ISSN 2545-4366
www.e-mja.finki.ukim.mk

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Vol. 5 No 3, October 2021

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaesthesia and Reanimation, Faculty of Medicine,
"Ss. Cyril and Methodius" University, Skopje, R.N. Macedonia

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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик.**

Предоперативна и Интраоперативна Аналгезија:
Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.
i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.
Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:
Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu , R Prabhavathi, 2015
Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.
Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.
На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,
На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**
Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2µg/kg, i.v. vecuronium 0.1mg/kg
Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.
Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:

Табела 1: *Споредба на средниот резултат на болка (ВАС) помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: *Споредба за потребите од tramadol помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	**8 (25.81%)**	**20 (64.52%)**	**0.002**

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

Заклучок: Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подлежни на оперативен зафат обезбедува **статистички задоволителна анелегизија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администитрира како превенција при оперативни зафати.

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i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

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- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
- **Ублажување на акутна и хронична болка**

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Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Publisher
Department of Anaesthesia and Reanimation
Faculty of Medicine
“Ss. Cyril and Methodius” University
Skopje, R.N.Macedonia

Proofreading
Daniela Nacevska Stojcevska

CONTENT

RISK OF PROSTATE CANCER IN MEN WITH BENIGN PROSTATIC HYPERPLASIA

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More than half of men aged over fifty have histologically verified prostate hyperplasia, while prostate cancer is the second in incidence and the sixth in mortality. The etiology of both conditions is still unclear, as there are many risk factors, but neither is the cause of the disease.

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) have undergone significant changes in diagnosis and treatment in the last fifty years. Revolutionary changes in the differentiation of benign from malignant alteration of the prostate occurred with the introduction of prostate-specific antigen (PSA) and sextant biopsy in the early 1980s. Since then, the most prostate cancers have been metastatic diseases without curative treatment. The discovery and use of alpha1 blockers and five alpha-reductase inhibitors significantly improved the lower urinary tract symptoms (LUTS), and thus considerably reduced the need for BPH surgery. The introduction of transurethral resection of the prostate (TURP) in the early 1980s made significant progress in the surgical treatment of BPH. Transurethral resection of the prostate reached a peak in 1987 and then decreased by 5% per year from 1999 to 2005. Despite this reduction, there was a 44% increase in total LUTS/ BPH surgical treatment, mainly caused by a 529% increase in thermotherapy or LASER treatment.

New knowledge of prostate anatomy has advanced the surgical technique for prostate cancer with the introduction of radical prostatectomy. With the use of new drugs such as antimuscarinic drugs, phosphodiesterase five inhibitors, Beta 3-agonists, phytotherapy and combination therapy, the treatment of BPH is significantly improved. The introduction of laparoscopy and robot-assisted laparoscopy in prostate cancer surgery reduces complications, blood loss, and duration of hospitalization with excellent long-term postoperative results. Today, BPH and prostate cancer have become diseases that can be perfectly controlled and pathophysiological changes almost normalized.

Worldwide today, there is a large pool of men who are undergoing BPH surgery. There is still a dilemma whether BPH and BPH surgery increase the risk of prostate cancer. A large epidemiological study from Denmark in 1980-2006 on 3,009,258 Danish men presented curious data that the risk of prostate cancer with multivariate-adjusted HRs for PCa incidence is 2.22 times higher in hospitalized men and 3.26 times higher in operated men from BPH. Corresponding HRs for PCa mortality were 2.00 for hospitalization and 7.85 for surgery compared to men without BPH.

A Swedish study of 86,626 men in 1964 – 1989 found that men with BPH in 4,875 cases developed prostate cancer, 2,260 were medicaments treated, 1,748 did undergo TUR P, and 824

underwent simple prostatectomy. The authors concluded that there was minimal risk of prostate cancer in patients with BPH compared to the general population (1% lower incidence and 2% excess mortality after the first five years).

Contradictory to these data, clinical studies have shown a minimal risk of only 1-3% for prostate cancer in patients undergoing BPH surgery over a follow-up period of 10 months to 27 years.

No clinical study indicates that BPH increases the risk of prostate cancer and that BPH is not a pre-malignant lesion.

ORIGINAL ARTICLE UDK: 616.65-006.6(497.7)"2002/2015"

PROSTATE CANCER AFTER SURGERY FOR BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Objective: To determine the incidence and characteristic of prostate cancer in patients with previous BPH surgery.

Materials and Method: In a retrospective study between 2002 and 2015, we analyzed patients who developed prostate cancer after surgery for BPH. Patients were examined by age, prostate volume, IPSS score, type and duration of the drug therapy, PSA values before and three months after surgery and the type of BPH surgery. In patients with prostate cancer, we estimated the time between BPH surgery and the occurring of cancer, Gleason score, TNM stage, type of therapy and survival. Follow-up for BPH patients was 3 months, and for the prostate cancer (PCa) group it was five years. Cox regression was used to determine the influence of various variables on the incidence of prostate cancer after BPH surgery.

Results: Incidence of prostate cancer was 1.69% (9 of 532 BPH surgeries) and was diagnosed significantly ($p<0.001$) more in patients who underwent open prostatectomy versus TURP. The mean time between BPH surgery and diagnosis of prostatic cancer was 7.2 years and did not correlate with investigated parameters. The value of IPSS in the BPH group was significantly higher compared to before PCa surgery ($p=0.012$). In the PCa group, PSA values decreased from 2.30±0.83 to 0.95±0.38ng/ml after three months and in the BPH group from 1.98±0.84 to 0.54±0.33ng/ml. PSA reduction rate for the PCa group was 58.4±11.6% versus 70.7±0.58% in the BPH group. In the Age-adjusted analysis, the PSA reduction rate was 0.050(0.001-0.937) HR (CI). In the PCa group, the serum PSA levels were 6.5 times increased (mean 14.97ng/ml) ($p=0.001$) compared to the BPH group. Before BPH surgery, the mean prostate volume was 60, 4 ccm, 5.3 ccm greater than in the cancer group. Two PCa patients had bone metastases. Radical prostatectomy was performed in 5 cases and four were treated with LHRH agonists and antiandrogens. One died three years after PCa diagnosis.

Conclusions: PSA reduction rate was borderline significant predictors of prostate cancer after BPH surgery.

KeyWords: *benign prostate hyperplasia, open prostatectomy, prostate cancer, PSA reduction rate, TURP.*

Introduction

There is controversy over whether benign prostatic hyperplasia or BPH surgery increases the risk of prostate cancer. Prostate cancer and benign prostatic hyperplasia are the two most common urological diseases in older men. Prostate cancer is the second most commonly diagnosed cancer in men accounting for 15% of all cancers diagnosed (1). Otherwise, BPH is present in 70% of men over 70 years and of all diagnosed prostate cancers, 80% of them had at the same time and BPH. Clinical BPH is present over 50% in men over 80 years. The incidence of prostate cancer increases about 15 years later than with BPH. In both diseases, the incidence and mortality increase with age (1-3). The worldwide difference in incidence existed between developed countries in Europe and America and Asia and the African continent (4,5). Both conditions are associated to epidemiological, hormonal, anatomical factors as well as the impact of inflammation, metabolic syndrome and genetic alterations (6-9).

As anatomical connections, the most cancers originate in the peripheral zone while BPH usually develops in the transition zone of the prostate (8,9). Well-known 5ARI therapy for BPH, reduced the relative risk of detecting prostate cancer by 25% over 7 years and reducing prostate size, as well as reducing the incidence of low-risk cancer (10-13). The ratio of oestrogens to androgens increases by 40% in older men and this may affect the natural course of BPH and CaP (14). Asians in the diet use phytoestrogens, which impact the lower prevalence of BPH and CaP compared to the Western diet (15).

Inflammation is associated to a 7.7-fold higher incidence of BPH. Fast-growing prostate may be a risk factor for developing prostate cancer. Several studies suggest an association between BPH and prostate cancer with certain genetic aberrations (16).

Large epidemiological and randomized controlled trials indicate a higher incidence of prostate cancer in patients who previously had BPH surgery. No causal link has been established between BPH surgery and the incidence of prostate cancer (17, 18).

Materials and Methods

In a retrospective study in the period from 2002 to 2015, we analyzed the number and characteristics of prostate cancers that occurred in the group of 532 patients who had previous BPH surgery. Patients who underwent surgery for BPH had follow-up for three months. Before surgery patients' PSA value were determined, as well as prostate volume, IPSS score and type and duration of previous drug treatment. At this point PSA value was controlled. Patients with elevated PSA above 4ng/ml had prostate biopsy and in case of positive findings, they were excluded from the study, as well as all patients who presented T1a-b stage on histopathological finding.

Patients who developed prostate cancer were analyzed for PSA values, prostate volume, IPSS score, type of BPH surgery, period between BPH surgery and prostate cancer diagnosis, TNM stage, Gleason score, as well as the type of therapy and survival. Patients with PCa had follow-up for a period of 5 years. Statistical analysis of all examined parameters was performed

in patients with prostate cancer, as well as correlation with parameters in the period of BPH surgery was made.

Statistical Analysis: Comparisons between the normally distributed variables were made with an independent Student t-test. If a non-normally distributed variable was involved in the comparison, then non-parametric methods were used. For comparisons of non-numeric variables, the Chi-squared test was used. To determine the relationship between numeric variables Person correlation was used. Cox regression was used to determine the influence of various variables on the incidence of prostatic cancer after BPH surgery. Hazard Ratios are given with 95% confidence intervals. SPSS statistical software (version 22.0 IBM, Armonk, NY, USA) was used; two-tailed $p<0.05$ was considered significant. Data are shown as mean ± standard deviation unless specified otherwise.

Results

Between 2002 and 2015, 532 patients were undergone to BPH surgery. Transurethral resection of the prostate (TURP) was performed in 476 patients (89.5%) and open prostatectomy (OP) in 56 (10.5%) of the cases. In a period from 3.1 to 12.4 years after BPH surgery, nine patients (1.69%) were diagnosed with prostate cancer (PCa), six in the group with TURP (1.26%), and three (5.35%) in the group with open prostatectomy (p=0.001). Table 1.

Twenty-two patients with clinical BPH were excluded from the study because of a finding of incidental, T1a, T1b prostate carcinoma.

Table 1. *Types of Benign Prostatic Hyperplasia Surgery done 2002-2015*

	BPH surgery (%)	TURP(%)	OP(%)
BPH(n,%)	532 (100)	476 (89,5)	56 (10,5)
PCa(n,%)	9 (1.69)	6 (1.26)	3 (5.36) p=0.001

BPH-benign prostatic hyperplasia, TURP-transurethral resection of the prostate, OP-open prostatectomy.

In twenty-nine patients with suspicion digital-rectal examination and PSA values, a prostate biopsies were done. In three of them, prostatic carcinoma was a diagnosis and they were excluded from the study.

The time from BPH surgery to the diagnosis of prostate cancer ranged from 37 to 149 months, with an average of 92.8 months (7.7 years). The first two patients with prostate cancer were detected in 2011, followed by two in 2013, two in 2014 and three in 2015.

The average age in the PCa group was 74.4±1.68 (66-82) years, which is 7.2 years higher than the age in the BPH group. The age at the time of BPH operation correlates with the age at the time of prostatic cancer operation (R=0.770; p=0.015). The IPSS score before the BPH surgery was 29.4±0.74 (25-33) points. The IPSS score after cancer diagnosis was 22.9±2.1 (12-33)

points, which is lower for 6.5 points than in the BPH group. (p=0.012). The mean prostate volume before BPH surgery was 60.4 ccm (26-92 ccm) and in the PCa group 55.1 ccm (27-97) which is 5.3 ccm greater volume than in the cancer group. Table 2.

