates between the two size categories, as shown in Table 1 and illustrated in Figure 1. Recurrence occurred in 5 of 27 patients (18.5%) with tumors ≤3 cm and in 9 of 46 patients (19.6%) with tumors >3 cm. No statistically significant association was observed between tumor size and recurrence (chi-square test, p=0.92). As shown in Table 2 and illustrated in Figure 2, recurrence rates were substantially higher in patients with multifocal tumors (40.0%) compared to those with unifocal tumors (11.5%). The association between tumor focality and recurrence was statistically significant (chi-square test, p=0.0066; Fisher's exact test, p=0.016).

Table 2. Relationship Between Tumor Focality and Recurrence During Follow-up

Tumor focality	No recurrence	Recurrence	Total	p value
Unifocal	46	6	52	
Multifocal	12	8	20	
Total	58	14	72	0.0066*

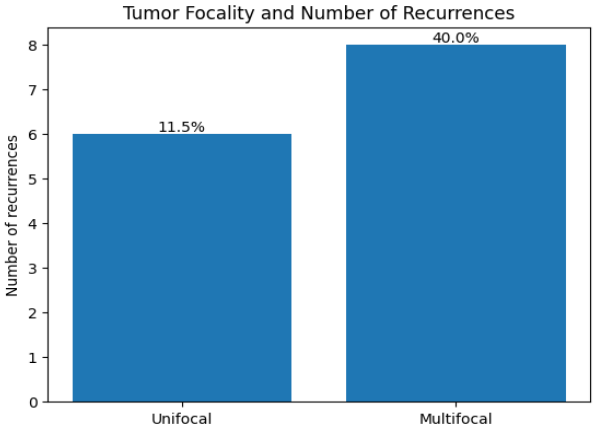

Fig. 1. Tumor Focality and Number of Recurrences
Bar chart showing the absolute number of recurrences by tumor focality; percentages indicate recurrence rates within each group.

Discussion

Tumor recurrence was observed in 19.4% of analyzed patients during the one-year follow-up period, which is consistent with previously reported recurrence rates in patients with low-risk non-muscle-invasive bladder cancer (NMIBC). Despite favorable pathological features, recurrence remains a common event in NMIBC, underlining the importance of identifying reliable prognostic factors even in low-risk disease [5,8]. Tumor size did not demonstrate a significant association with recurrence in the present cohort. Patients with tumors ≤3 cm and >3 cm showed nearly identical recurrence rates (18.5% *vs*. 19.6%), and statistical analysis confirmed the absence of a significant correlation. Although tumor size is included as a variable in established risk stratification models such as the EORTC risk tables, its prognostic value appears to be limited in selected low-risk groups [8,9].
Similar findings have been reported in studies suggesting that tumor size alone may not independently predict early recurrence when other favorable characteristics are present [10]. In contrast, tumor focality emerged as a strong and statistically significant predictor of

recurrence. Patients with multifocal tumors exhibited a substantially higher recurrence rate compared to those with unifocal disease (40.0% *vs*. 11.5%). This finding is in line with previous reports indicating that multifocality reflects a field cancerization effect of the urothelium, predisposing patients to tumor recurrence at multiple sites within the bladder [11-13]. The consistent statistical significance observed using both chi-square and Fisher's exact tests supports the robustness of this association.

The prognostic relevance of tumor focality has been well documented and is incorporated into current clinical risk stratification systems. Multifocal tumors are associated with increased recurrence risk due to the presence of widespread urothelial alterations and the potential persistence of microscopic lesions following transurethral resection [14]. These findings emphasize the need for careful cystoscopic assessment and close surveillance in patients with multifocal tumors, even when classified as low risk according to EORTC criteria.

Several limitations of this study should be acknowledged. The relatively short one-year follow-up period may underestimate late recurrences, and the single-center design limits the generalizability of the results. Additionally, the modest sample size may reduce the power to detect weaker associations with other clinicopathological variables. Nevertheless, the standardized diagnostic approach and homogeneous patient selection strengthen the internal validity of the study.

Conclusion

In conclusion, while tumor size did not significantly influence recurrence in this low-risk NMIBC cohort, tumor focality was strongly associated with an increased risk of recurrence. These findings support the role of tumor focality as an important prognostic factor and highlight the need for intensified surveillance strategies in patients with multifocal disease.

Conflict of interests: None declared.

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MMP

Case report

GRANULOMATOSIS WITH POLYANGIITIS: SUCCESSFUL REMISSION WITH CYCLOPHOSPHAMIDE AND MONTHLY METHYLPREDNISOLONE PULSES

ГРАНУЛОМАТОЗА СО ПОЛИАНГИИТИС: УСПЕШНА РЕМИСИЈА СО ЦИКЛОФОСФАМИД И МЕСЕЧНИ ПУЛСНИ ДОЗИ НА МЕТИЛПРЕДНИЗОЛОН

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Abstract

Granulomatosis with polyangiitis (GPA) is a rare autoimmune disorder causing inflammation of small and medium blood vessels. Most often affecting the upper and lower respiratory tracts alongside the kidneys, it may affect any other organ. The formation of granulomas, with necrotizing but not caseous appearance is also a key hallmark. Lung affection is the most common presentation in these patients, occurring up to 95%. Treatment mostly involves corticosteroids with immunosuppressants, either rituximab or cyclophosphamide, many achieving remission, but relapses are often, and hence close monitoring is paramount. Lung-dominant GPA with monthly prednisolone pulse doses is not a standard therapy. Here we present a case of a patient with heavily affected lungs and proteinuria but achieved remission with cyclophosphamide and methylprednisolone pulse doses with significant reduction of C-reactive protein.

Keywords: cyclophosphamide, methylprednisolone, treatment, remission, vasculitis

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Апстракт

Грануломатоза со полиангиитис (GPA) е ретко автоимуно нарушување кое предизвикува воспаление на мали и средни крвни садови. Најчесто ги зафаќа горните и долните респираторни патишта заедно со бубрезите, но може да зафати и било кој друг орган. Формирањето на грануломи, со некротизирачки но не казеозен изглед, е исто така клучен белег. Зафатеноста на белите дробови е најчеста презентација кај овие пациенти, јавувајќи се до 95%. Третманот најчесто вклучува кортикостероиди со имуносупресиви, било Ритуксимаб или Циклофосфамид, при што многумина постигнуваат ремисија, но релапсите се чести па затоа внимателното следење е од суштинско значење. Белодробно-доминантен GPA со месечни пулсни дози на преднизолон не претставува стандарден третман. Тука претставуваме случај на пациент со силно зафатени бели дробови и протеинурија, кој постигна ремисија со циклофосфамид и пулсни дози на метилпреднизолон со значително намалување на С-реактивниот протеин.

Клучни зборови: циклофосфамид, метилпреднизолон, третман, ремисија, васкулитис

Introduction

Granulomatosis with polyangiitis primarily affects the small vessels, with necrotizing granulomas and pauci-immune vasculitis mostly affecting the lungs and kidneys [1,2]. Detection of antineutrophil cytoplasmic antibodies directed against proteinase 3 (PR3-ANCA) strongly suggests GPA [3]. Diagnosis is based on a combination of clinical features, laboratory results, and most importantly, biopsy, mainly of the kidneys unless contraindicated, in which case a different site is selected, such as lungs, nose or sinuses [4]. The gold standard of treatment includes corticosteroids and immunosuppressants, such as cyclophosphamide for more severe forms, and rituximab as an alternative or in case of relapses with the former [1,3]. Here we present the case of a patient with severe affection of the lungs treated with corticosteroids and cyclophosphamide, but monthly methylprednisolone pulse doses

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have also been introduced showing remarkable clinical improvement.

Case report

A 58-year-old male patient presented at our Clinic with symptoms of headache, weakness, dyspnea and productive cough. The symptoms had started almost a year ago during which period he also reported having lost about 8 kg of body weight. Until then, he had always been treated by his primary care physician with antibiotics and symptomatic therapy.

Table 1. Laboratory results upon admission, showing impaired kidney function, high inflammatory markers and loss of proteins

Erythrocytes	4.18 10^12/L (3.8-5.8)	Urea	8.1 mmol/L (2.5-6.4)
Hemoglobin	12.1g/dl (11-16.5)	Creatinine	140 mmol/L (62-115)
Platelets	532 10^9/L (150-390)	Albumin	30.3 g/L (34-50)
Leukocytes	14.8 10^9/L (3.5-10)	CRP	86.9 mg/L (<5)
Proteinuria	0.92g/24h (0.1-0.3)	Diuresis	2800 ml

Due to persistent headaches, a neurological examination was performed, which revealed no neurological abnormalities. A chest X-ray showed metastatic deposits of varying size and location in the right hilar and basal regions, and a non-homogeneous oval tumor formation in the right infraclavicular area, with irregular transparent zones within it (Figure 1). On auscultation, crepitations were diffusely pronounced, which led to an urgent referral to the University Clinic for Pulmonology.

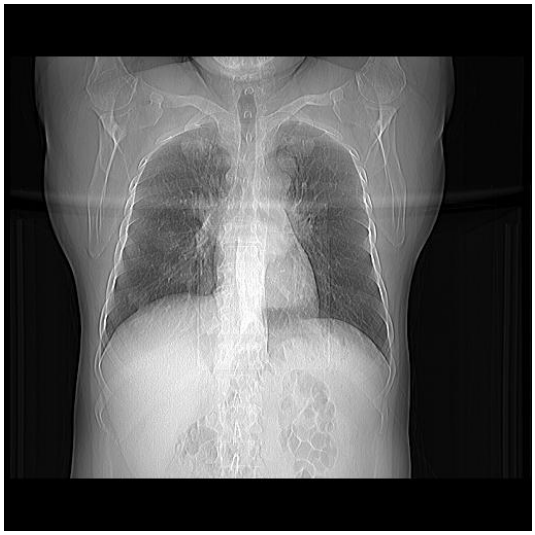


Fig. 1. Chest X-ray

Chest ultrasound bilaterally detected several small infiltrates, prompting a need for a chest CT scan. Two chest CT scans were performed in the span of 2 months which showed perihilar bronchiectatic changes and cavitary changes with thickened walls bilaterally, cavitary nodular changes with the largest measuring about 2.8 cm in diameter in the right anterobasal region. Thickened and inflamed walls of both main bronchi were noted, more pronounced on the right, with mild stenosis of the right interlobar branch. No stenosis of the trachea was observed (Figures 2, 3, 4 and 5).

Figures (2-5) Nov.2024, showing perihilar bronchiectatic changes with thickened walls bilaterally, cavitary nodular changes

Fig. 2

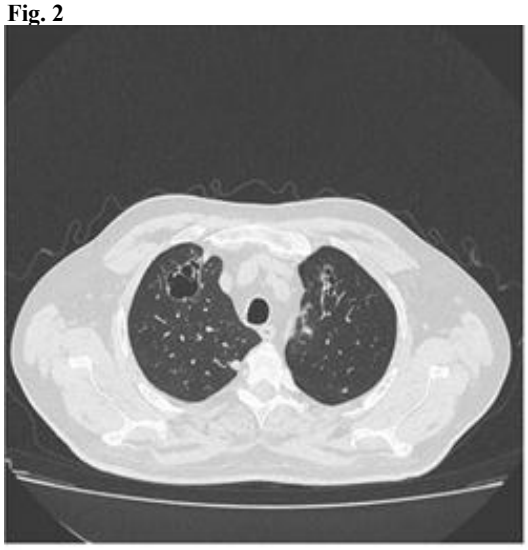
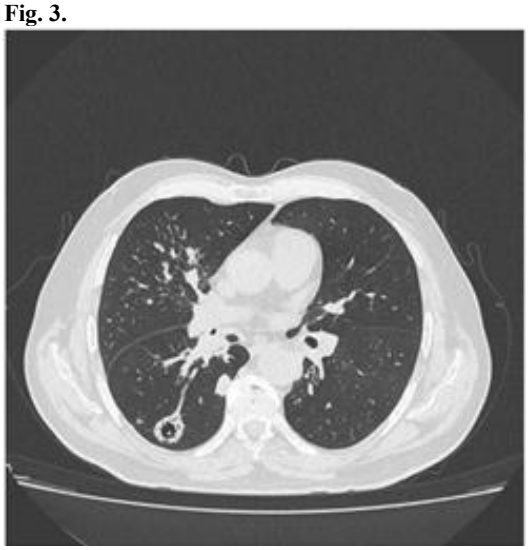


Fig. 3.



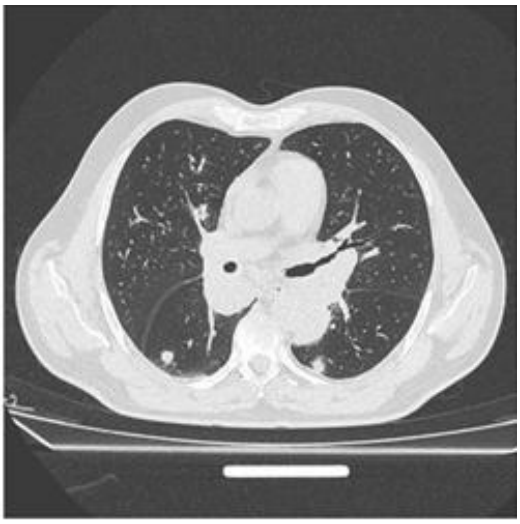


Fig. 4.

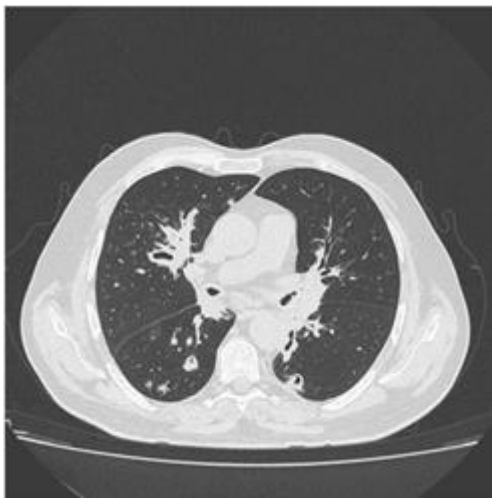


Fig. 5.

A urinary tract ultrasound showed that the kidneys were in a normal position and had a normal shape. The right kidney measured 125×56 mm, and the left kidney measured 133×67 mm, with its parenchyma being 25 mm, with a granular structure, disrupted corticomedullary differentiation, and increased echogenicity grade 2. No obstruction or stones were detected, and the urinary bladder showed no proliferative changes.

Table 2. Laboratory results after 8 months

Erythrocytes	4.1 10^12/L (3.8-5.8)	Urea	6.2 mmol/L (2.5-6.4)
Hemoglobin	11.9g/dl (11-16.5)	Creatinine	137 mmol/L (62-115)
Platelets	451 10^9/L (150-390)	Albumin	32.4 g/L (34-50)
Leukocytes	9.96 10^9/L (3.5-10)	CRP	6.1 mg/L (<5)
Proteinuria	0.19g/24h (0.1-0.3)	Diuresis	2550 ml

A rheumatology consultation was obtained, and serologic tests showed positive PR3-ANCA, further supporting the diagnosis.
With clinical symptoms, imaging and laboratory results, a kidney biopsy was performed, revealing acute leukocytoclastic vasculitis and pauci-immune complex glomerulonephritis, confirming the diagnosis of granulomatosis with polyangiitis.
Treatment with cyclophosphamide at 750 mg and methylprednisolone pulse doses at 500 mg was initiated. The patient's work tolerance improved, and his dyspnea almost completely resolved.

Discussion

The patient received 6 doses of cyclophosphamide at 750 mg monthly alongside 500 mg of methylprednisolone pulse doses. As maintenance therapy, he is placed on mycophenolate mofetil at 3 g, small doses of prednisolone, diuretics, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and given his age and high doses of corticosteroids, supplements with vitamin D and calcium were also prescribed. Induction of remission with cyclophosphamide and prednisolone with mycophenolate mofetil as maintenance is generally recommended and well tolerated [5,7]. The patient receives cyclophosphamide every three months now, but he continues to receive monthly methylprednisolone pulse doses at 500 mg. Pulse therapy has shown improvement in such cases [6], with our patient showing improvement as he continues his treatment almost a year later.

Conclusion

Granulomatosis with polyangiitis causes granulomatous inflammation in the lungs and glomerulonephritis, in this case, although the kidneys were affected, the primary concern were the lungs. Prompt initiation of therapy resulted in rapid clinical improvement. Cyclophosphamide remains a mainstay treatment, alongside corticosteroids and other immunosuppressants such as mycophenolate mofetil. Monthly methylprednisolone pulse doses are not part of the standard protocol, but in this case, they have shown good progress, suggesting potential for future considerations.

Conflict of interests: None declared.

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Case report

STERNBERG'S CANAL AS CAUSE FOR SPONTANEOUS CEREBROSPINAL FLUID RHINORRHEA – A CASE REPORT

STERNBERG КАНАЛ КАКО ПРИЧИНА ЗА СПОНТАНА РИНОРЕА – ПРИКАЗ НА СЛУЧАЈ

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Abstract

Sternberg's canal is an embryological defect where the posterior basisphenoid and lateral greater wing of the sphenoid bone fail to fuse, creating an abnormal connection between the sphenoid sinus and intracranial space, potentially leading to a meningoencephalocele in the lateral recess of the sphenoid sinus. We present the case of a 30-year-old male patient with unilateral clear nasal discharge, without a history of head trauma or cranial surgery. A computer tomography (CT) revealed a thickened wall of the left sphenoid sinus, filled with thick fluid. The constructive interference in steady state magnetic resonance imaging (CISS MRI) indicated a defect in the lateral recess of the left sphenoid sinus consistent with the presence of Sternberg's canal, and the B2 transferrin test returned positive. Given the complexity of the case, a multidisciplinary approach involving otorhinolaryngology and neurosurgery was undertaken and transnasal endoscopic duroplasty was planned. The patient had a good postoperative recovery and was discharged from the hospital after 2 weeks. Sternberg's canal is found in approximately 4% of adults presenting with spontaneous cerebrospinal fluid (CSF) rhinorrhea. We emphasize a trans-nasal trans-sphenoidal approach combined with a multi-layer closure technique, utilizing a fat plug, fascia temporalis and naso-septal flap. These methods aim to effectively seal the defect and restore integrity to the skull base. Persistent CSF leaks can be life-threatening, risking meningitis or brain abscesses. Repair of intrasphenoidal encephaloceles must prevent CSF leakage and central nervous system (CNS) infections.

Keywords: cerebrospinal fluid leak, skull base surgery, Sternberg`s canal, meningoencephalocele, trans-nasal trans-sphenoid approach

Апстракт

Стернберговиот канал е ембриолошки дефект каде што постериорниот дел од базата и латералното големо крило на сфеноидната коска не се спојуваат, создавајќи абнормална врска помеѓу сфеноидниот синус и интракранијалниот простор, што потенцијално доведува до менингоенцефалоцела во латералниот рецесус на сфеноидниот синус. Презентираме случај на 30-годишен машки пациент со едностран бистар назален исцедок, без историја за траума или кранијална операција. КТ скенирањето откри задебелен ѕид на левиот сфеноидален синус, исполнет со густа течност. CISS МРИ покажа дефект во латералниот рецесус на левиот сфеноидален синус што е во согласност со присуството на Стернберговиот канал, а тестот за трансферин Б2 даде позитивен резултат. Со оглед на сложеноста на случајот, беше преземен мултидисциплинарен пристап кој вклучува ОРЛ и неврохирургија и беше планирана трансназална ендоскопска дуропластика. Пациентот имаше добро постоперативно закрепнување и беше отпуштен од болница по 2 недели. Стернберговиот канал е присутен кај приближно 4% од возрасните кои се јавуваат со спонтана ринореја на цереброспинална течност. Нагласуваме транс-назален транс-сфеноиден пристап во комбинација со техника на повеќеслојно затворање, користејќи масен чеп, темпорална фасција и назосептален флап. Овие методи имаат за цел ефикасно да го затворат дефектот и да го вратат интегритетот на основата на черепот. Постојаните протекувања на цереброспиналната течност (CSF) можат да бидат опасни по живот, ризикувајќи менингитис или мозочни апсцеси.
Лекувањето на интрасфеноидните енцефалоцели мора да спречи протекување на CSF и инфекции на ЦНС.

Клучни зборови: истекување на цереброспинална течност, хирургија на база на черепот, Стернбергов канал, менингоенцефалоцела, трансназален трансфеноиден пристап

Introduction

The sphenoid bone develops from the ossification of several independent cartilaginous precursors: presphenoid and postsphenoid/basisphenoid centers (body of

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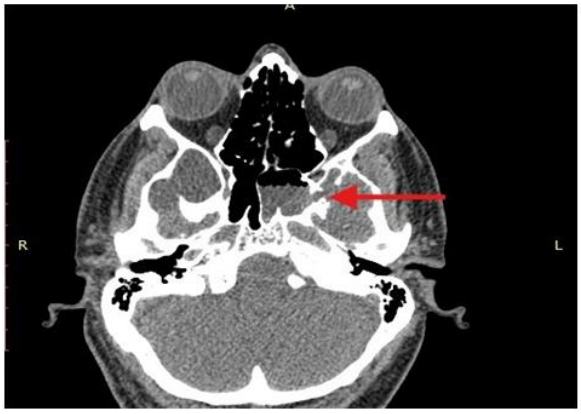
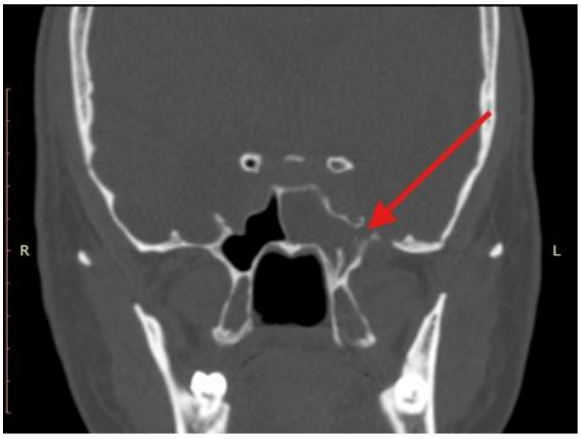
the sphenoid bone), orbitosphenoids (lesser wings), and alisphenoids (greater wings). Union of those ossified components results in formation of the sphenoid bone [1,2]. If the posterior portion of the bony fusion of the greater wings with the bone's body is incomeplete, it creates a lateral craniopharyngeal canal, which was described by Sternberg in 1888. Sternberg's canal is a congenital defect of the lateral craniopharyngeal wall with a channel coursing through and ends blindly into the sphenoid sinus. This weak defect allows the herniation of temporal lobe brain tissue into the lateral recess of sphenoid sinus. The existence of the Sternberg's canal has been reported only in 4% of adults. The most common clinical sign of this defect is spontaneous cerebrospinal fluid (CSF) rhinorrhea, a phenomenon where there is leakage of CSF through nasal cavity, in patients without previous history of trauma, surgery, tumor or radiation therapy [3,4]. Typically, it manifests as persistent, watery rhinorrhea, exacerbated by forward head flexion and occasionally associated with posterior nasal drainage. Others signs and symptoms of this entity are chronic headache, seizures and vertigo. Radiological assessment is crucial for diagnosis and targeting especially the location. Sinus CT with multiplanar reconstructions enables the identification of bony defects and pneumocephalus. At the same time, MRI remains the preferred modality due to its multiplanar capabilities and superior sensitivity in detecting CSF fistulas, encephaloceles, and arachnoidoceles, particularly on T2-weighted sequences with thin sections. The current gold standard to confirm the diagnosis of CSF rhinorrhea is Beta 2 transferrin. This test has a sensitivity of 100% and specificity of 71% [5,6].