Table 2. *Prostate cancer group: clinical parameters*

PCa N0	PCa age	PCa: year of diagnosis	Time from BPH surgery to PCa diagnosis months (years)	IPSS-BPH	IPSS before PCa diagnosis	Type of BPH surgery	PVol-BPH (ccm)	PVol-PCa (ccm)
1	74	2013	121 (10.1)	33	29	OP	59	45
2	82	2014	149 (12.4)	29	33	TURP	35	67
3	77	2015	91 (7.6)	30	23	OP	90	97
4	66	2015	87 (7.2)	28	23	TURP	37	32
5	76	2014	59 (4.9)	31	20	TURP	68	27
6	71	2011	80 (6.7)	29	12	OP	92	55
7	76	2015	85 (7.1)	25	22	TURP	26	60
8*	79	2011	126 (10.5)	29	17	TURP	85	35
9	69	2013	37 (3.1)	31	27	TURP	52	78
Mean +/-SD	74.4±1.68		92.8±11.5 (7.7±0.95)	29.4±0.74	22.9±2.10		60.4±8.32	55.1±7.71

PCa-prostate cancer, BPH-Benign prostatic hyperplasia, IPSS-The International Prostate Symptom Score, TURP-Transurethral resection of prostate, OP-open prostatectomy, PVol-prostate volume, – death*

The PSA value in the cancer group ranged from 6.9 to 45.9ng/ml, a mean of 15.0ng/ml before the prostatic biopsy. The PSA level before BPH surgery was 2.3ng/ml (1.1 to 3.4), and three months after those values were from 0.3 to 1.6ng/ml, mean 0.94ng/ml. In the cancer group, the PSA levels were 6.5 times increased (p=0.001) compared to the ones at the time of BPH surgery. PSA before BPH surgery correlated with PSA 3 months after BPH surgery (R=0.816; p=0.007). PSA before BPH surgery was significantly higher than 3 months postoperatively (p=0.001). PSA 3 months after BPH surgery was significantly lower than before prostatic biopsy (p=0.009).

All the patients in the cancer group had enlarged prostate volumes, significantly raised levels of PSA, and elevated IPSS score.

Five out of nine patients with prostatic cancer used alpha-blockers as monotherapy for BPH and 4 patients used combination therapy with alpha-blockers (AB) and 5 alpha-reductase inhibitors (5ARi). The mean duration of medical therapy before BPH surgery was 17.2 (3-35) months. The longer duration of the medical therapy was associated to lower IPSS before BPH surgery (R=0.757; p=0.018). There was no correlation found between alpha-blockers and combination therapy, duration of its usage and the appearance of the prostate cancer.

Regarding the Gleason score, six patients had 3+3 (International Society of Urological Pathology-(ISUP) 1), and three of them had a score of 3+4 (ISUP 2). Three of four patients with therapy with 5ARi had Gleason score ISUP1 and one had ISUP-2. Seven patients were in the T2N0M0 stage, two with metastatic disease in the T2NXM1b and T3NXM1b stage.

Radical prostatectomy was performed in four patients and the other five were treated with hormonal therapy (LHRH agonists and antiandrogens). The average age in the PCa group who underwent radical prostatectomy was 70.5 years (66-76) which is lower for 7.1 years than in the PCa group treated with hormonal therapy – 77.6 years (74-82). One patient died 3 years after the diagnosis of prostate cancer was established, at the age of 82 after he was treated with LHRH antagonists.

The patients in the prostate cancer group had significantly higher PSA 3 months after BPH surgery than patients in which cancer was not diagnosed (p=0.014). PSA reduction rate was significantly lower in patients in which prostatic cancer was diagnosed after BPH surgery than in those in the BPH group (p=0.032), Table 3.

Table3. *Prostate cancer group: clinical parameters PSA, MT, BPH surgery. Gleason score, PCa therapy TM stage*

PCa No	PSA before BPH surgery	PSA 3 months after BPH surgery	PSA before prostate biopsy	Type of MT before BPH surgery	Type of BPH surgery	Gleason score)	Treatment of PCa	TNM stage
1	2.1	0.6	9.1	AB+5ARi	OP	3+3	HT	T2NxMx
2	2.7	1.1	19.4	AB	TURP	3+3	HT	T2N0M0
3	1.3	0.8	45.9	AB	OP	3+4	HT	T3NxM1b
4	1.8	0.9	7.8	AB	TURP	3+4	RP	T2N0M0
5	3.1	1.3	13.7	AB+5ARi	TURP	3+4	RP	T2 NoM0
6	2.1	1.0	10.2	AB+5ARi	OP	3+3	RP	NoM0
7	1.1	0.3	7.4	AB	TURP	3+3	HT	T2NxMx
8	3.4	1.6	6.9	AB	TURP	3+3	HT	T2NxM1b
9	3.1	0.9	14.3	AB+5ARi	TURP	3+3	RP	T2NxMo
Mean±SD	2.3±0.27	0.9±0.13	15.0±4.1					

PCa – Prostate cancer, BPH-Benign Prostatic Hyperplasia, IPSS-The International Prostate Symptom Score, PSA-Prostate Specific Antigen, AB-alpha blocker, OP-Open Prostatectomy, TURP-Transurethral Resection of Prostate, MT-Medical Therapy, AB-alfa blocker, 5Ari-5 alfa reductase inhibitor, HT-hormonal therapy, RP-radical prostatectomy.

In the Cox regression analysis of the predictors of cancer incidence in patients after BPH surgery, only the PSA reduction rate was a borderline predictor in unadjusted analysis. In PCa group, PSA values decreased from 2.30±0.83 to 0.95±0.38ng/ml after three months and in BPH group from1.98±0.84 to 0.54±0.33ng/ml. PSA reduction rate was 58.4±11.6% for PCa group compared to70.7±0.58% in BPH group.

In the Age-adjusted analysis HR (CI), the PSA reduction rate was 0.050 (0.001-0.937) and was the sole predictor of prostate cancer incidence after benign prostate surgery (p=0.048), Table 4.

Table 4. *Cox regression analysis of predictors of prostatic cancer after benign prostatic surgery*

Variable	Unadjusted Analysis HR (CI)	p-value	Age Adjusted Analysis HR (CI)	p-value
BPH Surgery Age	0.980 (0.851-1.129)	0.777	0.980 (0.851-1.129)	0.777
BPH-IPSS	0.924 (0.987-1.301)	0.924	0.908 (0.744-1.300)	0.908
Prostate Volume (ccm)	1.011 (0.980-1.044)	0.484	1.013 (0.979-1.048)	0.452
PSA prior to BPH surgery (ng/ml)	1.045 (0.419-2.607)	0.925	1.123 (0.406-3.111)	0.823
PSA 3months postop (ng/ml)	3.842 (0.632-23.35)	0.144	4.797 (0.736-31.25)	0.101
PSA reduction rate (%)	0.055 (0.002-1.697)	0.097	0.050 (0.001-0.937)	0.048
AB+5ARi	4.432 (0.532-36.91)	0.169	4.435 (0.533-36.93)	0.168
AB	0.226 (0.027-1.879)	0.169	0.225 (0.027-1.877)	0.168
BPH surgery: TURP	0.540 (0.121-2.417)	0.420	0.524 (0.116-2.373)	0.401
BPH surgery: OP	1.851 (0.414-8.284)	0.420	1.901 (0.421-8.658)	0.401

BPH-Benign Prostatic Hyperplasia, IPSS-International Prostatic Symptom Score, PSA-Prostatic Specific Antigen, AB-Alpha blocker, 5Ari-5 alpha reductase inhibitors, TURP-Transurethral Resection of Prostate, OP-Open Prostatectomy.

Discussion

The main finding in our study was a low incidence and mortality of prostate cancer after BPH surgery. We also found that a PSA reduction rate three months after BPH surgery could be a predictor of prostate cancer.

Only 1.69% of patients with previous BPH surgery developed prostate cancer. Patients with prostate cancer who were treated with TURP compared to open prostatectomy (OP) had a 4.2-fold lower incidence. Swedish study by Chokkalingam et al. reported two times higher (2.96%) incidence of prostate cancer after BPH surgery in a group of 1,748 patients treated with TURP and 824 with open prostatectomy. They reported two times more patients with TURP than OP, but the most of them were undergone surgery before the 1980 s when TURP was routinely used (17).

Danish study by Ørsted et al. in 77,698 men who received surgical BPH treatment observed 3.48% of PCa patients and Kanno et al. from Japan presented a similar incidence of 3.2% patients with prostate cancer over 1 to 7 years in a cohort of 407 patients with TURP (18, 19). Carlson et al. in the cohort of 7,901 patients with previous TURP (1982-1997) reports increased standardized incidence ratio (SIR) for prostate cancer [1.26, CI 95% (1.17 – 1.35)], but not increased standardized mortality ratio (SMR), [0.59, CI 95% (0.47 – 0.73)](20). In contrast, Ørsted et al. found that clinical BPH was associated with a two-fold to three-fold increased risk of PCa incidence and a two-fold to eight-fold increased risk of PCa mortality. The authors emphasized that these data should not be used to infer causality. Kanno, Karlsson and Orsted in their studies presented two times higher incidence than ours. Armenian et al. also observed an increased risk of prostate cancer incidence after BPH surgery (21).

But, studies of Greenwald et al. on 800 men with BPH and Simons et al. on sample size on 4,800 men with BPH, did not find an association between BPH and increase risk of prostate cancer (22, 23).

Ørsted et al. reported the median age at PCa diagnosis of 72 years for PCa patients and 75 years for BPH patients, which was 2.2years and eight years higher than in our study.

We reported the meantime of 7.7 years from BPH surgery to the diagnosis of prostate cancer. In Wolff study time of appearance of all cancer cases was up to 7 years (24). Chokkalingam et al. found that patients with TURP developed prostate cancer after 6.5 years and patients with open prostatectomy one year later. Ørsted et al. presented the median time to diagnosis of PCa after surgery for clinical BPH of 3 years (range: 0-27 years). In the Tanaka study, 7 out of 319 cases of prostatic cancer had previous BPH surgery 22 months to 15 years ago (25).

Hua L in a Chinese study from 2004 analyzed twelve cases of prostate cancer after BPH surgery that appeared after 10 months to 14 years, 5.6 years on average.

We did not find a significant difference in the time of occurrence of prostate cancer in TURP and OP subgroups (7.5 years versus 8.1years). In a study from Japan by Kanno et al. in the period 1995 to 2003, 13 (3.2%) of 407 patients all with TURP, developed prostate cancer over 1 to 7 years. Kato et al. presented case of prostate cancer fourteen months after open prostatectomy in 1996 (26).

All studies showed a period of diagnosis of prostate cancer after BPH surgery from 10 months to 27 years.

Regarding the IPSS score, our PCa patients were severely symptomatic before the diagnosis of prostate cancer. Hua L et al. referred to mild to heavy symptoms according to IPSS (21).

We presented reduction values of PSA after three months on 0.94ng/ml which was a higher percentage of the reduction compared to the study of Wolff et al. where PSA was reduced from 6.8ng/ml to 2.2ng/ml after 48 months. We found that PSA levels were 6.5 times increased compared to the ones at the time of BPH surgery. In the Tanaka study, all prostate cancer presented a significant elevation of the PSA (6.4-399ng/ml) at the time of cancer diagnosis.

An important finding was a PSA reduction rate of 58.4% 3 months after BPH surgery compared to 70.7% in patients with BPH surgery who did not develop prostate cancer (p=0032) which was similar to Wolff's findings (24).

According to TNM classification and Gleason score, our patients were in low stage and grade, but two had metastatic disease. Kanno's findings were that 6 of 13 patients were moderately differentiated, the other 6 were with poorly differentiated cancer, also one with ductal carcinoma of the prostate. Hua L described that out of twelve cases 3 were in the T2 stage, 3 in T3 and six were with metastasis (21).

In our study, one patient died of prostate cancer with bone metastases. In Hua L study 3 of 12 patients died with metastatic disease.

The limits of our investigation were the small number of patients with prostate cancer, the short follow-up period of patients with BPH surgery. Our study was done in the PSA era, while large epidemiological studies were from the pre-PSA era.

Conclusion

BPH surgery did not increase risk of prostate cancer. PSA reduction rate was the sole predictor of prostate cancer incidence after benign prostate surgery.

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THE INCIDENCE OF NEONATAL SEPSIS AT A TERTIARY NEONATAL INTENSIVE CARE UNIT (A 9 MONTHS SURVEY)

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ABSTRACT

Introduction: Neonatal sepsis is severe infection that affect newborns in the first 28 days of live. The first 28 days of life of newborns are the most vulnerable period in life of newborns, known as neonatal period of live. Newborns may be infected before, during or after the birth. Neonatal sepsis as a blood stream infection could be presented like pneumonia, pyelonephritis, gastroenteritis, osteomyelitis, arthritis or meningitis in newborns. Neonatal sepsis can be diagnosed by clinical signs of sepsis or with a positive microbiological culture-culture proven sepsis.

Research Purpose: The purpose of this study is to show the incidence of neonatal sepsis, neonatal mortality caused by sepsis in early and late neonatal period, and the most common bacterial triggers of neonatal sepsis in the given period, among live-born newborns at the GOC-Skopje, treated at NICU in the first 28 days after delivery.

Material and Methods: This prospective analysis elaborates on incidence of neonatal sepsis, neonatal mortality caused by sepsis and the most common bacterial triggers of neonatal sepsis in live-born neonates in the first 28 days after delivery at the GOC-Skopje, in the period 01.05.2019-31.01.2020. The data is collected from the Data basis at NICU and the medical histories of women that gave birth and the histories of newborns at GOC-Skopje, during this period.

Results: During this period of 9 months at GOC-Skopje, there were 3,453 live-born newborns, out of which 445 newborns were transferred and treated at NICU. 124 of these newborns, developed clinically and laboratory signs of neonatal sepsis, or 36 on 1000 live-births. 32 (25.8%) of newborns which developed neonatal sepsis, died in neonatal period or 9 on 1000 live-births. The most common bacterial cause for neonatal sepsis were Klebsiella pneumoniae, followed by Staphylococcus aureus, Enterobacter species, Serratia marcescens and Escherichia coli.

Conclusion: The hospital neonatal sepsis and mortality from neonatal sepsis at GOC-Skopje is quite higher than in the developed countries of the world.

Keywords: *early neonatal period, GOC – Skopje, late neonatal period, neonatal sepsis, NICU.*

Introduction

Neonatal sepsis is severe infection that affect newborns in the first 28 days of live. The first 28 days of life known as neonatal period of live, is the most vulnerable period in life of newborns (1, 2). It is divided into early neonatal period – the first seven days of live of newborns and late neonatal period-from 8 to28 days of live. Newborns are infected before, during or after birth. Newborns are usually infected of some urogenital infections from mother-with colonization of bacteria when they are exposed in birth canal, from infected amnion fluid – chorioamnionitis before delivery, or can be exposed on infection after delivery at home or in the hospital (3). Other risk factors for sepsis in newborns is prematurity, low birth weight, invasive procedures during pregnancy like amniocentesis and cerclage, early breaks of amnion fluid – 18 or more hours before delivery, and some condition of newborns on delivery-reanimation, intravenous catheters, urinary catheter or some congenital diseases (4,5). The infection affects one or multi organ systems, with failure in the body, cardiac or respiratory failure and distress, shock, metabolic disorders, bad condition of newborn, lethargy, fever, temperature instability, vomiting, diarrhea, not feeding, bleeding and coagulopathy in newborn (6). Neonatal sepsis as a blood stream infection is presented like pneumonia, pyelonephritis, gastroenteritis, osteomyelitis, arthritis or meningitis in newborns (7). Neonatal sepsis is recognized by clinical signs of sepsis without or with a positive microbiological culture-culture proven sepsis (8). Sepsis in newborns diagnosed by clinical signs is with laboratory tests (blood test, PMN count, CRP, blood gases, electrolytes, PCT) and with microbiological culture (blood culture, urine culture, swabs from skin, nose, throat, mouth and lumbar puncture in meningitis). Ultrasound, X-rays and other imaging tests can be used for diagnosis of organ failure during septicemia (9,10). Sepsis in newborns is treated at Neonatal Intensive Care Unit (NICU), with intravenous fluids, antibiotics, medications for fever, nutrition, oxygen and respiratory support and sometimes with blood transfusion (11,12). The incidence of neonatal sepsis is different in developed and developing countries and depends from geographical regions. In the most developed countries the incidence of neonatal sepsis is one to eight on 1,000 live births, while in developing countries it varies from 49 to170 on 1,000 live births, depending on the development of the country and the health system (13). The survival rates of treated neonatal sepsis also vary worldwide and the risk for mortality is 3-30%. Sepsis in newborns develops as early-onset sepsis in the first 72 hours after delivery, or as a late-onset sepsis after 72 hours after delivery (14). Neonatal deaths from sepsis are usually divided as deaths in the early neonatal period in the first seven days of live and deaths of newborns at late neonatal period from 8 to28 days of live. Early-onset sepsis is a result of premature rupture of membranes, prematurity and low birth weight, GUI of mother in pregnancy and GBS infections in mother. Late-onset sepsis is usually result of prolonged hospitalization of newborns at NICU, cross-infections, use of intravenous catheters and endotracheal tubes or congenital anomalies of newborns (5). Neonates treated at NICU, are at increased risk for hospital-acquired infections (15). The most common cause of sepsis worldwide are bacterial infections, followed by fungi,

parasites and viruses (16). The most common bacterial agents of neonatal sepsis are Gram negative bacteria like: Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Hemophilus influence, Serratia marcescens, Proteus mirabilis, Enterobacter, Salmonella typhi … Gram positive bacteria: Streptococcus pneumoniae, Streptococcus pyogenes, GBS, Listeria monocytogenes, Enterococcus, Staphylococcus aureus, MRSA … Viruses like Echovirus, Enterovirus, Coxsackie, Adenovirus, Parainfluenza, Rhinovirus, HSV, RSV and Coronavirus. Candida albicans and other Candida species may be associated to neonatal sepsis (17). In different geographical regions and based on development of the health system of the country, various infective causes are the leading cause of neonatal sepsis.

Material and Methods

This prospective analysis elaborates on incidence of neonatal sepsis, neonatal mortality caused by sepsis and the most common triggers of neonatal sepsis in live-born neonates in the first 28 days after delivery, treated at NICU at the GOC-Skopje, in the period of 01.05.2019-31.01.2020. The data was collected from the Data basis at NICU and the medical histories of women that gave birth and the histories of newborns at GOC-Skopje during this period. Mortality from sepsis in neonates was divided as mortality in the first seven days after delivery, and from 8 to 28 days after delivery. Neonatal mortality from sepsis was sub-divided into groups by gestational age of newborns in: extremely premature, early premature, late premature and mature group of newborns, born >37 gestational week. From the obtained microbiological cultures – culture proven sepsis were singled out the most common bacterial triggers for neonatal sepsis at NICU.

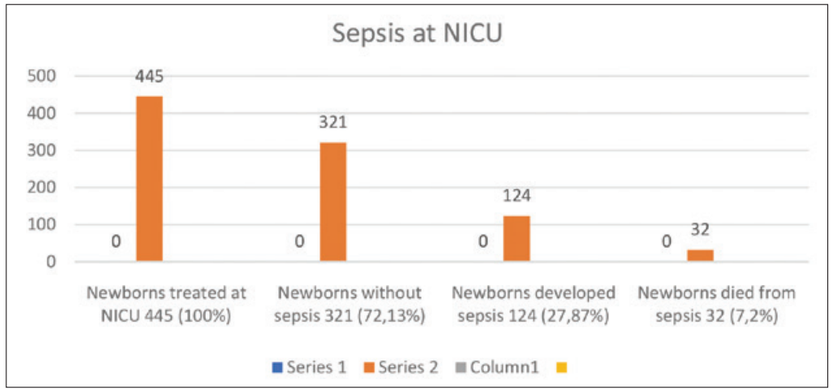
Inclusion criteria were: All born neonates at GOC-Skopje in the given period (9 months), live and deaths who developed sepsis in the first 28 days after delivery (neonatal period), neonates treated at NICU.

Exclusion criteria was: Developed sepsis and death from sepsis in newborns after 28 days of delivery.

Results

In this period of 9 months there were 3,453 live-born newborns, at GOC in Skopje. 445 (12.9%) of them were transferred and treated at NICU. The most of them were premature 414 (93%), born in less than 37 gestational weeks of pregnancy. 124 (27.87%) of newborns transferred at NICU, developed clinically and laboratory signs of sepsis and 32 (25.8%) of the newborns which developed sepsis died in neonatal period – **Figure 1**. The incidence of neonatal sepsis was 36 on 1000 live-births in the total number of births at GOC in Skopje in this period. 32 (7.2%) of whole newborns treated at NICU died with symptoms of sepsis during hospitalization at NICU. Hospital neonatal mortality from sepsis at GOC-Skopje in this period was 9 on 1,000 live-births.

Figure 1. *Number of neonates treated at NICU, neonates which developed sepsis and deaths from sepsis in neonatal period at NICU/ GOC-Skopje (9 months period)*



The incidence of neonatal mortality from sepsis at NICU was bigger as the gestational age of newborn decreased and was the highest in the group of extremely premature newborns, born in 22-27 gestational weeks of pregnancy, with mortality of28.6% in this group. Only one term newborn at 38 g.w., died from sepsis at NICU in this period, out of 31 term newborns treated at NICU. Table 1.

More of newborns with neonatal sepsis treated at NICU, died in late neonatal period from 8 to28 days of live – 17 (53%), while 15 (47%) of them died in early neonatal period. **Table 1**.

Table. 1. *Neonatal death from sepsis at NICU by gestational age in early and late neonatal period / GOC-Skopje*

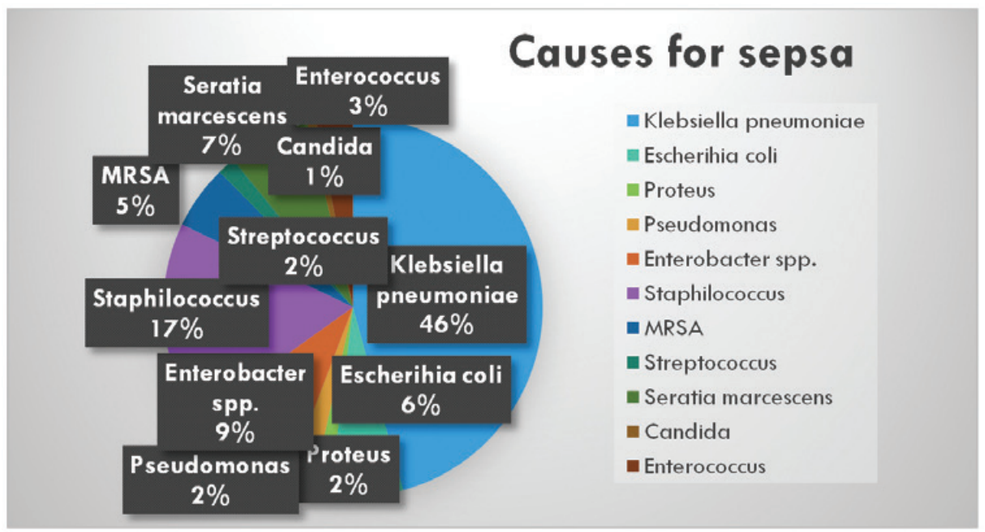
Gestational age of newborns	22-27 g.w. Extremely premature	28-32 g.w. Early premature	33-36 g.w Late premature	>37 g.w. Term newborns	Total newborns at NICU
Newborns treated at NICU	42 (9.4%)	154 (34.6%)	218 (49%)	31 (7%)	445
Died from sepsis 1-7 days	5 (11.9%)	7 (4.54%)	4 (1.83%)	1 (3.2%)	15
Died from sepsis 8-28 days	7 (16.7%)	4 (2.6%)	4 (1.83%)	0 (0%)	17
Total died from sepsis 1-28 days	12 (28.6%)	11 (7.14%)	8 (3.67%)	1 (3.2%)	32

In the group of extremely premature newborns 12 (28.6%) of newborns died with symptoms of sepsis. In early premature group of newborns, that number decreased and was 11 (7.14%), in the group of late premature newborns – 8 (3.67%) and only 1 (3.2%) newborn died with symptoms of sepsis (Table 1).

From 124 newborns treated at NICU with symptoms of sepsis, bacteria as a cause for sepsis was proven in 95 cases (76.6%) of them, by swabs or blood culture.

The most common isolated bacterial trigger for neonatal sepsis at NICU was Klebsiella pneumoniae with 44 (46%), followed by Staphylococcus aureus with 16 (17%), Enterobacter species 10 (9%), Serratia marcescens with7 (7%), Escherichia coli 6 (6%), MRSA 5 (5%), Enterococcus 3 (3%), Pseudomonas and Proteus with 2 (2%), Streptococcus 1 (1%) and Candida 1(1%). Figure2.

Figure2. *Presence of bacterial causes of neonatal sepsis at NICU/ GOC-Skopje*



Discusion

The study showed that there was a high incidence of hospital neonatal sepsis in newborns treated at NICU at GOC-Skopje in this period of 9 months. 36 newborns developed neonatal sepsis on 1,000 live births. Mortality in newborns which developed sepsis is also high, 9 on 1,000 live-born neonates died from sepsis at GOC-Skopje. In developed countries the incidence of neonatal sepsis is 1-8 cases on 1,000 live births, while in developing countries that number is much higher 49-170 per 1,000 live births. Mortality from neonatal sepsis worldwide vary from 3 to 30% and in some developing countries it is more than 50%. On our material 32 (25.8%) of neonates died with symptoms of sepsis, out of 124 which developed neonatal sepsis at NICU. Neonatal mortality from sepsis is the highest in extremely premature newborns-born from 22 to 27 gestational weeks with 28.6% of them and decreases with increasing of gestational age of neonates. Prematurity is one of the biggest risk factors for developing of neonatal sepsis, and the prevention of prematurity will decrease the incidence of neonatal sepsis. Klebsiella pneumoniae was obtained in 46% of bacterial proven neonatal sepsis at NICU and the most of newborns with sepsis died in late neonatal period in 8-28 days after delivery, which means that prolonged hospitalization and nosocomial infections have an important role in the occurrence of neonatal sepsis at NICU.