Case report

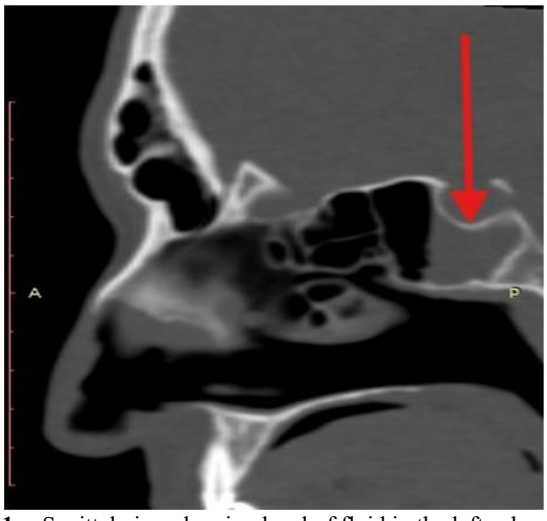
We present the case of a 43-year-old male patient, referred to our hospital from neurosurgery due to suspected nasal liquorrhea. A CT scan of the head was performed, which showed sphenoid sinus filled with content suspicious for CSF and defect of the bone. On ENT examination, the patient reported only a discharge of clear fluid from the nose without previous trauma, surgery, or radiation. However, a deviation of the nasal septum to the right was noted, with the presence of a crista and clear, translucent fluid. To define the diagnosis, the nasal contents were sent for examination and detection of B2 transferrin, and an MRI of the brain was performed with a cisternography protocol. It showed complete filling of the left sphenoid sinus with fluid content and presence of secretion level, asymmetry with slight septation from the inferolateral aspect. There was a slight nodular protrusion of the brain parenchyma on the left side at the level of the sphenoid sinus, which confirmed the existence of the defect and protrusion of meningoencephalocele in the left sphenoid sinus. A positive finding for B2 transferrin was also obtained, which proved nasal cerebrospinal fluid. These findings verified a defect in the lateral recess of the left sphenoid sinus - in the Sternberg's canal.



1.a. Axial view showing level of fluid in the left sphenoid sinus

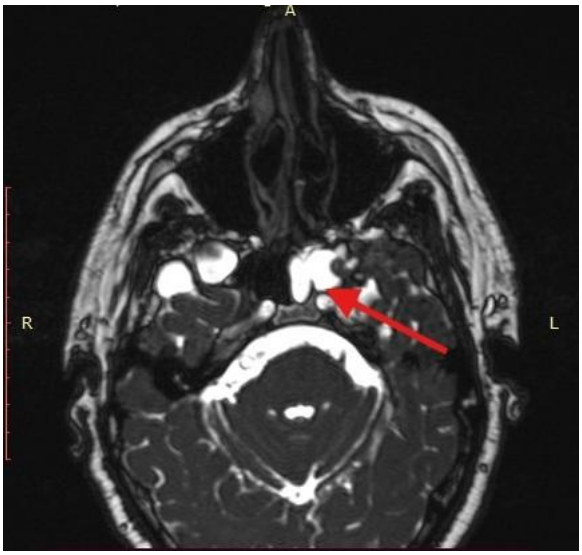


1.b. Coronal view showing the defect in the lateral recess of the left sphenoid sinus

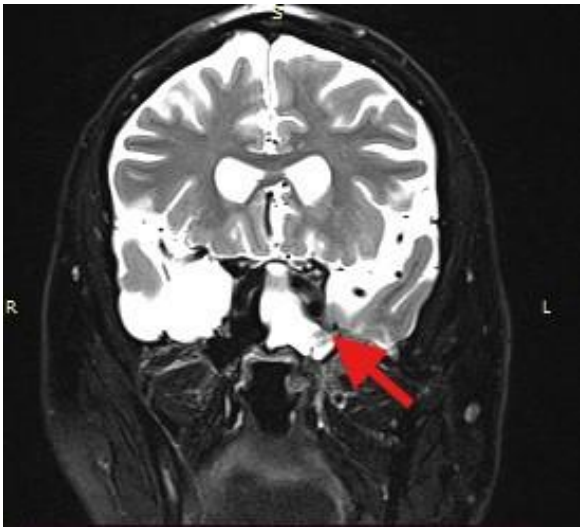


1.c. Sagittal view showing level of fluid in the left sphenoid sinus

Fig. 1. CT scans before surgery



2.a. Axial T2 view showing hyperintensity in the left sphenoid sinus



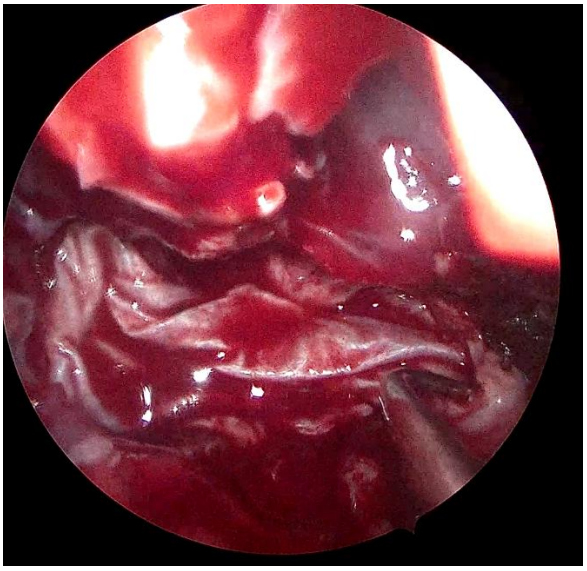
2.b. Coronal T2 view showing meningoencephalocele

Fig. 2. MRI scans before surgery

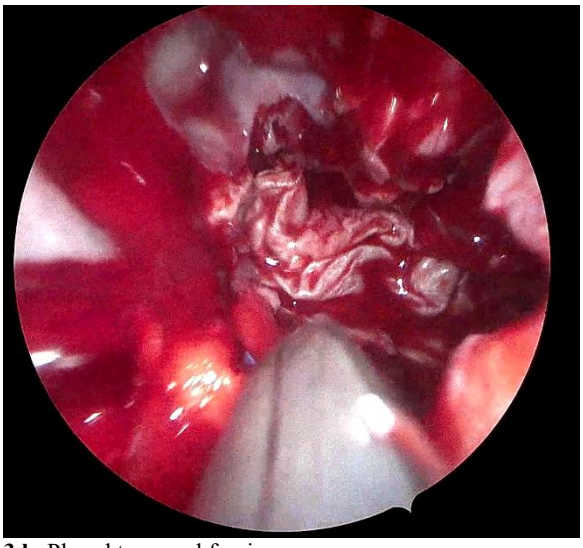
The patient was admitted and planned for surgical treatment - transnasal duroplasty.

Under general endotracheal anesthesia, paraumbilical fat and fascia from the right temporal muscle were prepared. Using endoscopic technique and navigation system, the ostium of the right sphenoid sinus was identified and a nasoseptal flap was prepared and placed in the nasopharynx.

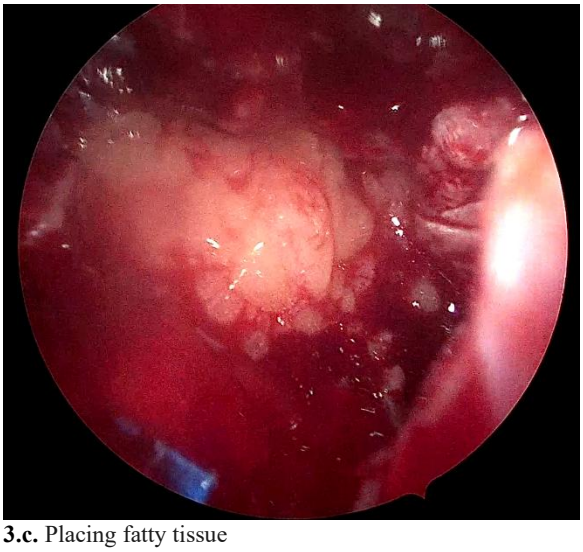
A wide antrostomy of the left maxillary sinus was made, the posterior wall of the maxillary sinus towards the pterygoid space was partially removed, *a. sphenopalatina* was identified and cauterized. Part of the greater wing of the sphenoid bone was removed. The posterior part of the septum was removed, which allowed binostrill approach. The anterior wall of the sphenoid sinus was completely removed, revealing a meningoencephalocele, in the lateral recession- Sternberg's canal. With the help of cauterization, the



3.a. *Placing temporal fascia*



3.b. Placed temporal fascia



3.c. Placing fatty tissue

Fig. 3. Intraoperative view of reconstruction

meningoencephalocele that had prolapsed into the sphenoid sinus was reduced. The bone defect was also shown, the bone irregularities of the sphenoid sinus and the posterior ethmoids were smoothed.
Then, reconstruction was approached-a overlay temporal fascia was placed, the sphenoid sinus was filled with fatty tissue; next, a nasoseptal flap was placed and the plastic was secured with a gel foam and foley catheter. Silicone catheters were placed on both sides of nose and tamponade with iodoform vaseline tampons.
The patient's postoperative course was uneventful and he was discharged home after 14 days.

Discussion

Sternberg's canal is found in approximately 4% of adults presenting with spontaneous CSF rhinorrhea. We emphasize a trans-nasal trans-sphenoidal approach combined with a multi-layer closure technique, utilizing a fat plug, fascia temporalis, and naso-septal flap. These methods aim to effectively seal the defect and restore integrity to the skull base. Endoscopic endonasal trans-sphenoid surgery (EETS) is increasingly used for sellar, suprasellar, intraventricular, retro-infundibular, and invasive tumors. Pre-operative CT and MRI scans and preoperative endoscopic visualization can provide useful anatomical information. Then, the imaging for navigation during surgery can be used. The binostril approach provides a wider working area. Most of the recent reports favor EETS in terms of safety, quality of life and tumor resection, hospital stay, better endocrinological, and visual outcome. Cerebrospinal fluid leakage (CSF) can be repaired with fibrin glue, fat, temporal fascia and vascularized nasoseptal flap. Multilayer technique, using autologous materials such as fat, temporal fascia, bone, and mucoperiosteum, is frequently used for large defects [7,8]. In recent cases, dural opening has been sutured [9]. The trans-septal approach preserves the total septum, which can be used for future reconstructions [10].

Conclusion

This case represents a rare presence of Sternberg's canal in the sphenoid sinus that caused spontaneous leakage of cerebrospinal fluid, which interfered with the normal functioning of the patient and increased the risk of brain infections, such as meningitis and brain abscesses.
CT and MRI have an important role in establishing the diagnosis, giving a detailed view of the patient's anatomy, which may vary, as well as the location of the defect. They can also be used for navigation during surgery. However, the most important thing is the repair of the defect with multilayer closure that must prevent leakage of cerebrospinal fluid and infections of the CNS.

Conflict of interests: None declared.

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Case Report

RARE CASE OF SKENE'S GLAND CYST WITH NON - INVASIVE TREATMENT DURING PREGNANCY - A CASE REPORT

РЕДОК СЛУЧАЈ НА ЦИСТА НА СКЕНЕОВА ЖЛЕЗДА СО НЕИНВАЗИВЕН ТРЕТМАН ЗА ВРЕМЕ НА БРЕМЕНОСТ – ПРИКАЗ НА СЛУЧАЈ

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Abstract

Introduction. A Skene's gland cyst is a fluid-filled sac that develops near the opening of the urethra in women, caused by a blockage of the Skene's gland duct. The cause of an adult onset is barely unknown and this condition is relatively rare in pregnancy. Non-invasive management represents a viable treatment option, and with appropriate clinical care, it can allow for successful continuation of pregnancy and vaginal delivery, thereby avoiding the need for cesarean section solely due to Skene's gland cyst.

Case presentation. We report the case of a 24-year-old primigravida, with large Skene's gland cyst SIU+++ (Stress incontinentio urinae) that was diagnosed few months before pregnancy. During the course of the pregnancy, the Skene's gland cyst ruptured spontaneously. The patient was managed conservatively with parenteral antibiotic therapy, meticulous local cleansing, and direct instillation of a topical antibiotic into the cyst capsule. This approach resulted in resolution of symptoms without further complications and the pregnancy progressed uneventfully. The patient underwent successful spontaneous vaginal delivery without further complications.

Conclusion. Large Skene's gland cysts may cause significant discomfort in pregnant patients and have the potential to impede vaginal delivery as well as delivery planning. In this case, non-invasive management achieved a favorable outcome, which was crucial in the successful continuation of pregnancy. Proper diagnosis and appropriate treatment of Skene's gland cyst should not be considered a contraindication to spontaneous vaginal delivery.

Keywords: Skene's gland cyst; pregnancy; non-invasive treatment; vaginal delivery

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Апстракт

Вовед. Цистата на Скенеовата жлезда претставува со течност исполнета формација која се развива во близина на отворот на уретрата кај жените, како резултат на опструкција на изводниот канал на Скенеовата жлезда. Причината за појава во возрасна доба најчесто е непозната, а оваа состојба е релативно ретка за време на бременост. Неинвазивниот пристап во третманот претставува одржлива терапевтска опција и со соодветна клиничка грижа, може да овозможи успешно продолжување на бременоста и вагинално породување, со што се избегнува потребата од царски рез исклучиво поради присуството на циста на Скенеовата жлезда.