Conclusion

To reduce the rate of neonatal sepsis, it is necessary to improve the prospective studies at NICU and GOC-Skopje, as the biggest neonatal and perinatal center in the country. Improving the antenatal care, investments in health system conditions and effective programs for protection of mothers and neonates, prevention of genital-urinary infections during pregnancy and prevention of prematurity, will result with decreased incidence of neonatal sepsis. Efficient and adequate care and adequate resuscitation of newborns after delivery at NICU, raising hygiene standards and prevention of nosocomial infections, are of great importance for reducing neonatal sepsis and mortality from sepsis.

Abbreviations: GOC-Skopje: Gynecology and Obstetrics Clinic-Skopje; NICU: Neonatal Intensive Care Unit; G.W.: gestational week; GUI: genital-urinary infections.

Acknowledgements: We would like to thank to all participants in this study and to a publisher for publishing of this article.

Authors Contribution: All authors participated in conception of this manuscript and approved publication.

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ORIGINAL ARTICLE UDK: 616-089.5-098.168

CHALENGES IN POSTOPERATIVE PEDIATRIC ANALGESIA

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ABSTRACT

Postoperative analgesia in children is important in many aspects. Due to sensitization-hyperalgesia phenomenon, acute postoperative pain can be transformed into chronic pain, which poses larger responsibilities to the anesthesiologists.

Aiming to discover the situation in our institution, a longitudinal observational study was made, which lasted one month. A total of 53 anesthetized children were analyzed regarding the level of postoperative pain. The postoperative pain was estimated in the early postoperative period in Post-anesthesia care unit (PACU) and at the Ward, using the CHEOPS behavioral scale and the Wong-Baker FACES pain rating scale in older children.

The obtained data were statistically analyzed. The results showed that all 53 patients were anesthetized in general anesthesia. The airway was secured with a tube (85.9%) or laryngeal mask. Fentanyl IV was the unique opioid applied during the maintenance of anesthesia. Non-opioid analgesics (acetaminophen-paracetamol and metamizole), tramadol or caudal blocks were intraoperatively used. The postoperative pain assessment showed that the pain, in general, was poorly understood, with mean scores of 4.35±3.35.

It was concluded that the analgesic approach to the patients was unequal, and further efforts for establishment of the institutional protocol and pain services are necessary.

Key Words: *analgesic drugs, children, pain, pain assessment, postoperative analgesia.*

Introduction

Postoperative analgesia in children is important from the health, psychological and social aspects. According to recent studies, a severe pain in children is the reason for the long-lasting consequences which are the same as in adults (1). It has been shown that inflammatory pain causes physical cell changes which are responsible for sensitization-hyperalgesia phenomenon and development of chronic pain present in children in the same proportions as in adults (2). Thus, it is very important to treat acute pain, and to provide sufficient postoperative analgesia in children.

The pain management in children is still underestimated, and hence, the last three decades have been dedicated to provide better analgesia for children, resulting in a remarkable improvement in the pediatric pain management (3). These efforts have been taken step by step. The

development of the appropriate methods for assessment of pain in children (Tridimensional evaluation of the pain), the understanding of building confidence by both – the children and the adults, and the education of the professionals for appropriate pain treatment of children, have been some of the few key points in providing pain relief.

The introduction of some simple organizational changes in the hospitals, for example the establishment of an "Acute pain service", has been a crucial approach for better analgesia in the postoperative period of the children (4).

We are witnesses of the development of several protocols and guidelines in pediatric postoperative analgesia (1,4,5).

The pain is an individual experience and the self-evaluation of the pain is a gold standard for its measurement. But, in some age groups of children the self-report could be difficult or impossible. In such circumstances, a proxy's, parent's or guardian's opinion and observations are used. The main assessment methods are based on:

1. Measurement of the individual experience or self-evaluation by using pain rating scales: VAS, or "faces" pain scales such as the Wong – Baker FACES pain rating scale (6, 7);
2. Observational/ Behavioral that measures behavioral changes associated with pain (by parent's, nurse's or guardian's report);
3. Physiological that measures physiological changes associated with pain (tears, color of the skin, hearth rate – HR, blood pressure – BP and others).

Luo J. in 2017 presented the advances in objective pain assessments; one of them being pain assessment independent from patients' participation and the other-assessment suitable to be applied in children. Both of them are based on different physiological parameters, such as photo-plethysmography (PPG – sympathetic cardiac and vascular response), analgesia nociception index (ANI), skin conductance (SC – vascular sympathetic response) and pupillometry – measurement of the pupil reflexes (8).

The most of the assessment methods are based on the combination of the previously mentioned ones, and are based on three-dimensional measurement, self-evaluation/ observation, behavioral and physiological parameters, expressed in scores. Commonly used postoperative pain scales are FLACC (face, legs, activity, cry, consolability) and CHEOPS (Children Hospital of Eastern Ontario Pain Scale) (9).

For an accurate pain assessment, the assessors have to be experienced with the use of the pain scale and, moreover, they have to take into consideration the age of the children and the environment. All obtained data (scores) must be well documented and consequently, the most appropriate pain-relief drugs must be chosen.

Aim of the Study

Aiming to improve the postoperative pediatric analgesia in our institution, we have made a short longitudinal observational study in order to get insights into the current situation.

There is still no pain service in our institution and the unified protocol for postoperative pediatric analgesia has not been upgraded. The recent situation has permitted to all anesthesiologists to follow their own protocols for postoperative pediatric analgesia. The analgesia is provided "on demand". When a child complains of having pains, the nurses give him/ her analgesics (in general recommended by a surgeon or an anesthesiologist).

Regarding this situation, several questions have emerged:

1. What type of postoperative analgesia is used?
2. Which one of the used analgesic regimens is the most efficient?
3. Is preemptive analgesia used? When is it administered?
4. Does the type of premedication have any influence on postoperative analgesia?
5. Does the use of N2O have influence on postoperative pain?

Material and Method

After receiving the approval by the Clinical Ethics Committee, the study was performed at the Department for Pediatric Anesthesia in the Clinic for Anesthesia, Resuscitation and Intensive Care, in a tertiary hospital in Skopje, Republic of North Macedonia.

In order to answer all questions, a protocol for the study was designed, whereby data of preoperative, peroperative and postoperative analgesia were noted. The participation in the study was voluntary and the study was realized in a period of one month (from 1st of March to1st of April 2021). Written informed consent from the participants in the study was obtained.

Without an institutional protocol for postoperative analgesia, the anesthesiologists were asked to manage the pain as in their everyday routine.

Data were noted in a list by an independent person, a volunteer. The list was structured in three parts: 1. Data about patients and performed surgery; 2. Details about the timing of the surgery, type of anesthesia with the used anesthetics and the used intraoperative analgesia; 3. The assessment of the pain in the early postoperative period in Post-anesthesia Care Unit (PACU) and afterwards at the Clinic of Pediatric Surgery (CPS).

The CHEOPS behavioral scale was used for 1-5 years old children and the Wong-Baker FACES pain rating scale for the older ones.

The study included all children who received anesthesia during the study period, regardless the age and the type of surgery.

Data from 53 patients were obtained. Patients were aged from 3 months to 14 years, and underwent major, subumbilical and mild surgery.

The obtained data were statistically analyzed: general data (demographics, type of surgery and time of anesthesia), data about the drugs used for anesthesia, and data about the postoperative analgesia (type, drugs, doses and postoperative scores in PACU and at the CPS). Descriptive data were presented in numbers and percentages (n/%), mean and standard deviation (M±SD). For comparison of pared data, t-student test was used where $p<0.05$ was significant.

Results

The study was carried out by 7 anesthesiologists, who have knowledge and experience in relieving postoperative pain at different ages and knowledge about the use of pain assessment techniques.

This study included 53 operated children, male *vs*. female ratio 36:17, age range from 3 months to 14 years. 24.5% of the children in this study were younger than 3 years. The distribution of demographic data is shown in Table 1.

Table 1. *Demographic characteristics of the observed children during anesthesia and surgery*

<table>
<tr><td rowspan="2">Gender</td><td rowspan="2"></td><td colspan="2" rowspan="2">Ages in months & years (M±SD)</td><td rowspan="2">BW (M±SD)</td><td>Surgery n/%</td><td colspan="2" rowspan="2">Timing of anesthesia in minutes (No of patients &%)</td></tr>
<tr><td>Major surgery 13 (24.5%)</td></tr>
<tr><td></td><td></td><td><3 y months</td><td>>3-14 years</td><td></td><td>Bone fractures 7 (13.2%)</td><td>30-60 min</td><td>29 (54.71%)</td></tr>
<tr><td>Male</td><td>36 (67.9%)</td><td rowspan="2">14.5±6.4</td><td rowspan="2">7.24±3.2</td><td rowspan="2">25.74±14.1</td><td rowspan="2">Sub umbilical 29 (54.7%)</td><td>60-120 min</td><td>20 (37.7%)</td></tr>
<tr><td>Female</td><td>17 (32.0%)</td><td>120 + min</td><td>4 (7.5%)</td></tr>
<tr><td>Total No.</td><td>53</td><td>13</td><td>40</td><td>53</td><td rowspan="2">Other 4 (7.5%)</td><td colspan="2">M ± SD</td></tr>
<tr><td>%</td><td>100</td><td>(24.52%)</td><td>(75.4%)</td><td>100</td><td colspan="2">77,641 ± 29,329</td></tr>
</table>

The average time of anesthesia was 71.64 ± 29.3 minutes and the majority of the patients underwent subumbilical surgical interventions (54.7%).

The most of the patients were managed in general anesthesia (88.68%). The airway was secured with endotracheal tube in 84.9% of the cases. Oral premedication with syrup midazolam was preferred. The induction in general anesthesia was IV with propofol with lidocaine, fentanyl, and neuromuscular blockers (rocuronium or succinylcholine in emergent cases). Anesthesia was maintained with fentanyl and sevoflurane, with oxygen in air (50/50 vol%) without the use of N_2O. Sevoflurane for induction was used only in 4 cases of children younger than 3 years.

Tables 2 and 3 show numbers and percentages of the type of anesthesia and the used drugs during induction and maintenance of anesthesia.

Table 2. *Type of anesthesia used in this study*

<table>
<tr><th colspan="2" rowspan="2">Type of the secured airway</th><th colspan="2">Premedication</th><th rowspan="2">Without N2O</th><th colspan="2" rowspan="2">Type of Anesthesia</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Airway</td><td>4 (7.5%)</td><td rowspan="4">42 (79.24%)</td><td rowspan="4">11 (20.75%)</td><td rowspan="4">53</td><td>General</td><td>47 (88.68%)</td></tr>
<tr><td>Tube</td><td>45 (84.9%)</td><td>GA+CB</td><td>5 (9.4%)</td></tr>
<tr><td>LM</td><td>4 (7.5%)</td><td>GA+ RB</td><td></td></tr>
<tr><td></td><td></td><td>GA on FM</td><td>4 (7.5%)</td></tr>
<tr><td>Total</td><td>53</td><td>42</td><td>11</td><td>53</td><td></td><td>53</td></tr>
<tr><td>%</td><td>100</td><td>79.24</td><td>20.75</td><td>100</td><td></td><td></td></tr>
</table>

Legend: *LM – Laryngeal mask; GA – general anesthesia; CB – Caudal block; RB – regional blocks; FM – Face mask.*

Table 3. *Drugs used for induction and maintenance of anesthesia*

<table>
<tr><th>Parameters</th><th>Induction to anesthesia</th><th>No (%) of patients</th><th>Management of anesthesia</th><th>n/%</th></tr>
<tr><td rowspan="5">Anesthetic agents</td><td>Fentanyl</td><td>52 (98.1%)</td><td>Fentanyl</td><td>9 (16.9%)</td></tr>
<tr><td>Propofol + lydocaine</td><td>51 (96.2%)</td><td></td><td></td></tr>
<tr><td>Sevoflurane</td><td>4</td><td>Sevoflurane</td><td>3 (5.6%)</td></tr>
<tr><td>Midazolam</td><td>6 (11.3%)</td><td></td><td></td></tr>
<tr><td>Sevo +fentanyl</td><td></td><td>Sevo + fentanyl</td><td>41 (77.3%)</td></tr>
<tr><td>Agents for caudal block</td><td>Bupivacaine
Bupivacaine + tramadol</td><td>5 (9.4)
1 (1.8%)</td><td></td><td></td></tr>
<tr><td>Neuromuscular blockers</td><td>Rocuronium bromide
Succinilcholine</td><td>45 (84.9%)
2 (3.7%)</td><td>Rocuronium</td><td>14 (26.4%)</td></tr>
<tr><td>Allergy or asthma prevention</td><td>Corticosteroids
Salbutamol Spray</td><td>3 (5.6%)
2 (3.7%)</td><td></td><td></td></tr>
</table>

In 6 patients, as prevention for postoperative pain (Table 4), after induction, caudal block with bupivacaine 0.125% was applied (in 5 patents), and tramadol as adjuvant in one patient. Perioperatively paracetamol was given 30 minutes before the end of surgery in 35 patients, out of whom 8 patients for different reasons got adjuvants (midazolam, metamizole, MgSO4, corticosteroids and propofol).