Приказ на случај. Прикажуваме случај на 24-годишна примигравида со голема циста на Скенеовата жлезда и изразена стрес-инконтиненција на урина (SIU+++), дијагностицирана неколку месеци пред бременоста. Во текот на бременоста, цистата спонтано руптурираше. Пациентката беше третирана конзервативно со парентерална антибиотска терапија, темелна локална тоалета и директна инстилација на топикален антибиотик во капсулата на цистата. Овој пристап доведе до целосна резолуција на симптомите без понатамошни компликации, а бременоста продолжи уредно. Пациентката имаше успешно спонтано вагинално породување без дополнителни компликации.

Заклучок. Големата циста на Скенеовата жлезда може да предизвика значителен дискомфорт кај бремените пациентки и да има потенцијал да го отежне вагиналното породување, како и планирањето на начинот на породување. Во прикажаниот случај, неинвазивниот менаџмент резултираше со поволен исход, што беше клучно за успешно продолжување на бременоста. Соодветната дијагностика и правилниот третман на цистата на Скенеовата жлезда не треба да се сметаат за контраиндикација за спонтано вагинално породување.

Клучни зборови: циста на Скенеовата жлезда; бременост; неинвазивен третман; вагинално породување

Introduction

Skene's glands, also called paraurethral glands, of the female prostate are paired glands located in the anterior vaginal wall adjacent to the distal urethra. They are situated on the either side of the urethral meatus, usually at 4 o'clock and 8 o'clock positions. Their duct open into the urethra or just adjacent to the external urethral orifice. Embryologically, they are homologues of the male prostate, both arising from the urogenital sinus [6,7].

The Skene's glands play a secretory role; they produce a clear, mucoid secretion that contributes to vaginal lubrication. Their secretion contain prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), similar to the male prostate [6]. Secretions may also include glucose, fructose and creatinine, suggesting a role in maintaining the local urogenital environment. The Skene's glands are also involved in female ejaculation. Some evidence suggests that Skene's glands contribute to the fluid expelled during female ejaculation. PSA and fructose detected in this fluid indicate their secretory activity. Protection of the lower urinary tract with their mucous secretion may help protect against ascending urinary tract infections, acting as a barrier [6,7].

Skene's gland cysts are occasionally reported in newborns as a congenital abnormality and rarely reported in adults. The cause of Skene's gland cyst at birth is unclear, but in adults, it is speculated that obstruction of the ducts may be secondary to infection and inflammation [1,4]. Skene's gland cysts are rare at any age, and the incidence varies from 1 in 7,000 to 1 in 2,000 newborns [3,6]. Obstruction of the Skene's duct can result from: infection, inflammation or trauma, post-surgical or postpartum changes, developmental anomalies especially in neonates, rarely Skene's cyst can form congenitally due to failure of ductal canalization and idiopathic. Skene's gland cysts typically are asymptomatic and found incidentally. However, symptom cysts may include: dyspareunia, dysuria, frequent urination, recurrent urinary tract infections, palpable periurethral mass and rarely acute urinary retention [5,7]. The diagnosis of Skene's gland cyst can be made on physical examination plus imaging, especially MRI and ultrasound, to determine location and its association with adjacent organs. Because Skene's gland cysts are rare, it is crucial to distinguish them from other more common or clinically significant lesions. Differential diagnosis of Skene's gland cysts is Bartholin's gland cyst, Gartner duct cyst, urethral diverticulum, urethral caruncle, Müllerian cyst, imperforated hymen with hydrocolpos, and rarely, congenital lipoma, epithelial inclusion cysts, ureterocele, endometriosis, ectopic ureterocele, uterovaginal prolapse, and adenocarcinoma. There is no standard management of Skene's gland cyst, it depends on symptoms, cyst size and presence of infection. Skene's gland cysts require individualized management. However, there are two methods-conservative management and surgical management [1,2,6].

The aim of this case report was to present the case of a female with a large, symptomatic Skene's gland cyst during pregnancy.

Case report

The patient was a 24-year-old woman, gravida 1, para 0, with no comorbidities in her past medical history and beef allergy. Pre-pregnancy, the patient first was diagnosed with TU *cysticum vaginae suburethralis*, referred for urology consultation and cyst removal.

MRI on pelvis presented 2x3 cm Skene's gland cyst, inflamed, filled with thick content, with mild compression on posterior urethral wall. In the meantime, the patient unexpectedly conceived, and her next visit was for the first trimester screening.

After the first trimester screening, the patient remained asymptomatic until the 28th week of gestation, when she presented with dysuria, urinary frequency with involuntary leakage, and progressive enlargement of the cyst. The Skene's gland cyst was enlarged (3x4 cm), with yellowish color, soft, non-tender, with capillary vascularization. At that time, urine culture and vaginal /cervical swabs were recommended, and conservative monitoring of the cyst was continued. Initial urine analysis demonstrated bacteriuria, and the patient was managed with antibiotics and anti-edematous therapy. Although a subsequent urine culture was sterile, the patient continued to experience persistent dysuric symptoms.

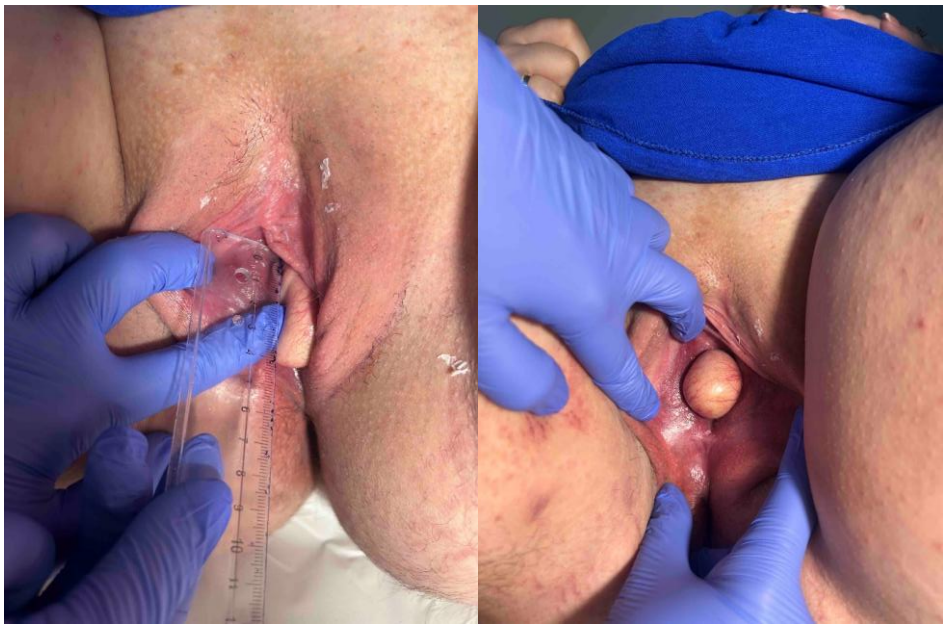

Fig. 1. Large Skene's gland cyst in relationship to other external genital structures

At her next follow-up visit, at 35+2 weeks of gestation, spontaneous rupture of the cyst was noted. The patient was hospitalized with diagnosis *graviditas* ml IX (35+2 g.w); *cystis glandula Skene's rupta*, *stress incontinentio urinae* gr II / III. Upon admission, all clinical and laboratory investigations were performed according to protocol.

Laboratory findings: Le=9.52 x 109/L, Hgb=118 g/L, HCT=0.35 %, PLT=242 x 109/L CRP-11.8, LDH-273, and urinary status was normal. An ultrasound was performed and it showed single live fetus, adequate amniotic fluid volume, placenta located on the posterior wall, cervical length 36 mm, and fetal biometry BPD=90 mm, HC-314 mm, AC=310 mm, FL=74 mm. Vaginal examination showed *portio vaginalis uteri* (PVU)-sacralized, external cervical os (OUE)-fingertip dilated, membranes intact. NST-reactive, without uterine activity.

During hospitalization, the patient received systemic antibiotic therapy (lendacin 2 gr/24 h), thromboprophylaxis, local antiseptic and local antibiotic treatment (garamycin), and meticulous local vulvar and vaginal cleansing and hygiene. Microbiological swabs from the cervix and vagina were obtained, which returned negative.

The patient was discharged in a good general condition; the symptoms of stress urinary incontinence following cyst rupture and drainage resolved spontaneously, with no progression of obstetric findings, and normal local examination. She was prescribed oral antibiotic therapy (tbl. pancef of 400 mg) for 7 days, probiotic supplementation and regular vulvar hygiene.

At her subsequent follow-up visits, both cardiotocography (CTG) and ultrasound findings were within normal ranges.

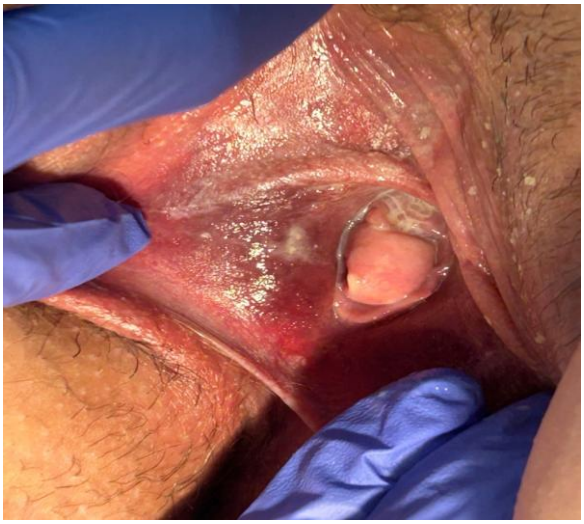

Fig. 2. Skene's gland cyst after rupture

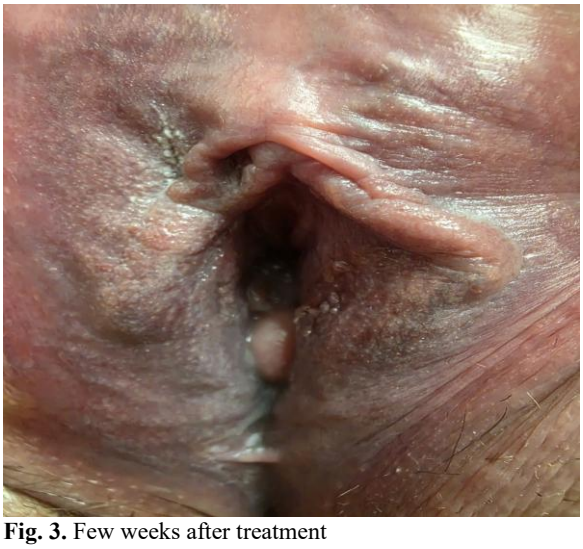

Fig. 3. Few weeks after treatment

On August 29, 2025, the patient was admitted to our clinic with diagnosis *graviditas* ml X (39+6 g.w); RVS 29.08.25/03:40h); *cystis glandula Skene rupta*; *obesitas*. Fetal growth parameters remained within normal range. At the final ultrasound, fetal biometry showed: BPD-94 mm, HC-335 mm. AC-350 mm, Fl-79 mm. Labor progressed spontaneously. A healthy female infant weighing 3800 g and measuring 52 cm was delivered with an Apgar score 8/9 at one and five minutes. A small spontaneous vaginal laceration occurred during delivery, and an episiotomy was performed. Both the laceration and the episiotomy were sutured postpartum.