Table 4. *Intraoperative types applied in analgesia and timing (n/%)*

<table>
<tr><th>Methods</th><th>Premedication</th><th>Caudal block</th><th>Perioperative</th><th>Postoperative</th></tr>
<tr><td>n/%</td><td>42 (79.24%)</td><td>5 (9.4%)</td><td>35 (66%)</td><td>28 (52.8%)</td></tr>
<tr><td rowspan="2">Drug:
Dose</td><td rowspan="2">Syr. Midazolam PO – 0.5 mg/kg BW</td><td rowspan="2">Bupivacaine 0.125% Epid-2.5 mg/kg BW</td><td>Paracetamol I.V. 15 mg/kg/BW</td><td>Paracetamol I.V. 15 mg/kg/BW</td></tr>
<tr><td>27 (50.94%)</td><td>6 (11.3%)</td></tr>
<tr><td rowspan="8">&Adjuvants</td><td rowspan="8">Corticosteroids or Spray salbutamol 3 (5.6%)</td><td rowspan="8">Tramadol 1 (1.8%)</td><td>Midazolam 0.15/kg BW</td><td>Metamizole</td></tr>
<tr><td>1(1.8%)</td><td>21 (39.6%)</td></tr>
<tr><td>Metamizole 25 mg/kg BW</td><td>Tramadol</td></tr>
<tr><td>2 (3.77%)</td><td>1 (1.8%)</td></tr>
<tr><td>MgSO4 3 (5.6%)</td><td></td></tr>
<tr><td>propofol 2 (3.77%)</td><td></td></tr>
</table>

Table 4 illustrates that more than half of the patients (52.8%) needed postoperative analgesia, paracetamol, metamizole and tramadol.

Table 5 presents data of the pain assessment made in the post-anesthesia care unit and in the CPS, 3 hours after discharge from the PACU.

Out of 53 children, only 6 did not feel pain during their stay in PACU. More than half did not cry, only 20.7% cried loudly, and only one child was agitated. At the CPS the majority of the children were without pain, did not cry and were calm. The average scores of the CHEOPS pain scale at the PACU was 4.35±3.35 and at the CPS 2.9±1.94.

Table 5. *Measurement of the analgesic effect on the first postoperative day*

Time	PACU	WARD	Additional analgesia
Self-report or parents No pan	6 (11.3%)	46 (86.7%)	Paracetamol n=6
Mild	22 (41.5%)	5	
Moderate	23 (43.3%)	1 (1.8%)	
Severe	1 (1.8%)	1 (1.8%)	
Crying 1 2 3	11 (20.7%) 14 (26.4%) 28 (52.8%)	7 (13.2%) 46 (86.7%)	Metamizole n=23
Activity Agitated Mild agitated Calm	1 (1.8%) 9 (16.9%) 30 (56.6%)	1 (1.8%) 46 (86.7%)	Tramadol n=1
Pain scores (M±SD) 0-12	4.35±3.35 Max-11 Min-0	2.9±1.94 Max-6 Min-0	

When analyzing the obtained data, the focus was set on the perioperative analgesic methods. There were patients who received other analgesics during anesthesia and patients who received no analgesics. Patients without analgesics consisted the control group (n=16); patients who received only paracetamol were group 1 (n=25); those with paracetamol and adjuvant group 2 (n=6) and with caudal block group 3 (n=5). The main idea was to find the differences in the analgesic scores between the groups. Groups were not homogeneous and hence, profound statistical analyses could not be done. The average values of the obtained pain scores are presented in Table 6. These values show that the use of caudal block provides better, but insignificant ($p>0.05$) analgesia in comparison to the other used preemptive methods.

Table 6. *Differences in pain scores in the groups (M ± SD)*

Analgesic method	Ages (y)	BW (kg)	Time (min)	Pain Scores	p
Gr 1 n=26 PCM	6.73 ± 4	29.38 ± 14	83.65 ± 28	3.73 ± 3	0.074445
Gr 2 n=6 PCM+	5.66 ± 3.26	23.3 9 ±10	105 ± 33	5.5 ± 3.5	0.442536
Gr 3 n=5 CB	5.3 ± 2.1	19.6 ± 4.5	82 ± 24	3.4 ± 3.9	0.16798
Control Gr n=16	5.37 ± 4.4	23.11 ± 5.4	81.3 ± 38	5.25 ± 3.5	0
p	0.31	0.44	0.48		

$p<0.05$ significant

Legend: **Gr 1-***received preoperative paracetamol;* **Gr 2-** *received paracetamol with adjuvants;*
Gr 3 – *received caudal block*
Control Gr – *patients without peroperative analgesia*

Discussion

This small and short study was focused on the early postoperative period (the first 6 hours), when patients are in the PACU and in the ward of CPS. The main features of the postoperative pain are that it is acute and severe, and exists at the first and the second postoperative day, with a tendency for progressive decline in the next few days (5). The first few postoperative hours are the most important when the pain is the most severe. In this period, the postoperative pain is in collision with the awakening from anesthesia which plays an important role in the process of experiencing pain by the children. All the components of the anesthesia, the premedication, the maintenance with opioids, and the intraoperative use of analgesics or regional anesthetics have their contribution in the process of postoperative analgesia (10).

Despite the advances in the development of the pharmacological novelties for efficient pain relief, the postoperative pediatric analgesia has stayed largely inadequate, which also has been demonstrated in this study (pain scores 4.35±3.35). Zemsky *et al*. in 2003 discussed that inadequate analgesia had a negative impact on children, with consecutive bad memories and disturbing outcomes (11). This knowledge has helped in understanding that an aggressive prevention of the pain during all procedures is the right way to the efficient postoperative pain relief. In addition to the general principles of the treatment, an adequate assessment is also necessary along with a multimodal approach to the treatment (12). In our study in PACU, parents cuddled their children, which made them to be calm and more confident and collaborative (13). In this context, the use of premedication, intraoperative supplements such as N_2O, opioids (fentanyl), analgesics and regional analgesic techniques are parts of this multimodal approach (14).

Fentanyl was used for induction in 98% of the cases and for maintenance of anesthesia as a supplement to sevoflurane in 95% of the patients, and this explains the relatively small need for additional analgesia.

When analyzing the effects of the intraoperative use of non-opioid drugs and regional techniques, it was found that methods for evaluation of the pain intensity were convenient. The participants were accommodated to the use of CHEOPS (Children Hospital of Eastern Ontario Pain Scale) and the Wong-Baker FACES pain rating scale. The evaluation of the pain showed that children who received caudal block immediately after induction, had the best scores (3.4 ± 3.9). These results are similar to those obtained in a previous study conducted by the same authors (15). Nowadays, the perioperative use of regional local anesthetic blocks (penile block, TAP and others) has an increasing trend and their use in pediatric anesthesia is preferred (16).

The intraoperative use of non-opioid drugs as preemptive analgesia, paracetamol with or without adjuvants, used in this study, also contributed to reaching better pain scores than in the control group (3.73±3 *vs*. 5.25±3.5). These differences were insignificant because of the non-homogeneous groups and the small samples. Adjuvants were used in 6 cases where surgery lasted longer (105±33 minutes) and the obtained pain scores were 5.5±3.5, which were worse than in the control group. The used adjuvants to paracetamol were midazolame 1 mg, given to all children

weighing over 10 kg, or tramadol 1 mg/kg, or corticosteroids (urbasone 1 mg/kg, dexasone 0.1 mg/kg) and Mg 25 mg/kg. All of them have properties to enhance the analgesic effects (17).

The used analgesics in the postoperative period in PACU and at the ward of the CPS were three non-opioids agents – paracetamol, metamizole and tramadol. In the literature, it is widely recommended the use of nefopam for postoperative pain relief, an analgesic with opioid sparing effect as paracetamol, which chemical structure is unrelated to the other analgesics. Its use in pediatric analgesia at a dose of 1-2 mg/kg IV bolus /6 h has been poorly studied, and is not used in our country (18). For a long period metamizole has been withdrawn from use because of its ability to provoke a life-threatening agranulocytosis. Its short usage as an analgesic for postoperative pain relief shows its favorable properties (pain scores in the ward were 2.9±1.94, ranging from 6 (max) to 0 (min)) (19).

Reports on the use of opioids for postoperative analgesia in children are controversial (20). In general, their use is advised in the patients with a very severe pain, as in cardiac surgery, spine surgery, pectus excavates and large orthopedic repairs. Rigorous monitoring is necessary, especially in cases where sleep apnea is present (16, 21). The major surgical interventions in this study were in the abdomen (M. Hirshprung, St post atresio oesophagi and ileus), where the combination of paracetamol with metamizole or tramadol provided a sufficient analgesia, without any influence on bowel movements.

The new analgesic techniques promote intraoperative use of anti-hyper-analgesic compounds – N-methyl-D-aspartate (NMDA) receptor antagonist as ketamine and gabapentin. Also, dexamethasone with its anti-inflammatory properties plays an important role in postoperative pain (22). One meta-analysis has confirmed that alpha 2 agonists (clonidine, dexmedetomidine) used as adjuvants to general or regional anesthesia have opioid sparing effect in postoperative anesthesia and can be used with success in pediatric surgery (23).

This study has shown that all participants in the study use different protocols, which is similar to the findings of a survey about the practices of pediatric surgeons in postoperative pain management (24).

Limitation of the Study

To obtain more accurate results, the number of the observed samples should be more than 100. This study was made in a short period of time, and only 58 anesthetized children were analyzed. More profound analysis included small (heterogeneous) groups, which caused difficulties in the interpretation of the results.

Conclusion

Recent postoperative analgesia was insufficient and not uniformed. Thereby, it emphasized the necessity of establishing a written postoperative analgesic protocol for general use (for anesthetists and surgeons in the ward at the Clinic of Pediatric Surgery). It should be based on

recommended guidelines, where the analgesic approaches are tailored in line with the diagnosis. This protocol providing tools for efficient pain assessment, and postoperative pediatric analgesia for all categories of operated children will enable unified use of analgesic drugs for efficient pain relief. The opening of an acute pain service working 7/24 is an urgent need and crucial for better postoperative analgesia of operated children. But, the benefits of this study are presentation of the current situation and recommendations concerning what should be done.

Acknowledgments

We thank anesthesiologists, participants in this survey who gave anesthesia in the study period in the pediatric operating theaters, which anesthetic lists were analyzed (Nadica Andonovska, Azbi Agushi and Marta Treneva). Thanks to the volunteer doctor Teodora Stojanovska who collected the data. Special thanks to Professor Rosalinda Isjanovska, whose consideration about the statistical approach and suggestions were very valuable.

Authors Contribution

MSh and VD designed the study; VD and LjD handled the organization of the study and were active participants in the study. DA and AK were active participants in the study and wrote some parts of the manuscript and designed the tables. VD and MSh gave the final approval of the study and the manuscript.