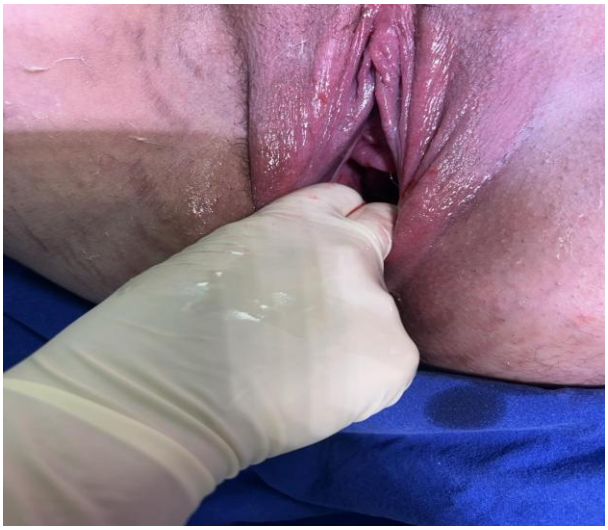

Fig. 4. During labor

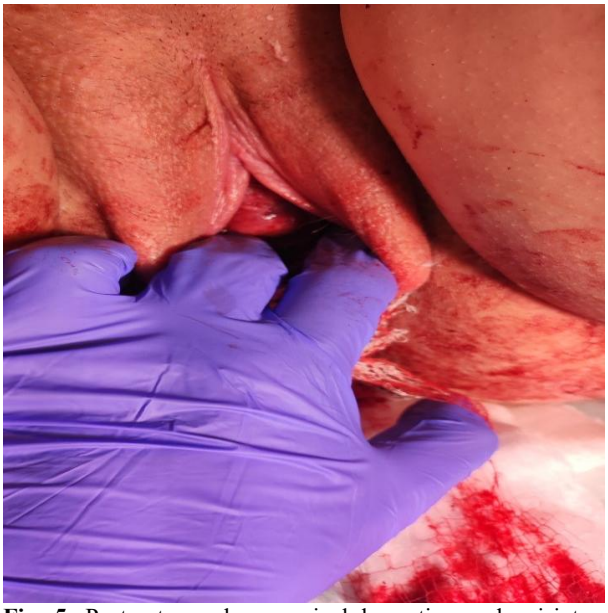

Fig. 5. Postpartum where vaginal laceration and episiotomy were performed

The postpartum period proceeded without complications, and the patient and the newborn were discharged on day 3 postpartum, both in stable condition.

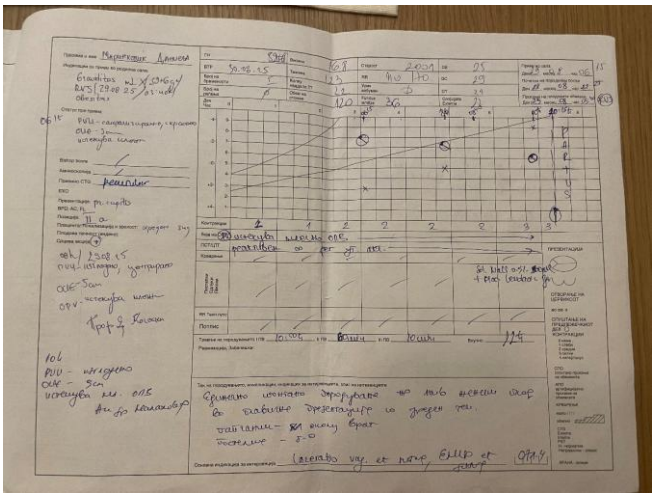

Fig. 6. The partograph of the delivery

Discussion

Skene's gland cysts are rare paraurethral lesions, and their occurrence or exacerbation during pregnancy is even less commonly reported [1,5]. These cysts can remain asymptomatic but may present with dysuria, urinary frequency, or stress urinary incontinence when enlarged or inflamed. In this case, the patient's cyst enlarged during pregnancy, causing dysuric symptoms and stress incontinence. MRI was essential in confirming the diagnosis and differentiating the cyst from urethral diverticula or other paraurethral masses [4,6]. Conservative management during pregnancy, including monitoring, pelvic hygiene, and antibiotic therapy in case of infection, is preferred due to the risks associated with surgical intervention [1,5,6]. Spontaneous rupture, as observed in this case, is uncommon but can be managed successfully with local wound care, antibiotics, and close monitoring [1,6].

A significant outcome of this case is the successful resolution of the symptoms with non-invasive, pharmacological approach, avoiding the risks of surgery during pregnancy. Furthermore, the patient delivered vaginally without complications, demonstrating that Skene's gland cysts should not be considered a contraindication to spontaneous vaginal delivery when managed appropriately [1,5].

Conclusion

Skene's gland cysts during pregnancy are rare but can lead to urinary symptoms and local complications. Conservative management with careful monitoring is safe, with definitive surgical treatment deferred until postpartum [1,5,6]. Spontaneous rupture can occur but may resolve with appropriate local and systemic therapy.

This case emphasizes that a significant therapeutic success can be achieved with a non-invasive, medical management, and that the presence of a Skene's gland

cyst should not be regarded as a contraindication to spontaneous vaginal delivery [1,5]. Early recognition, appropriate imaging and a multidisciplinary approach are key to favorable maternal and fetal outcomes.

Conflict of interests: None declared.

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MMP

Case report

WERNICKE ENCEPHALOPATHY IN YOUNG PATIENT AFTER GASTIC SLEEVE SYRGERY

ВЕРНИКОВА ЕНЦЕФАЛОПАТИЈА КАЈ МЛАДА ПАЦИЕНТКА ПО ОПЕРАЦИЈА ЗА СТЕСНУВАЊЕ ЖЕЛУДНИК

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Abstract

Introduction. Wernicke encephalopathy is an acute neurological disorder caused by thiamine deficiency and classically presents with confusion, ataxia, and ocular abnormalities. Although commonly associated with chronic alcoholism, WE is increasingly recognized in patients following bariatric surgery due to malnutrition, reduced nutrient absorption, and persistent vomiting. Early diagnosis is essential to prevent irreversible neurological damage and progression to Korsakoff syndrome.

Case presentation. We report the case of a 35-year-old woman who developed Wernicke encephalopathy two months after laparoscopic gastric sleeve surgery. The patient experienced prolonged vomiting, poor oral intake, vertigo, progressive confusion, gait instability, and bilateral horizontal nystagmus. Initial brain computed tomography was unremarkable. Magnetic resonance imaging (MRI) subsequently demonstrated symmetrical T2 and FLAIR hyperintensities within the medial thalami and periaqueductal gray matter, pathognomonic for Wernicke encephalopathy. Prompt treatment with high-dose intravenous thiamine and supportive nutritional therapy was initiated, resulting in gradual neurological improvement, although mild residual memory impairment persisted at discharge.

Discussion. Wernicke encephalopathy is a neurologycal emergency resulting from thiamine deficiency and impaired cerebral energy metabolism. The condition remains frequently underdiagnosed because the classic triad is not always fully present. Untreated Wernicke encephalopathy can progress to irreversible neurologycal damage, including Korsakoff syndrome. Early administration of intravenous thiamine is essential to improve outcomes and prevent permanent sequelae.

Conclusion. Wernicke encephalopathy remains a potentially fatal yet reversible condition when recognized early. Clinicians should maintain a high suspicion in any patient that had gone bariatric surgery and presents with vomiting, especially if it is associated with neurological symptoms. Increased awareness and early intervention are essential to reducing the morbidity associated with this underrecognized neurological disorder.

Keywords: Wernicke encephalopathy, vitamin B1, thiamine deficiency, gastric sleeve surgery, MRI

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Апстракт

Вовед. Верникеовата енцефалопатија (ВЕ) е акутно невролошко нарушување предизвикано од дефицит на тиамин, со класичен тријас од конфузија, атаксија и окуларни абнормалности. Иако најчесто се поврзува со хроничен алкохолизам, ВЕ сè почесто се јавува по баријатрична хирургија поради малнутриција, намалена апсорпција и перзистентно повраќање. Раната дијагноза е клучна за спречување на Корсаков синдром.

Приказ на случај. Прикажуваме случај на 35-годишна жена која развила ВЕ два месеци по гастректомија. По долготрајно повраќање и слаб орален внес, пациентката развила вертиго, прогресивна конфузија, нестабилно одење и билатерален хоризонтален нистагмус. Мозочниот CT скен бил уреден, но магнетната резонанца (MRI) покажала симетрични T2/FLAIR хиперинтензитети во медијалните таламуси и периакведукталната сива маса, патогномонични за ВЕ. По итен третман со високи дози интравенски тиамин и супортивна терапија, следело невролошко подобрување со благо резидуално оштетување на меморијата при испишување.

Дискусија. Верникеовата енцефалопатија е невролошка итност каде ненавременото лекување води до иреверзибилни оштетувања. Состојбата често останува недијагностицирана бидејќи класичниот тријас не е секогаш целосно присутен, а уредниот CT скен не ја исклучува болеста. Раната администрација на тиамин е од суштинско значење за позитивен исход.

Заклучок. Верникеовата енцефалопатија е потенцијално фатална, но реверзибилна состојба. Клиничарите мора да имаат висок степен на сомнеж кај

пациенти со баријатрична хирургија и перзистентно повраќање, особено ако е придружено со невролошки симптоми. Поголема свесност и брза интервенција се клучни за намалување на морбидитетот.

Клучни зборови: Верникова енцефалопатија, Витамин Б1, недостаток на тиамин, операција за стеснување на желудник, магнетна резонанца.

Introduction

Wernicke encephalopathy (WE) is a relatively rare but potentially life-threatening neurological disorder caused by a deficiency of vitamin B1 (thiamine). Thiamine plays an essential role in cerebral energy metabolism, and its deficiency leads to brain lesions primarily in regions such as the mammillary bodies, thalamus, and brainstem. The classic clinical triad includes ataxia, ocular motor dysfunction (ophthalmoplegia or nystagmus), and cognitive impairment, particularly memory loss and confusion [1].

Despite the well-defined clinical features, Wernicke encephalopathy often remains an underrecognized condition. The estimated prevalence in the general population varies between 0.4% and 2.6%, but autopsy studies suggest that up to 80% of cases remain undiagnosed during patients' lifetime [2]. This substantial underdiagnosis contributes significantly to morbidity and mortality, as timely treatment with thiamine can lead to substantial recovery, whereas delays may result in irreversible brain damage or progression to Korsakoff syndrome-a chronic neuropsychiatric condition characterized by severe memory impairment [3].

Wernicke encephalopathy is most commonly associated with chronic alcoholism due to the effects of ethanol on thiamine absorption and metabolism. However, non-alcoholic cases are increasingly recognized in a variety of clinical settings, including malnutrition, hyperemesis gravidarum, malignancies, hemodialysis, and conditions of prolonged vomiting or poor nutriational intake [4-6]. One particularly important and growing context for Wernicke encephalopathy is in patients who have undergone bariatric surgery, such as laparoscopic gastric sleeve surgery. Postoperative dietary restrictions, vomiting, and reduced nutrient absorption can precipitate thiamine deficiency in these patients, posing a risk for development of Wernicke encephalopathy [7,8].

Case Presentation

A 35-year-old female was admitted to our clinic approximately four days after the initial onset of neurological symptoms. Her medical history was significant for laparoscopic gastric sleeve surgery performed two months prior as a treatment for morbid obesity. Postoperatively, the patient experienced difficulty tolerating solid food and had frequent episodes of vomiting, which significantly reduced her oral intake and contributed to a state of poor nutrition.

Initially, the vomiting was sporadic and somewhat manageable but later became more recurrent and accompanied by severe vertigo. The patient was treated with intravenous fluids and antiemetic medication, which temporarily improved her symptoms. However, over the subsequent days, her condition deteriorated with the emergence of neurological deficits.

Concerned about the possibility of an acute intracranial event, an immediate computed tomography (CT) scan of the brain was performed, which showed no evidence of hemorrhage, infarct, or other acute pathology.

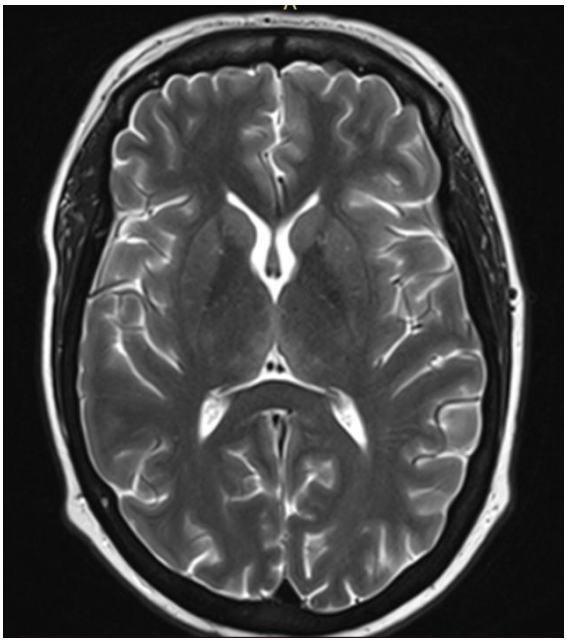

Fig. 1. MRI T2 with bilateral thalamic lesions

Given the progressive neurological signs and her recent history of gastric surgery with nutritional compromise, the patient was transferred to our tertiary care facility for further evaluation. On examination, the patient demonstrated marked confusion and disorientation. She was unable to stand independently due to worsening ataxia and exhibited bilateral horizontal nystagmus. Detailed neurological assessment revealed persistent disorientation, memory loss, and ophthalmologic findings consistent with ophthalmoplegia. An urgent magnetic resonance imaging (MRI) scan was performed, which demonstrated lesions characteristic of classic Wernicke encephalopathy, particularly symmetrical hyperintensities in the medial thalami and periaqueducl gray mater on T2-weighted and FLAIR sequences.