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CASE REPORT UDK: 616.37-006.2

RARE CASE PRESENTATION OF DERMOID CYST OF PANCREAS

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ABSTRACT

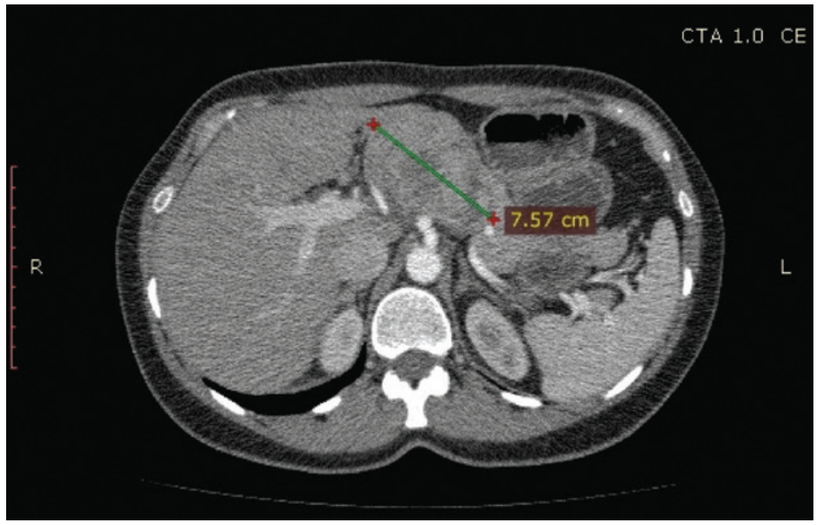
Teratomas are classified as either mature or immature, and according to tissue density can be classified to solid or cystic, also known as "dermoid cyst." Immature teratomas are generally solid, histologically undifferentiated malignant tumors. Mature cystic teratomas (MCTs) in the pancreas are extremely rare with small number of cases reported in the literature. The most common location of the mass is in the head/ body of the pancreas. Diagnosis of teratomas is challenging, since there are no peculiar imaging findings, or characteristic serum markers. We present a case of a 42-years-old woman with a mature cystic teratoma in the head of the pancreas incidentally found at ultrasound imaging, who after surgical treatment remained asymptomatic. This case emphasizes the necessity of specific diagnostic tools and increased awareness about MCT, when a pancreatic cystic lesion is disclosed.

Key Words: *dermoid cyst, laparotomy, pancreatic cyst.*

Case Report

A 42-years-old female patient was referred to the ultrasound department due to mild back pain for several weeks. Medical history did not reveal any relevant diseases or habits. On thorough physical examination, her abdomen was soft and no palpable abdominal mass was present. The laboratory findings including serum tumor markers: carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), were within normal range. Nonetheless, abdominal ultrasound disclosed well-defined retroperitoneal mass measuring 7.9 cm × 3.5 cm × 5.6 cm, adjacent to celiac trunk. The ultrasound appearance displayed mixed tumor pattern containing cystic and solid components, with absent vessels on color Doppler examination. Under the suspicion of pancreatic cystic tumor, contrast-enhanced CT scan was performed, revealing 7.5 × 4.6 cm bilobulated, homogeneously attenuating, low density retroperitoneal tumor (Figure 1).

Figure1. *Abdominal CT scan*



She was referred to the surgical department and few weeks later, laparoscopic treatment was performed. The precise origin of the tumor was determined intraoperatively; the cyst was found to arise from the pancreatic head, adherent to the stomach, celiac trunk and retroperitoneum. Radical tumor excision was achieved, and operative specimen measuring 8.8 × 4.3 × 5 cm revealed soft tissue mass encapsulated in a thin wall, containing yellow-whiteish material with a caseous appearance. Histological examination defined cystic lesion, lined by mature squamous epithelia with regular layer stratification, yet with different width. Beneath the surface, within the keratinous debris mixed sweat and adipose glands, rare hair follicles and multinuclear giant cells of "foreign body type" were present, suggesting mature cystic teratoma of pancreas. There was no evidence of malignancy. The final diagnosis was dermoid cyst of pancreas. Postoperative course was uneventful; patient was discharged 7 days after surgery. At 12 and 24-months follow-up, she was asymptomatic, in excellent condition, without any evidence of recurrence.

Discussion

Pancreatic dermoid cysts are exceptionally rare, about 50 cases have been reported in the literature since 1918, when the first case was published by Kerr and al., in 55 years old female patient (1). Pancreas is the slightest possible primary site of extragonadal teratomas. Diagnosis of teratomas is challenging due to absence of precise preoperative diagnostic tools or pathognomonic findings.

The most common physical finding is a palpable abdominal mass and/ or abdominal tenderness. Sometimes symptoms arise from the "mass effect" or pressure of the tumor lesion on neighboring organs/ tissues. Tumor usually arises in the head (44%) or body of the pancreas. Tail is on the third place by frequency, with only 12% (2). The lack of pathognomonic findings and insufficient diagnostic tests, make these pancreatic tumors hard to be recognized (3). An

imaging classification system has been proposed based on morphologic features of the lesion (4). Apart from patient's clinical presentation, treatment decision is influenced by tumor size and location, tumor histological features, patient's age and performance status and surgical risk.

Teratomas are germ cell tumors arising from a pluripotent stem cell, derived from at least two of the three germinative layers (ectoderm, endoderm and mesoderm). These tumors originate from some deviant germ cells (at the time of neural groove closure) that have been stopped during embryonal migration towards the gonads. Commonly teratomas are classified as mature, immature and specialized or monodermal. This classification is taking into account tissue components and tumor maturity. The nature of mature teratoma is benign, since its components are mature tissues, likewise immature teratoma comprises of undeveloped tissues that are mitotically active and generally considered as malignant. The third type of monodermal or specialized teratomas are usually subtype of mature teratomas. Further division is according to tissue density, either solid or cystic, later known as "dermoid cyst".

Dermoid cysts, the most commonly develop within the ovaries and testis, however extragonadal localization in cranium, neck, mediastinum, omentum, retroperitoneum and sacrococcygeal region have been described (5,6).

Patients with pancreatic cyst may complain on nonspecific gastrointestinal symptoms such as abdominal pain, pain in the back, nausea, vomiting, weight loss, anorexia, fatigue, and fever (7). Laboratory findings are usually non-specific, unless the lesion obstruct the flow of biliary or pancreatic fluid. Serum levels of CEA and CA19-9, which are traditionally used for the evaluation of cystic neoplasms of the pancreas, are considerably low in patients with dermoid cysts, like in our case. Dermoid cysts of the pancreas are true cysts with wall lined by a single layer of keratinizing stratified squamous epithelium, while the underlying tissue content may have elements of adnexal tissue, sebaceous glands, lymphoid tissue, and even inflammatory cells (8).

The differential diagnoses of pancreatic cystic lesions include pseudocysts, benign cystic tumors like mucinous and serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN), as well as neoplastic cysts and solid pseudopapillary tumor. Although ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are helpful, findings are not usually pathognomonic (9,10). Mucinous cystic neoplasm (MCN) are true cystic neoplasms developed separate from the ductal system. Serous cystadenomas might be microcystic or macrocystic. Intraductal papillary mucinous neoplasm (IPMNs) composed from mucin-producing columnar cells and grosser than 10 mm have a malignant potential. The lesions show papillary proliferation, cyst formation, and varying degrees of cellular atypia (11). Solid pseudopapillary tumors are rare type of pancreatic lesions that are histologically characterized by the presence of degenerative pseudopapillary, loosely cohesive cells with grooved nuclei and aggregates of large hyaline globules (12). A completely different entity like lymphoepithelial cysts, the mostly located in the pancreas (tail and body, followed by the head and neck), relates dermoid cysts, and may be distinguished by the absence of hair follicles or sebaceous glands, which are more frequently

associated to the later one. Moreover, mucinous epithelium, hair follicles and sebaceous glands are found in dermoid cysts, rather than in lymphoepithelial or epidermoid cysts. One more particular feature in favor of dermoid cyst is presentation with suppurative infections, which is not so frequent in other "squamous lined" pancreatic cysts (13).

Final diagnosis of MCTs is established with histopathological evaluation, that includes complete sampling of the cystic wall. 7 – 10% of retroperitoneal teratomas have been reported to be malignant (14). Therefore, whenever a pancreatic cyst is intraoperatively suspected for being a teratoma, total resection is imperative (15). When the course of the disease is poor, or the tumor is inaccessible for total excision, partial excision and external drainage, can be performed (16).

Fortunately, in our case total excision of MCT was successfully and even more favorably, laparoscopically performed.

Conclusion

Dermoid cysts of pancreas are the mostly benign lesions. Macroscopically the tumors can be mobile or fixed, firm or cystic, and smooth or nodular. Only small percentage of mature teratomas may develop into malignant forms. The differential diagnosis includes all other cystic lesions of the pancreas, serous and mucinous cystadenomas, papillary cystic neoplasms, and pancreatic pseudocysts. Management of cystic pancreatic lesions depends of their nature and size; the patient in our case was appropriately referred to surgery for further treatment. We can conclude that "awareness of existence of cystic teratomas of pancreas" is the clue for the correct diagnosis of these tumors.

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HIGH ENERGY TRAUMA OF THE UPPER EXTREMITY WITH TRACTION INJURY OF THE BRACHIAL PLEXUS

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ABSTRACT

As a severe peripheral nerve injury, brachial plexus lesion can cause limitation in every-day home and workplace activities. Hereby, we present a patient with high-energy trauma of the upper extremity. The examination showed motor weakness of the upper extremity and no flexion and extension in the wrist and fingers with sensibility impairment. The examination and mechanism of injury indicated traction lesion of the brachial plexus. MRI showed postganglionic stretch injury. Treatment of choice was physical therapy. To evaluate the function of the upper extremity after the injury, we used the DASH score. Four months post injury, the patient has flexion and extension in the wrist and fingers. The mechanism of injury and the magnitude of forces that caused the injury can guide as to the extent of the brachial plexus lesion. Analyzing the acquired information, a plan for initial treatment can be established. On point treatment can increase patient's quality of life with better outcome.

Introduction

High energy trauma is the most common cause of brachial plexus palsy in adults. As severe peripheral nerve injury, it causes functional damage because movements in the shoulder, arm, wrist, hand and fingers, as well as sensations are controlled by the brachial plexus (1).

Number one cause for brachial plexus injury are the motorcycle accidents, followed by workplace accidents, sports injuries, gunshot wounds and inappropriate operating positioning. From patient's point of view it is also devastating, causing significant loss of function and ability to perform tasks in daily living, home or work related (2).

The treatment and the outcome of these kinds of injuries are different, depending on the severity of the lesion and the timing of intervention. This paper presents a case with work place associated injury. It aims to show how cases can present and how can be followed and rehabilitated.

Case Presentation

Fifty-nine-years old patient was referred to our clinic with injuries inflicted by metal cutting machine with rollers and belts on the same day of the injury. Initial examination showed avulsion of the skin on the right scapula with deltoid muscle lesion and bone fragments of the scapula. The injured tissues and surrounding skin showed second degree burns by the heated belt. Another skin injury on the right elbow was present with a 2 cm long laceration.

Further physical examination showed neurological deficit of the right arm including limited range of motion in the elbow and no active motor function in the wrist and fingers. The patient reported no pain, only impaired pins and needles sensation. There was no abnormality of the radial and ulnar pulse. Differential diagnosis of closed traction lesion of the brachial plexus was obtained based on initial assessment and the type of injury. Plain X ray was done that confirmed an avulsion fracture of the acromion. No other fractures were noted.

The patient was admitted and operated under monitored anesthesia care. Operative treatment was performed only to attend the wounds. A debridement of the wounds and primary closure was done. The burned skin area was treated conservatively with Vaseline gauze dressing. The brachial plexus injury was initially managed by putting the affected arm in a sling.

An MRI was performed 24 hours after the injury. Although the findings were limited, it showed no neurotmesis and indicated postganglionic stretch injury of the plexus. An EMG was performed 3 weeks after the injury suggesting that the lesion is not degenerative. Based on the findings, no surgical treatment was indicated.

During the hospitalization, the patient was regularly examined and the brachial plexus injury was evaluated. To assess the function of the upper extremity after the injury, we used the DASH **(Disabilities of the Arm, Shoulder and Hand)** score through detailed DASH questionnaire. The patient was asked about performing different physical activities, both work obligations and self-care. The scale score ranges from 0 to 100. Zero meaning no disability, to 100 meaning complete disability (3). Some motor function in the fingers was already noted on the fifth day after the injury. The DASH score measured 87.5. Physical therapy was immediately started and continued after discharge. Regular check-up appointments and evaluation were done. Additional surgical treatment with skin graft was advised for treatment of the burn on the right shoulder; however the patient declined it and therefore conservative treatment with dressings was continued.

The EMG done seven weeks after the injury confirmed the clinical improvement and showed signs of spontaneous recovery. Four months post-injury, the range of motion in the elbow was normal, fingers' and wrist's flexion and extension were present. No pain was noted. The DASH score five weeks after hospital dismissal was 10.

Discussion

The most common cause of adult traumatic brachial plexus injury is closed trauma with the mechanism being either compression or traction. If the brachial plexus injury is caused by traction, the nerve may be avulsed from the root, injured or significantly stretched. It can be presented with complete paralysis or some other form of motor, sensor of sympathetic disturbance. Impairments can be transient or may result in intractable palsy. The other concern is the level of the injury

which can be preganglionic, postganglionic or a combination of both (4). The postganglionic injury is also divided in two groups: supra and infraclavicular.