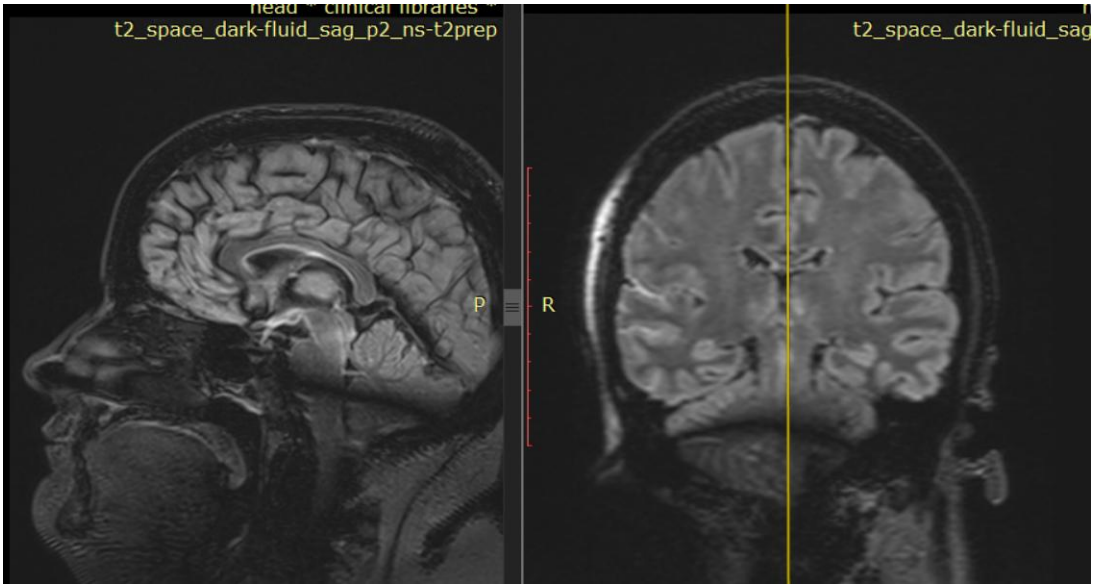

Fig. 2. FLAIR showing periaqueductal

Upon establishing a presumptive clinical and radiological diagnosis of Wernicke encephalopathy, prompt treatment with intravenous thiamine was initiated (300 mg daily for the first three days, transitioned to 200 mg daily for the subsequent three days, followed by 100 mg daily for 10 days until discharge). Supportive care, including hydration and nutritional supplementation, was also provided. Over the following weeks, the patient showed gradual improvement in cognitive functions and motor coordination, although some residual mild memory impairment persisted at the time of discharge [9-11].

Discussion

Wernicke encephalopathy is an acute neuropsychiatric emergency primarily caused by thiamine deficiency, which disrupts key enzymatic processes in brain metabolism. The condition can present with varying symptoms, but the classic triad of ataxia, encephalopathy (confusion, memory loss), and ophthalmoplegia remains a hallmark of diagnosis. Early recognition and intervention are critical to prevent irreversible neurological damage.

This case underscores the significant risk of developping WE in patients following bariatric surgery, particularly laparoscopic gastric sleeve procedures. Such surgeries are increasingly common worldwide due to the rising prevalence of obesity and represent effective interventions for weight loss and metabolic improvements. However, the resulting alterations in gastrointestinal anatomy can severely compromise nutrient absorption, leading to deficiencies in essential vitamins and minerals, including thiamine.

Vomiting is a common postoperative complication that further exacerbates nutritional deficiencies by reducing oral intake and causing losses of nutrients. Prolonged vomiting, as observed in this patient, is particularly concerning and should raise suspicion for potential thiamine depletion. Many case reports and series have documented WE and other micronutrient deficiencies developing in the weeks to months following bariatric surgery.

The diagnosis of WE remains clinical, supported by neuroimaging findings but often challenging due to variability in presentation and lack of specific laboratory tests. In this case, MRI was instrumental in confirming the diagnosis, showing typical lesions in the thalami and brainstem regions. However, absence of findings on CT scan should not exclude the diagnosis, emphasizing the importance of clinical judgment in initiating empiric thiamine treatment.

Treatment with high-dose parenteral thiamine is the mainstay of therapy and should be started promptly once Wernicke encephalopathy is suspected. Delays can result in permanent neurological sequelae, including Korsakoff syndrome, which is characterized by profound and irreversible memory deficits and confabulation.

Our case serves as a reminder for clinicians to maintain a high index of suspicion for Wernicke encephalopathy in any patient with risk factors for malnutrition and neurologic symptoms, especially those with recent bariatric surgery. Routine monitoring of nutritional status and thiamine levels after surgery may aid early detection, and prophylactic thiamine supplementation should be considered in high-risk individuals.

Conclusion

We emphasize the critical need for awareness among healthcare professionals regarding the risk of Wernicke encephalopathy following gastric sleeve surgery. Persistent vomiting, particularly when coupled with neuro-

logical symptoms such as confusion, ataxia, or ocular abnormalities, must prompt immediate evaluation for potential malnutrition and thiamine deficiency.

Early intervention with intravenous thiamine can prevent irreversible brain damage and significantly reduce the risk of progression to Korsakoff syndrome. Regular monitoring, nutritional support, and patient education about the signs of deficiency are essential in postoperative care.

In summary, Wernicke encephalopathy is a preventable and treatable condition if identified early. Clinicians managing post-bariatric surgery patients should maintain vigilance for symptoms suggestive of thiamine deficiency and act swiftly to initiate treatment.

Conflict of interests: None declared.

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Case report

IMAGING ASSESSMENT OF PELVIC FOLLICULAR LYMPHOMA

ИМИЦИНГ ЕВАЛУАЦИЈА НА ПЕЛВИЧЕН ФОЛИКУЛАРЕН ЛИМФОМ

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Abstract

Introduction. Follicular lymphoma is an indolent subtype of non-Hodgkin lymphoma that commonly presents with generalized lymphadenopathy and, less frequently, with atypical extranodal or pelvic involvement. Clinical presentation may mimic primary gynecologic disease, making imaging essential for accurate characterization and staging. This case emphasizes the diagnostic value of CT and MRI in evaluating a pelvic mass with associated lymph node enlargement.

Case Presentation. A 50-year-old woman presented with abdominal pain and progressive left lower limb edema. Initial ultrasonography demonstrated an enlarged uterus with multiple myomas and a heterogeneous vascular pelvic lesion. Contrast-enhanced CT revealed an enlarged uterus measuring 86×80 mm with altered morphology and heterogeneous enhancement, accompanied by paraaortic, paracaval, iliac, and left inguinal lymphadenopathy up to 35×30 mm. MRI confirmed diffuse uterine myomatosis and multiple enlarged lymph nodes in the left ovarian fossa and inguinal region with marked diffusion restriction. A diagnostic uterine curettage was additionally performed in order to exclude a primary gynecologic malignancy. CT-guided core biopsy of the left inguinal lymph node was performed, followed by surgical excision, and histopathological analysis confirmed follicular lymphoma.

Discussion. The imaging findings represented a diagnostic challenge, as the pelvic mass initially suggested primary gynecologic pathology. CT and MRI were crucial in demonstrating extensive nodal disease and imaging characteristics suggestive of lymphoproliferative disorder. Although initial core biopsy indicated reactive changes, surgical excision was required for definitive diagnosis, highlighting limitations of needle biopsy in certain cases. The widespread distribution of lymphadenopathy supported a systemic hematologic disease rather than isolated pelvic pathology.

Conclusion

This case highlights the importance of multimodality imaging in patients presenting with pelvic masses and atypical features. CT and MRI findings of diffuse lymphadenopathy and diffusion restriction should raise suspicion for lymphoma. Histopathological confirmation remains essential for final diagnosis, particularly when initial biopsy results are inconclusive.

Keywords: follicular lymphoma, pelvic mass, lymphadenopathy, multimodality imaging, non-Hodgkin lymphoma

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Апстракт

Вовед. Фоликуларниот лимфом претставува бавно прогредирачки подтип на нон-Хочкин лимфом, кој најчесто се презентира со генерализирано зголемување на лимфните јазли, додека екстранодалната и пелвичната манифестација се релативно ретки. Клиничката презентација може да имитира примарна гинеколошка патологија, поради што имиџинг дијагностиката има клучна улога во точната карактеризација и проценка во распространетоста на болеста. Овој случај ја нагласува значајната улога на компјутеризирана томографија и магнетна резонанца во евалуацијата на пелвична маса придружена со лимфаденопатија.

Приказ на случај. Пациентка на 50-годишна возраст е упатена на клиничка евалуација поради абдоминална болка и прогресивен едем на левата потколеница. При гинеколошки преглед и трансвагинален ултразвук беше детектирана волуминозно зголемена матка со повеќекратни миоматозни промени, како и хетерогена солидно-цистична пелвична лезија со изразена васкуларизација на доплер-инвестигација.

Реализирана е компјутеризирана томографија со контрастни серии на абдомен и мала карлица, при што се визуализира волуминозно зголемена матка со димензии 86×80 mm и хетерогена структура, како и лимфаденомегалија во парааорталните, па-

ракавалните, илијачните и левата ингвинална ложа. Магнетната резонанца потврди дифузна миоматоза и повеќекратно зголемени лимфни јазли со изразена рестрикција на дифузијата. Изведена е дијагностичка киретажа со цел исклучување на примарен гинеколошки малигнитет. КТ-водена core биопсија на лимфните јазли во левата ингвинална ложа покажа реактивни промени без докази за малигнитет, додека дефинитивната дијагноза беше воспоставена по хируршка ексцизија, со хистопатолошка потврда на фоликуларен лимфом.

Дискусија. Имиџинг наодите претставуваа дијагностички предизвик поради иницијална суспекција за гинеколошка неоплазма. КТ и МРИ беа клучни за детекција на генерализирана лимфаденомегалија и карактеристики сугестивни за лимфопролиферативно заболување. Ограничената дијагностичка вредност на core биопсија ја истакна потребата од хируршка ексцизија за дефинитивна дијагноза. Дистрибуцијата на промените укажуваше на системска хематолошка болест.

Заклучок. Мултимодалниот имиџинг е клучен во проценката на пелвични маси со атипична клиничка презентација. КТ со контрастни серии овозможува прецизна проценка на степенот на болеста и лимфаденопатијата, додека МРИ обезбедува супериорна ткивна карактеризација со детекција на рестрикција на дифузијата, наод што е сугестивен за лимфопролиферативен процес. Хистопатолошката анализа останува златен стандард за дефинитивна дијагноза.

Клучни зборови: Фоликуларен лимфом; пелвична маса; лимфаденомегалија; мултимодален имиџинг; нон-Хочкин лимфом

Introduction

Follicular lymphoma is an indolent B-cell non-Hodgkin lymphoma characterized by slow progression and a tendency for widespread nodal involvement. Although it most commonly presents with generalized lymphadenopathy, extranodal and atypical pelvic manifesttations may occur and can closely mimic primary gynecologic pathology. This overlap often leads to diagnostic uncertainty, particularly when a pelvic mass is the dominant clinical finding. Cross-sectional imaging, especially CT and MRI, plays a central role in identifying disease distribution, characterizing tissue morphology, and guiding further diagnostic procedures. This case highlights the importance of multimodality imaging in the evaluation of a complex pelvic mass associated with extensive lymphadenopathy [1,2].

Case Presentation

A 50-year-old female patient presented with abdominal pain and progressive swelling of the left lower limb. Initial pelvic ultrasonography revealed an enlarged uterus with multiple myomatous nodules and a heterogeneous vascular pelvic lesion, raising suspicion for a primary pelvic malignancy.