The type of injury is determined by the position of the upper limb. Enquiring the patient's position during the injury will lead us to the mechanism of injury. The level of injury can be determined by the movements of the shoulder, upper arm, lower arm, hand and wrist. This will show which part of the brachial plexus is injured, whether it is upper or lower brachial plexus injury. Signs of Horner's syndrome and sensory dermatome distribution should also be checked.

This patient was injured with a metal cutting machine and his upper limb was elevated and pulled by the belts of the machine. The initial physical examination showed motor and sensory impairment of the upper limb. Shoulder's abduction and elbow's flexion and extension were partially impaired, while no wrist and fingers' flexion and extension were noted. After detailed examination assessing both motor and sensory components of every muscle group and based on the mechanism of injury, a diagnosis for postganglionic infraclavicular lesion of brachial plexus was noted. The axillary artery is located too close to the lateral, medial and posterior cord and up to 50% of the infraclavicular brachial plexus lesions have accompanying artery rupture. After examination of the radial and ulnar pulse, if any abnormality is noted, vascular imaging as arteriography or angiography should be performed (5). This was not the case here.

After physical examination, radiographic evaluation should be included. Plain standard X ray will show fractures of the clavicle, spine, ribs, scapula or humerus. Depending on the concomitant injury and type of injury (pre or postganglionic) decision for priority of treatment is made.

MRI is one of the modalities that currently is the mostly used to evaluate brachial plexus injury. It is noninvasive, and shows high image quality of the brachial plexus (2). Especially, it is useful for postganglionic brachial plexus visualization and distinguishing benign or malignant lesion. One of the most important investigation and valuable to make surgical and therapeutic decision is Electromyography (EMG). EMG as a diagnostic tool can help to determine if the lesion is complete, can determine the severity of axon lesion and localization of the lesion. EMG is performed within 4 to 6 weeks after the injury, to register spontaneous recovery after closed traction injury (6). The decision of the used modality of investigation is still the preferred choice of the clinician.

Based on the clinical manifestation and results of the MRI and EMG, a conservative strategy for treatment was indicated. Conservative management consists of extensive physical therapy and use of assistant devices as splints or slings to prevent uncontrolled passive movements of the affected upper limb.

Follow up of the patient is mandatory to evaluate the outcome of the treatment. Being a very limiting condition with everyday activities and work life, DASH score can be used to determine the severity of the injury. The Disabilities of the arm, shoulder and hand (DASH) outcome measure is a 30-item questionnaire that seeks information about the ability of the patient to execute different kinds of activities ranging from eating, doing sports, writing, cutting grass.

The DASH score was published in 1996 in the American Journal of Industrial Medicine. It can present function and symptoms in patients with muscle disorders of the upper limb. At intervals defined by the examiner, it can evaluate changes in physical function (3). After the decision of treatment, regular appointments with the patient were kept. Extensive physical therapy, clinical follow up based on the DASH score and EMG studies, showed good recovery.

Conclusion

Brachial plexus palsy in adults is a result of a high energy trauma in the majority of cases. Detailed clinical assessment guides us to more precise diagnosis. The mechanism of injury and the magnitude of forces that caused the injury are a good indicator as to the extent of the brachial plexus lesion. Analyzing the acquired information, a plan for initial treatment can be established. Additional guidance in injury management can be obtained with MRI and EMG. On point treatment can increase patient's quality of life with better outcome. That is why physical examination and diagnosis are key points of type of treatment for brachial plexus injury.

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AUTOIMMUNE HEMOLYTIC ANEMIA IN A COVID 19 PATIENT

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ABSTRACT

The specific case at hand, which is the first case reported in North Macedonia, combined with prior literature review, describes that COVID-19 infection can be associated with AIHA.

This case involves a 63 years old male patient with diabetes mellitus type 2 (DM2) and essential hypertension (HT) who tested polymerase chain reaction (PCR) positive for COVID-19 infection. Seven days prior to hospitalization, the patient had already been receiving symptomatic and antimicrobial therapy in order to treat symptoms of fever, headache and cough. He was admitted to hospital with confirmed bilateral bronchopneumonia demonstrated with chest x-ray.

His hospital stay was complicated by autoimmune hemolytic anemia (AHIA) and chest pain. Normocytic anemia and hyperbilirubinemia were confirmed. D-dimer and C-reactive protein were elevated. During his hospital stay, patient's hemoglobin decreased from 103 g/L to 54 g/L, and further workup demonstrated lactate dehydrogenase up to 2209U/L and creatinine kinase levels up to 224U/ml. He was treated with dexamethasone and acid folic, also substitution for AIHA was implied with decanted erythrocytes. Inflammatory markers were down-trended and hemoglobin stabilized.

Key Words: *Autoimmune hemolytic anemia, Covid-19*

Introduction

The current COVID-19 pandemic which was initially reported in the Chinese province of Hubei and has rapidly spread throughout the world, has caused situations that have generated social changes in the normal dynamics of life for the general population, not excluding healthcare workers in particular (1).

Until today, in the Republic of North Macedonia there have been registered approximately 190,000 patients with COVID-19, out of which 170,000 have been cured and 6,600 died.

COVID-19 disease manifests wide range of clinical implications, starting with classic symptoms of fever, dry cough, dyspnea and various complications, such as: pneumonia and acute respiratory distress syndrome, renal failure, thrombosis, cardiomyopathy, acute pancreatitis and 'long COVID 19'. Another described, but rare complication is AIHA, usually in patients with comorbidities, such as hematologic, autoimmune, malign and various infectious disease (2). This is a phenomenon that needs further exploration due to prevalence, but also for treatment and clinical features (3,4).

The patient has no other major risk factors that would indicate hemolysis, such as malignancy or hematologic dyscrasia or exposition to medications known to cause drug induced AIHA. This case highlights the importance of laboratory data such as hemoglobin, D-dimer, lactate dehydrogenase (LDH), creatin kinase (CK), neutrophil/ lymphocyte ration as markers of prognosis and severity of COVID-19 infection.

Case Presentation

A 63-years-old male, without addictions, with a history of uncontrolled DM2 insulin dependent and essential HT presented to the emergency room complaining of dyspnea headache, cough, chest pain and fever in the preceding days. His COVID-19 PCR testing by nasopharyngeal swab was positive. He was admitted to the Clinic of Infectious Diseases (COVID-19 department). Symptoms were present 7 days before testing, and 5 days before hospitalization, fever of 38.5°C and dry cough were noted. He had been treated with symptomatic and antimicrobial therapy, Azythromicyne for 6 days and Cefixime for 2 days. On admission, his blood pressure was 130/65 mmHg, heart rate 88/min, respirations 20/min, temperature 37.6°C, O_2 saturation was 96% without need of oxygen supplementation. Despite regular chronic antihypertensive drugs (Enap 10 mg 2×1) and insulin (Humulin 26ie+0+14ie), it was started with antimicrobic therapy of the third generation cephalosporine and thromboprophylaxis therapy with low molecular heparin (Enoxaparine). Chest x-ray showed left side bronchopneumonia with need for hospital treatment according to Pneumonia Severity Index (Figure 1a and 1b). His blood tests on admission and during hospital treatment are shown in Table 1.

On D-5 of admission, we noticed deterioration of condition with development of jaundice of skin and eyes, dyspnea, without bleedings or melena, but with need for oxygen supplementation with oxygen face mask (6l/min, SpO2 94-96%). Routine blood analysis showed decrease on hemoglobin levels to 63 g/L with progressive reduction in the next two days, high levels of total bilirubinemia 88 mg/dl with predomination of indirect bilirubinemia 63 mg/dl, lactic dehydrogenase 1883U/ml and creatine kinase levels 224U/ml with progressive elevation during next two days. Hematologic examinations showed Coombs positive autoimmune hemolytic anemia. The lowest hemoglobin level was 54 g/L, mean corpuscular volume (MCV) 104, rise on reticulocyte presentation (13%), peripheral blood mask with neutrophilia, 3% erythroblasts, macrocytosis and anisocytosis, positive direct and indirect Coombs test (DAT). The findings in laboratory examinations confirmed AHIA, so the treatment was started with corticosteroids (intravenous dexamethasone 8 mg twice daily) and substitution with decanted erythrocytes.

On D-8 of hospitalization the patient complained for chest pain, and cardiologic evaluation was performed (electrocardiogram, troponin levels 110 … 89,4pg/ml, CK-MB 21U/l) and acute myocardial injury was excluded. The antihypertensive drugs by cardiologist recommendation were switched on calcium channel blocker (tbl. Amlopin 10 mg 1×1) (Figure 2a/2b).

Hemoglobin levels started to rise on D-7 of treatment with dexamethasone and after substitution with 4 doses of erythrocytes. He was also successfully weaned off the supplemental oxygen (SpO2 96-97% on room air). Afterwards the treatment of hemolysis was switched with oral glucocorticoid (tbl. Prednisone 1 mg/kg body weight) with weekly reducing of doses for 10 mg. Treatment with oral glucocorticoid lasted 10 weeks until the levels of hemoglobin and reticulocytes were normal. The hematologic evaluation lasted for three upcoming months. The patient was successfully discharged on D-22 with normal values of hemoglobin and bilirubin, with resolution of malaise and resolution of icterus. After discharge the patient was continuously on hematological check-up for a period of 10 weeks.

Figure *1a/1b*

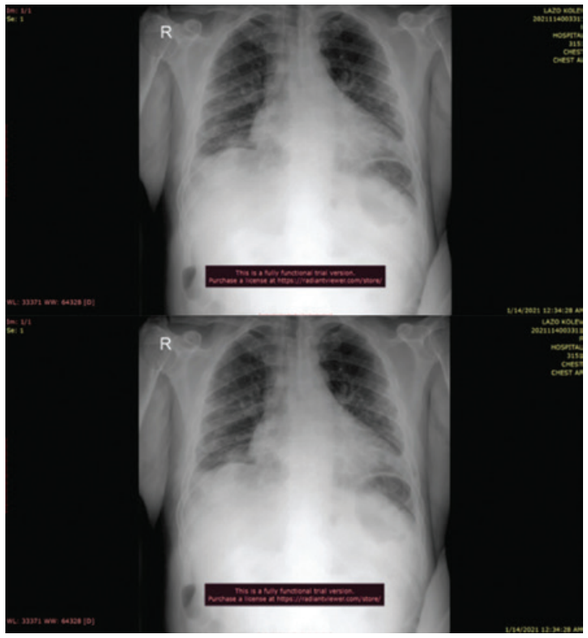
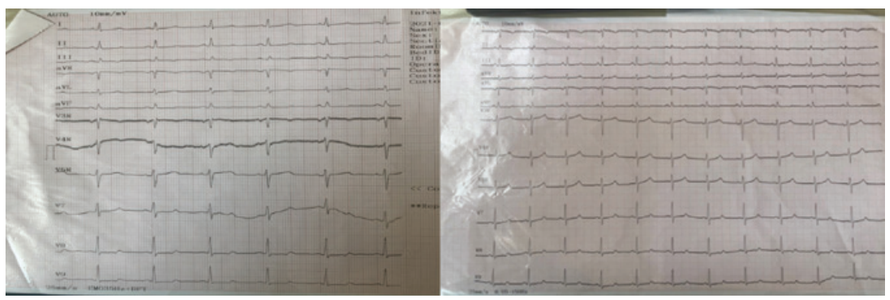