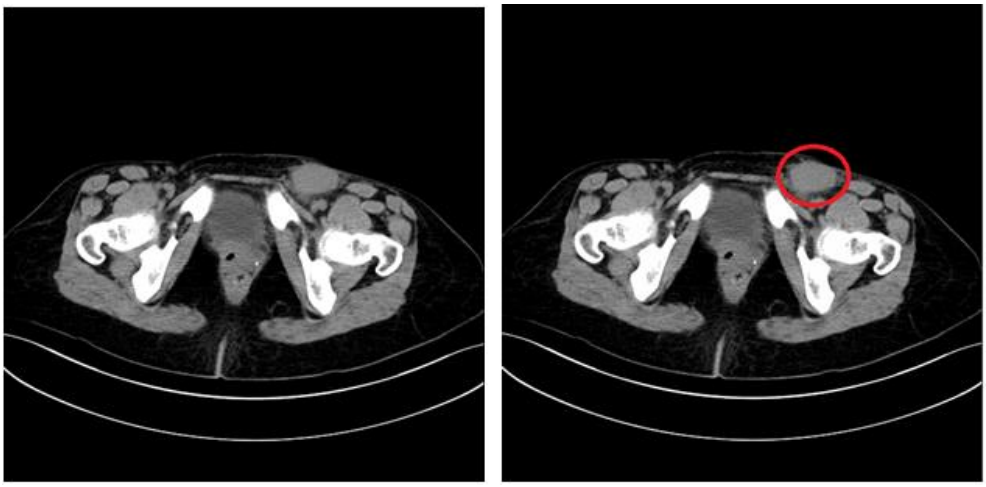

Fig. 1. Axial computed tomography (CT) scans demonstrate enlarged lymph nodes with altered morphology in the left inguinal region

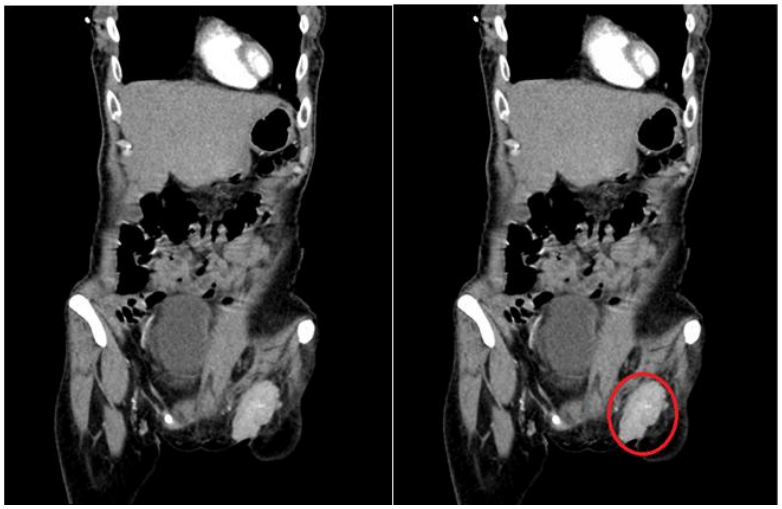

Fig. 2. Coronal computed tomography (CT) scans demonstrate enlarged lymph nodes with altered morphology in the left inguinal region

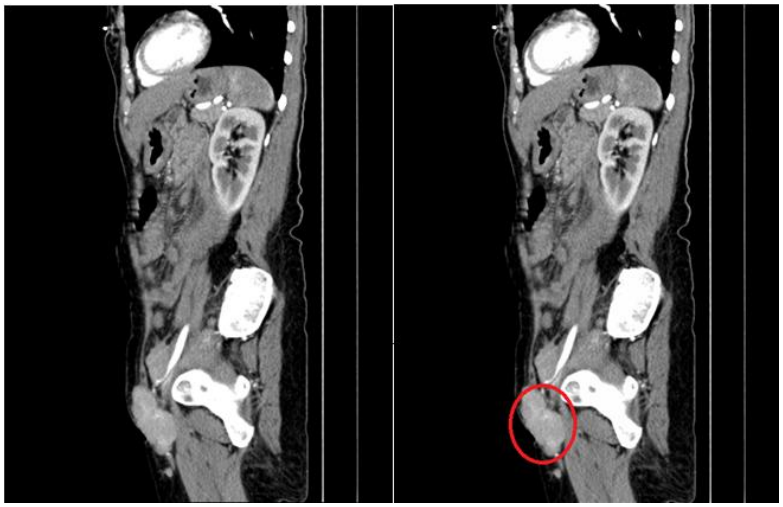

Fig. 3. Sagittal computed tomography (CT) scans demonstrate enlarged lymph nodes with altered morphology in the left inguinal region

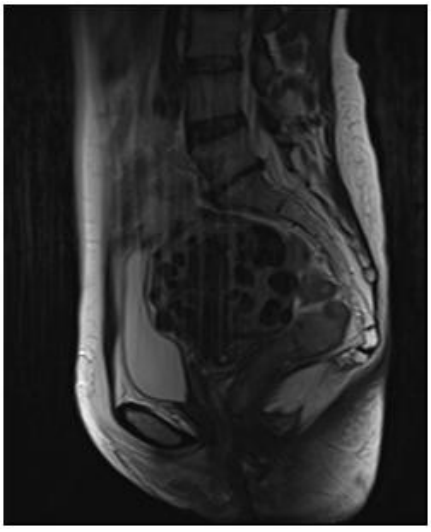

Fig. 4. Sagittal T2-weighted MRI sequence of the pelvis demonstrating an enlarged myomatous uterus with multiple intramural and subserosal leiomyomas

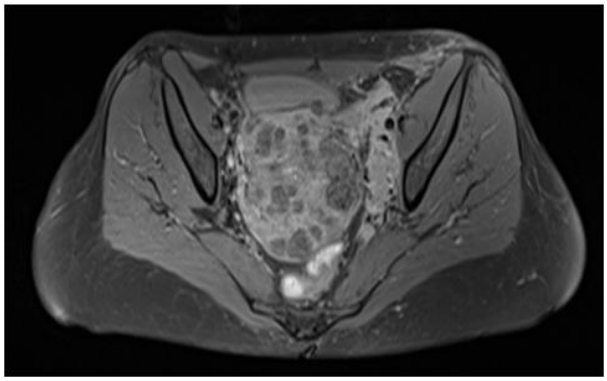

Fig. 5. Axial diffusion-weighted imaging (DWI) MRI sequence

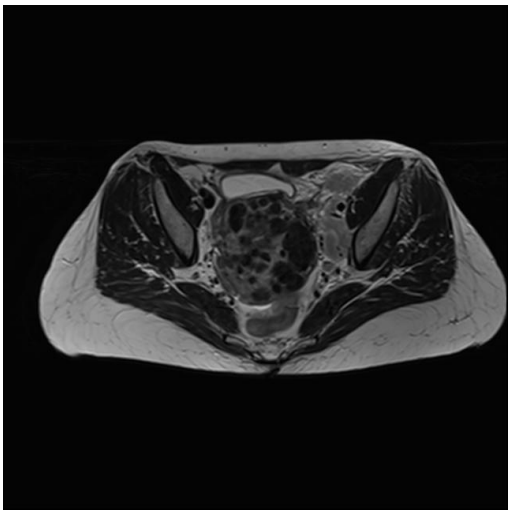

Fig. 6. Axial T2-weighted MRI sequence of the pelvis showing multiple uterine leiomyomas

Contrast-enhanced CT of the abdomen and pelvis demonstrated a significantly enlarged uterus measuring 86×80 mm with altered morphology, heterogeneous post-contrast enhancement, and poorly defined endometrial structures. In addition, extensive lymphadenopathy was identified involving paraaortic, paracaval, iliac, and left inguinal regions, with the largest nodal conglomerates measuring up to 35×30 mm. Diagnostic curettage of the uterine cavity was performed in order to exclude primary gynecologic disease [3,4].

Subsequent MRI of the pelvis confirmed diffuse uterine myomatosis and multiple enlarged lymph nodes in the left ovarian fossa and inguinal region. These lymph nodes demonstrated marked diffusion restriction, suggesting a high likelihood of lymphoproliferative disease. No definite signs of direct invasive pelvic organ infiltration were observed.

An ultrasound- and CT-guided core biopsy of the left inguinal lymph node was performed; however, due to persistent clinical and radiologic suspicion, surgical excision was subsequently undertaken. Histopathological and immunohistochemical analysis confirmed the diagnosis of follicular lymphoma [5,6].

Discussion

This case illustrates a significant diagnostic challenge, as the initial imaging findings closely resembled a primary gynecologic pelvic process. The enlarged uterus with heterogeneous enhancement and associated pelvic mass effect initially raised concern for primary uterine pathology. However, the presence of widespread lymphadenopathy across multiple anatomical regions was a key feature suggesting a systemic process rather than isolated pelvic disease.

CT provided essential information regarding disease extent and nodal distribution, while MRI contributed superior soft-tissue characterization and demonstrated diffusion restriction within affected lymph nodes, a finding commonly associated with high cellularity lesions such as lymphoma.

Although initial core needle biopsy suggested reactive lymphadenitis, this was not concordant with imaging findings. This discrepancy underscores the known limitations of small-sample biopsies in lymphoproliferative disorders, particularly in heterogeneous or partially involved nodes. Definitive diagnosis required surgical excision, which allowed adequate tissue sampling for accurate histopathological and immunophenotypic assessment.

The case emphasizes the importance of correlating imaging findings with clinical and pathological data, especially in cases with discordant biopsy results. Multisite lymphadenopathy, including paraaortic and inguinal involvement, further supported a systemic hematologic malignancy rather than localized pelvic disease.

Conclusion

This case demonstrates the critical role of CT and MRI in the evaluation of patients presenting with pelvic masses and atypical clinical features. Imaging findings such as diffuse lymphadenopathy, nodal conglomeration, and diffusion restriction should prompt consideration of lymphoproliferative disease in the differential diagnosis. While imaging is essential for detection and staging, histopathological confirmation remains mandatory for definitive diagnosis. In cases where core biopsy results are inconclusive, surgical excision should be considered to avoid diagnostic delay and ensure appropriate management.

Conflict of interests: None declared.

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MMP

Case report

COMPLETE RECOVERY FOLLOWING SURGICAL REPAIR AND PLATELET RICH PLASMA (PRP) ADJUVANT THERAPY OF A CHRONIC ACHILLES TENDON RUPTURE (CATR): A CASE REPORT

ПОТПОЛЕН ОПОРАВОК ПО ХИРУРШКИ ТРЕТМАН И АДЈУВАНТНА ТЕРАПИЈА СО ПЛАЗМА БОГАТА СО ТРОМБОЦИТИ (ПБТ) ПРИ ХРОНИЧНА РУПТУРА НА АХИЛОВА ТЕТИВА (ХРАТ): ПРИКАЗ НА СЛУЧАЈ

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Abstract

Introduction. Chronic Achilles tendon rupture (CATR) is a neglected or inadequately treated Achilles tendon rupture persisting for 4-6 weeks after injury, resulting in incomplete or abnormal healing.
Case Description. A 59-year-old man presented with persistent right ankle pain and limping 6 weeks after conservative treatment of a right Achilles tendon rupture. Examination revealed a step-like deformity over the distal posterior lower leg, inability to bear weight, stand on toes, or push off the ground, and positive Thompson's and Matles' tests, consistent with CATR. Given the patient's good general condition and moderate activity level, surgical treatment was indicated. V-Y tenoplasty with Bunnell tenorrhaphy was performed through a posterior approach. After 6 weeks of immobilization in a below-knee cast with 30° plantar flexion, physical therapy was initiated. Two months postoperatively, the patient reported mild pain, discomfort, and a 10° plantar flexion deficit. He subsequently received three ultrasound-guided peritendinous platelet-rich plasma (PRP) injections followed by an additional rehabilitation cycle. Two months later, he was pain-free, with full right ankle joint range of motion and complete triceps surae muscle strength.
Discussion. CATR commonly results from delayed or inadequate initial treatment, leading to tendon retraction, muscle atrophy, and impaired push-off strength. V-Y tenoplasty with Bunnell tenorrhaphy restores tendon length and provides biomechanical stability to support healing. Residual postoperative pain and limited plantar flexion prompted adjuvant PRP therapy to enhance tendon recovery. Combined rehabilitation and biologic augmentation resulted in pain relief, restored ankle joint range of motion, and full triceps surae muscle strength.
Conclusion. Most CATRs require surgical management, while non-operative treatment is reserved for patients with poor prognostic profiles. PRP may reduce pain and support functional tendon regeneration. This case highlights the importance of timely diagnosis, appropriate surgical technique selection, and the potential benefit of biologic augmentation combined with rehabilitation in optimizing functional outcomes.

Keywords: chronic Achilles tendon rupture (CATR), V-Y tenoplasty, Bunnell tenorrhaphy, platelet rich plasma (PRP), rehabilitation

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Апстракт

Вовед. Хроничната руптура на Ахиловата тетива (ХРАТ) претставува занемарена или несоодветно третирана руптура на Ахиловата тетива што опстојува 4-6 седмици по повредата, резултирајќи со нецелосно или несоодветно заздравување.
Приказ на случај. Маж 59 годишна возраст се жали на постојана болка околу десниот скочен зглоб и накривување 6 седмици по спроведен конзервативен третман поради руптура на десната Ахилова тетива. Клинички беше утврдена скалеста деформација на дисталната постериорна регија на десната потколеницата, неможност за оптоварување на ногата, стоење на прсти или оттурнување со стопалото од подлогата, како и позитивни Thompson-ов и Matles-ов тест, што оди во прилог на ХРАТ. Со оглед на добрата општа здравствена состојба и умереното ниво на физичка активност, беше индициран хируршки третман. Со постериорен пристап, се направи „V-Y" тенопластика и „Bunnell" тенорафија. По 6 седмици имобилизација со потколена гипсена чизма со десното стопало поставено во 30° плантарна флексија, беше започната физикална терапија. Два месеци пост-оперативно, пациентот се жалеше на минорна болка, дискомфор и

заостанување на 10° плантарна флексија. Три дози плазма богата со тромбоцити (ПБТ) беа аплицирани перитендинозно под водство на ултразвук, а потоа следуваше дополнителен циклус на рехабилитација. Два месеци подоцна, пациентот беше без болка, со целосен опсег на движење во десниот скочен зглоб и комплетна мускулна сила на triceps surae.

Дискусија. ХРАТ најчесто настанува како резултат на одложен или несоодветен иницијален третман, што доведува до ретракција на тетивата, мускулна атрофија и нарушена сила за плантарна флексија. „V-Y“ тенопластиката со „Bunnell“ тенорафија овозможува реставрација на должината на тетивата и биомеханичка стабилност што го поддржува заздравувањето. Резидуалната пост-оперативна болка и ограничената плантарна флексија беа индикација за адјувантна ПБТ терапија со цел подобрување на тетивното заздравување. Комбинираната рехабилитација и биолошка терапија резултираа со отстранување на болката, враќање на потполен опсег на движење во десниот скочен зглоб и целосна мускулна сила на triceps surae.

Заклучок. Повеќето ХРАТ бараат хируршки третман, додека конзервативно се лекуваат пациенти со неповолен прогностички профил. ПБТ може да придонесе за намалување на болката и поттикнување на функционална регенерација на тетивата. Овој случај ја нагласува важноста на навремената дијагноза, соодветниот избор на хируршка техника и потенцијалната корист од биолошка терапија комбинирана со рехабилитација за оптимизирање на функционалниот исход.

Клучни зборови: Хронична руптура на Ахилова тетива (ХРАТ), V-Y тенопластика, Bunnell тенорафија, плазма богата со тромбоцити (ПБТ), рехабилитација

Introduction

Chronic Achilles tendon rupture (CATR) depicts a complex and often underestimated sequela of acute Achilles tendon injury, characterized by delayed diagnosis or inadequate initial treatment leading to persistent functional impairment. Typically defined as a rupture neglected or untreated for more than 4-6 weeks, CATR results in retraction of tendon ends, scar tissue interposition, and muscle atrophy, which collectively compromise tendon continuity and biomechanical strength [1-9]. Epidemiological studies indicate that the incidence of Achilles tendon ruptures has risen steadily over recent decades, largely due to increased participation in recreational sports among middle-aged adults. Among these, up to 25% of cases may evolve into chronic ruptures when the initial injury is missed or mismanaged [2].

Patients with CATR usually present with visible and palpable gap along the tendon course, altered gait, reduced push-off power, and weakened plantar flexion. There are two most commonly used clinical tests that help in diagnosing a suspected Achilles tendon rupture. The first one is known as Thompson or Simmonds' test. The patient is positioned prone on the examination table; the examiner squeezes the calf muscles on the suspected side, and an absence of plantar flexion of the same side of the foot indicates a positive test [9]. The other test is known as Matles test. The patient is, again, positioned prone on the exam table, both knees are flexed to 90 degrees and if the foot on the suspected side falls to its neutral position, i.e. dorsiflexion, then the test is positive [10]. Imaging modalities such as ultrasonography and magnetic resonance imaging aid in characterizing the size of the tendon defect, the quality of the remaining tissue, and guiding surgical planning [2]. Contemporary management emphasizes surgical reconstruction, as non-operative treatment rarely restores satisfactory function in chronic cases. Various reconstructive techniques-including V-Y tenoplasty, fascial turndown flaps, tendon transfers (notably from the flexor hallucis longus), and allograft or synthetic augmentation - have been proposed, with the choice depending on gap length, tissue quality, and patient-specific functional demands [1,11,12].

Despite advances in surgical strategies and postoperative rehabilitation protocols, there are still no universal guidelines regarding the optimal approach. Recent literature highlights the importance of individualized treatment algorithms that integrate defect size assessment, biological augmentation, and early functional rehabilitation to optimize outcomes. Nevertheless, long-term studies suggest that even after successful repair, residual calf weakness and reduced endurance are common, underscoring the need for ongoing refinement of both surgical and rehabilitation protocols [1, 11].

Case report

A 59-year-old male patient presents with persistent pain around the right ankle and limping. 6 weeks prior, he suffered from rupture of the right Achilles tendon which was treated conservatively. The patient has a visible step-like deformity on the dorsal distal third of the lower right leg, is unable to bear weight on his right leg nor stand on his toes or push-off the ground, with positive Thompson and Matles tests. A clinical diagnosis of CATR was made. A decision for surgical treatment of the ruptured tendon was based upon the patient's good condition and moderate physical activity level. The patient received preoperative right popliteal sciatic nerve block and was positioned prone on the operating table. The operating field was prepared and draped in sterile fashion. Using the posterior app-

roach, an Achilles tendon defect of approximately 4 cm was observed i.e. Myerson type II (2) CATR. The surrounding superficial fascial and paratenon layer were carefully preserved to achieve optimal wound closure while tendon debridement was performed. The V-Y tenoplasty technique was performed, designing a V-shaped part in the gastrocnemius aponeurosis. Then, the V-shaped part was slowly torn and pulled towards the distal stumps with caution until the gap was bridged. A 1/0 non-absorbable suture was used to repair the V and the distal stumps together with the Bunnell technique. A 2/0 absorbable suture was used to suture the proximal incision in a Y configuration. After reconstruction of the Achilles tendon rupture, the paratenon layer was sutured with 2/0 absorbable sutures, then the skin was closed with 2/0 non-absorbable sutures using the vertical mattress technique. The patient was immobilized for 6 weeks in a below-knee cast with the foot in 30° plantar flexion. After removing the cast, the patient was advised to start physical therapy. 2 months after the surgery, the patient had slight pain and discomfort, improved range of motion in the right ankle joint lacking 10° of plantar flexion. A mutual decision for platelet rich plasma (PRP) adjuvant therapy was agreed upon. In the following three weeks, the patient received three peritendinous PRP injections under ultrasonographic guidance and went through another cycle of physical therapy. 2 months after the PRP treatment and physical therapy, the patient was pain free, had full range of motion in the right ankle joint and complete triceps surae muscle force.

Discussion

CATR represents a challenging condition in orthopedic practice, often resulting from delayed diagnosis or failed conservative treatment of an acute rupture [1-9]. In the present case, a 59-year-old male developed persistent pain, weakness, and gait disturbance following conservative management of an acute Achilles tendon rupture, leading to a diagnosis of CATR six weeks post-injury. This timeline aligns with the literature defining chronic rupture as one diagnosed more than 4 to 6 weeks after the initial injury, during which tendon ends retract and fibrous tissue interposes, thereby compromising healing potential [1-9].

The patient's clinical findings-step-like deformity, inability to perform single-leg heel raise, positive Thompson and Matles tests were consistent with a chronic rupture presentation [2,9-12]. These signs, coupled with functional impairment, necessitated surgical intervention, given that conservative management in chronic cases often fails to restore strength and function, particularly in active or middle-aged individuals [1,11,12].

The size of the Achilles tendon defect is a crucial factor which dictates the surgical reconstruction approach. In 1999, Myerson described a scheme (Table 1) for surgical treatment of CATR based on the size of the defect [13]. In addition to the size of the defect, several other factors contribute to the treatment choice, including patient's age, activity level, comorbidities, and the condition and quality of the soft tissue envelope [1,11,12].

Table 1. Surgical treatment for CATR according to Myerson's classification system based on the size of the tendon defect [12,13].

Achilles Tendon Defect Size	Surgical Procedure
1-2 cm	End-to-end anastomosis and posterior compartment fasciotomy
2-5 cm	V-Y lengthening, augmented with tendon transfer if needed
>5 cm	Tendon transfer alone or in combination with V-Y advancement or turndown

Surgical repair remains the gold standard for CATR, with the choice of technique depending on the size of the tendon defect, tissue quality, and patient characteristics. In this case, the combination of **V–Y tenoplasty** and **Bunnell tenorrhaphy** provided both length restoration and secure end-to-end approximation, based on Myerson's classification and patient's characteristics. The V-Y tenoplasty allows advancement of the proximal gastrocnemius-soleus aponeurosis to bridge the tendon gap, while the Bunnell tenorrhaphy ensures strong longitudinal fiber alignment, promoting effective load transmission and healing [1,11,12,14].

Postoperative immobilization in plantar flexion for six weeks is commonly used to protect the repair and minimize tension across the tendon [15]. Subsequent physiotherapy focusing on gradual mobilization, strengthening, and proprioception is crucial for functional recovery [16]. The patient's initial postoperative progress-with residual pain and limited plantar flexion-was within expected parameters for the early rehabilitation phase following chronic repair.

The decision to introduce **platelet-rich plasma (PRP)** as an adjuvant treatment was clinically reasonable given the persistent discomfort and suboptimal tendon flexibility at two months post-surgery.

PRP contains high concentration of autologous growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), all of which enhance collagen synthesis, neovascularization, and tendon matrix remodeling [17,18]. Evidence in the literature regarding PRP efficacy in tendon healing is mixed; however, several studies suggest it may accelerate recovery, reduce pain, and improve tendon structure when used in conjunction with physiotherapy [19].

Following three ultrasound-guided peritendinous PRP injections and a second cycle of physical therapy, the patient demonstrated full restoration of ankle range of

motion and triceps surae muscle strength, with pain resolution. These outcomes underscore the potential benefit of PRP as a supportive adjunct in enhancing tendon healing and optimizing functional outcomes after surgical reconstruction of chronic Achilles tendon rupture.

Conclusion

Overall, this case highlights the importance of individualized management strategies in CATR, integrating surgical repair, structured rehabilitation, and biologic augmentation. Early recognition of tendon retraction and appropriate surgical planning are key to restoring normal biomechanics. Moreover, the successful incorporation of PRP therapy in this patient suggests a promising role for biologic interventions in the multidisciplinary management of chronic tendon injuries.

Conflict of interests: None declared.

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УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски Медицински Преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. Изворни трудови
2. Соопштувања за клинички и лабораториски искуства
3. Прикази на случаи
4. Од практика за практика
5. Едукативни статии
6. Вариа е (писма од редакцијата, општествена хроника, прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови. Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП. Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот(ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет. Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (mld@unet.com.mk ; info@mld.mk) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол. Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. email); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистичка обработка, пишување на трудот). Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и соопштувањата го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати,

дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: **вовед** со целта на трудот, **методот, резултати** (со нумерички податоци) и **заклучоци**. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик.

Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) listata na Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните SI единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот методи.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем. Заклучоците треба да не бидат подолги од 150 зборови.

1. **ПРИЛОЗИ** Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации). Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата материјал и методи). Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

2. **ЛИТЕРАТУРА**

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со

цртичка, на пр. [3-6]. Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):

а) статија во списание (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: и сор.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

б) заеднички автор GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) без автор - анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).

г) поглавје во книга или монографија Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

Уплата за испечатен труд во списанието ММП изнесува 3.000,00 денари и се уплаќаат на жиро сметката на:

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Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД – 3162 557.