Figure*2a/2b*



Variable	Reference	07.01.20	11.01.20	12.01.20	13.01.20	15.01.20	19.01.20	25.01.20	29.01.20
Hb(g/l)	(115-180)	103	63	54	75	138	136	129	132
RBC (x10-3)		2960	1620	1500	2030	4360	4510	4140	4200
WBC (x10-3)	(4.0-11.0)	8.3	43.8	53	51.5	26.5	8.4	7.7	7.9
Platelet (x10-3)	(150-400)	458	887	889	675	432	294	376	277
Hem (%)	(41-50)	0.28	0.16	0.14	0.2	0.38	0.39	0.37	0.39
Neut	(0.25-0.70)	0.65	0.74	0.73	0.72	0.75	0.66	0.68	0.74
Lymphocytes	(0.21-0.25)	0.24	0.17	0.18	0.21	0.19	0.20	0.21	0.17
Monocytes		0.11	0.09	0.09	0.07	0.06	0.12	0.11	0.08
NLR		2.8	4.3	4.0	3.4	3.9	3.3	3.2	4.3
CRP (mg/l)	(0-10)	171	21		23		4	1	
CK(U/l)	(30-170)	49	224		240		130	20	
LDH (U/ml)	(120-246)	470	1883		2209		807	352	
ALT(U/l)	(10-52)	37	66		47		94	78	
AST(U/l)	(10-47)	46	76		52		41	18	
Potassium (mmol/l)	(3.5-5.5)		4,6		4.2		4.2	5.3	
Sodium (mmol/l)	(135-145)		136		134		130	135	
Globulines (g/l)	(20-35)		31		29				
Albumines (g/l)	(34-54)		30		28				
Tot. proteins (g/l)	(60-83)		60		58				
Lipases (U/l)	(60-140)		215		125				
GGT(U/l)	(0-30)		100		85		116	130	
Amylase(U/l)	(40-140)		99		133				
AP(U/l)	(60-142)		95		84				
Ind. bilirubin (mmol/ll)	(1.71-20.5)		57		27		20	14	
Direct bilirubin (mmol/l)	(1.7-5.1)		31		15		5	4	
Tot. bil. (mmol/l)	(3.4-12.0)		88		42		29	18	
Creatinine (mmol/l)	(30-170)		62		55		48	52	
Urea (mmol/l)	(1.7-8.3)		9.7		7.2		7.2	6.6	
Fe+(mmol/l)	(12.5-26)				39.9		21.4	22.6	
Calcium (mmol/l)	(2.2-2.7)				2.04		2.12	2.23	
Glucose (mmol/l)	(3.9-5.6)				18		11.8	10.5	
CK-MB(U/l)	(5-25)				21		19		
Troponin I (pg/ml)	(<34.2)				110.3	89.4			

Variable	Reference	07.01.20	11.01.20	12.01.20	13.01.20	15.01.20	19.01.20	25.01.20	29.01.20
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Neut	(0.25-0.70)	0.65	0.74	0.73	0.72	0.75	0,66	0.68	0.74
Lymphocytes	(0.21-0.25)	0.24	0.17	0.18	0.21	0.19	0,20	0.21	0.17
Monocytes		0.11	0.09	0.09	0.07	0.06	0,12	0.11	0.08
NLR		2.8	4.3	4.0	3.4	3.9	3.3	3.2	4.3
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Lypases (U/l)	(60-140)		215		125				
GGT(U/l)	(0-30)		100		85		116	130	
Amylase(U/l)	(40-140)		99		133				
AP(U/l)	(60-142)		95		84				
Ind. bilirubin (mmol/ll)	(1.71-20.5)		57		27		20	14	
Direct bilirubin (mmol/l)	(1.7-5,1)		31		15		5	4	
Tot. bil. (mmol/l)	(3,4-12,0)		88		42		29	18	
Creatinine (mmol/l)	(30-170)		62		55		48	52	
Urea (mmol/l)	(1.7-8.3)		9.7		7.2		7.2	6.6	
Fe+(mmol/l)	(12.5-26)				39.9		21.4	22.6	
Calcium (mmol/l)	(2.2-2.7)				2.04		2.12	2.23	
Glucose (mmol/l)	(3.9-5.6)				18		11.8	10.5	
CK-MB(U/l)	(5-25)				21		19		
Troponin I (pg/ml)	(<34.2)				110.3	89.4			

Table 1: Laboratory parameters during hospital day (RBC – red blood cells, WBC – white blood cells, NLR – neutrophil lymphocyte ratio, CRP – C reactive protein, LDH – lactic dehydrogenase, CK – creatin kinase, GGT-gama glutamil transferasa, AP-alkaline phosphatase)

Hemostasis (06.01.2021): Tr 307; Htc:31.8%; PT:10.77s; APTT-32.5s; TT-17.6; D-dimer 1090.74 ngr/ml;

Hemostasis (11.01.2021): Tr 655; Htc:15.8%; PT:13s; APTT-21.9s; TT-19.2s; D-dimer10192 ngr/ml;

Hemostasis (18.01.2021: Tr 256; Htc:40.3%; PT:11.25s; APTT-22.3s; TT-25.3s; D-dimer 1053 ngr/ml;

Hemostasis (25.01.2021): Tr 306; Htc:37.5%; PT:13.4s; APTT-25.9s; TT-25.7s; D-dimer 983.9 ngr/ml;

Clopidogrel test (P2Y)[s]{0-106} : 49 :P: AntiXa-therapy [IU]{0,5-1,2}: 0.1.

Table 2. *Laboratory findings after discharge*

	Variable					
Day		04.02.21	25.02.21	11.03.21	01.04.21	22.04.21
Hb	g/l	139	144	149	127	135
Le	10-3	14.5	10.9	10.5	10.2	5.4
Tr	10-3	173	197	217	484	271
Rt	%	3.6	2.7	2.3	3.7	
Ly	%			5.1		
MCV	Fl				90	
Glycemia	mmol/l	13	19		8.0	18.0
d-dimer	ngr/ml	260	250	340		680
AST	U/l		30			
ALT	U/l		104			

Discussion

Autoimmune hemolytic anemia is an autoimmune disease as result of specific autoantibodies towards specific antigens in the surface of erythrocytes, that results in breakdown of erythrocytes. AIHA can be primary or idiopathic, and secondary due to other autoimmune disorders, such as malignancies and infections. Some studies have demonstrated AIHA as complication in COVID-19 positive patients without underlying malignancies or autoimmune disorders. The etiology of hemolytic anemia is unknown, but various genetic and ambient factors can play role in the development of the disease. To the best of our knowledge, we reported the first case of autoimmune hemolytic anemia during COVID 19 infection in our country.

According to a study conducted in few clinical centers in the Saudi Arabia, anemia is a risk factor for development of severe COVID-19 infection. AIHA is one of the reasons for developing anemia. Recent results showed that 14% of patients with anemia in the intensive care units and 9% in the non-intensive care, have had positive direct antiglobulin test and spherocytosis (5).

The median time between the first COVID-19 symptoms and AIHA onset is nine days (range 4-13 days).

Autoimmune hemolytic anemia is second by frequency autoimmune disease, after autoimmune thrombocytopenia. Both of the autoimmune diseases often appear in the fold of other diseases, such as malign lymphoproliferative or different infectious diseases, the most often caused by viruses. Pathogenesis of autoimmune hemolytic anemia is multifactorial and involves disturbances of regulatory and autoreactive B and T lymphocytes.

AIHA is an acquired rare condition that develops when autoantibodies are produced against self-antigens on the RBCs, condition which leads to their destruction by the reticuloendothelial system or complement-mediated cell destruction. Many infectious diseases caused by bacteria or viruses, such as Cytomegalovirus, Epstein-Barr virus, Coxsackie virus, Parvovirus B19, Hepatitis C virus, mycoplasma and several concurrent lymphoproliferative disorders, can provoke AIHA. However, the exact mechanism behind this viral-induced cell destruction is unknown, although the most trusted one might be attributed to molecular mimicry, which leads to self-reactive lymphocytes and unresponsiveness to self-antigens (6,7).

Common laboratory findings in AIHA include anemia, which can range from mild to severe depending on hemolysis. Platelet count and white blood cell count are usually within normal limits, even though counts can be low in some cases of bone marrow suppression from viral infection. Peripheral smear is remarkable for red cell agglutination and spherocytosis. As result of hemolysis, bone marrow responses with increased reticulocyte count. LDH and indirect bilirubinemia is elevated. The positive direct antiglobulin test (DAT) represents attachment of complement C3D and immunoglobulins IgG, IgM, IgA to erythrocyte membrane (8).

Our aim in presenting this case is to remind clinicians of the importance on recognizing AIHA as a potential sequela of COVID-19 and to monitor positive patients in the future to hasten treatment and predict the clinical course potentially. A systemic review by Taherifard et al. (2021) highlighted the association of COVID-19 to autoimmune anemias with stress on testing for COVID-19 in sudden anemias in appropriate clinical settings (9).

Conclusion

The association between AIHA and COVID-19 remains to be elucidated. In many cases, AIHA occurred in COVID-19 positive patients with a history of malignancies or autoimmune comorbidities. However, more research is required to examine the link between COVID-19 and AIHA in patients with minimal or no comorbidities.

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MATERNAL LOW-GRADE INFLAMATION AND ADVERSE EFFECT ON PREGNANCY

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ABSTRACT

Aim: Maternal chronic inflammation in recent years has been blamed as key reason for poor obstetric outcomes. It was proposed that pathogens or inflammatory mediators could reach to the fetus triggering adverse pregnancy outcome. C-reactive protein (CRP) is a marker of infection and inflammation. This study was designed to evaluate whether the elevated level of CRP in the first and in the third trimester influenced the incidence of preterm delivery and fetal growth restriction.

Material and Methods: Acase-control study, 110 pregnant women with single live pregnancy were recruited at our hospital. These women had undergone CRP analysis during the antenatal visits for the first trimester, Down syndrome screening, and again in 32nd-33rd week of pregnancy.

Results: The levels of CRP in the first semester tended to be higher in the preterm delivery patients and patients with fetal growth restriction compared to the term deliveries. Elevated CRP in the third trimester (Wald=4.58 / p<0.05 (p=0.03)), had the greatest impact on the preterm delivery. Pregnant women who had increased CRP values by 7.76 times (Exp (B)=7.76) in the third trimester are more likely to experience preterm delivery than pregnant women who had normal CRP values. The impact of maternal CRP is significant (95.0% CI: 1.19-50.65 / p<0.05). Elevated levels of CRP during the third trimester of pregnancy lead to increased risk for preterm delivery and fetal growth restriction. Further studies need to explore the role of chronic inflammation and maternal immune response, because if we understand the pathological mechanisms, we will know how to prevent adverse pregnancy outcomes.

Key Words: C-reactive protein, fetal growth restriction, preterm delivery

Introduction

The preterm delivery and low birth weight children are the main cause of perinatal mortality and morbidity in the world, which represents a significant medical and economic burden on the society (1,2,3). There is evidence that the infection and low-grade inflammation from distant sites of the fetoplacental unit may play a role in adverse obstetric outcomes. Maternal chronic infection, caused by imbalance of endogenous flora, can cause chronic low-grade inflammation in the body. Anaerobic human flora causing chronic inflammation are suspected of being able to spread into the amniotic cavity, or acting indirectly through systemic dissemination of inflammatory mediators and prostaglandins, and can lead to a negative outcome of a pregnancy. Today, scientific evidence suggests that this inflammation, can impact fetal wellbeing (4,5). Immune regulatory changes in the early pregnancy prevent maternal immune response towards the fetus, tuning the immune system to a new level (6). CRP is a nonspecific acute-phase reactant and sensitive serum marker of systematic inflammation (5). CRP levels increase in infection and in the response tononinfectious exposures. Elevated CRP levels are associated to increased risks for cardiovascular disease, diabetes type 2 and other chronic disease in the human, and in pregnant women with increased risks for adverse pregnancy outcomes (7,8). Several studies have shown association between elevated CRP and preterm birth and fetal growth restriction, but other did not show the same association (9,10,11). The purpose of this study is to determine whether elevated level of CRP in mother in the first and in the third trimester affects the onset of a poor outcome of pregnancy, such as preterm delivery and intrauterine growth retardation.

Materials and Methods

In the study, 110 pregnant women with single live pregnancy were recruited at our hospital at the antenatal visit for the first trimester Down syndrome screening. In this visit, the participants had undergone CRP blood analysis. The second blood analysis was at 32nd-33rd week of pregnancy. The participants were followed-up until delivery to observe the study outcomes.

Inclusion criteria: pregnant women from 11 to13 week of pregnancy, with single live pregnancy.

Exclusion criteria: multiple gestation, uterine anomaly and surgery, history of second trimester abortion or preterm delivery, cerclage in present pregnancy, history of SGA births.

Methods: The gestational age of the subjects was assigned using menstrual history and the first trimester sonographic findings in which the crown-rump length was measured. Maternal venous blood samples were collected at the antenatal visit and transported to the hospital laboratory for processing with high sensitivity enzyme-linked immunosorbent assay (ELISA).

Information about gestational age at birth, weight and gender, of the newborn was obtained from medical records.

The data was analyzed with the SPSS computer program (version 17). In the analysis of the series with attribute data, percentages of the structure (%) were determined, and the differences between the three groups were tested using the Pearson Chi-square test, the Fisher Exact test/ Monte Carlo Sig. (2-sided), (p). In the series with numerical data, Descriptive Statistics was developed, the distribution of data was tested with: Kolmogorov-Smirnov test; Lilliefors test; Shapiro-Wilks test (p), and the differences between the three pregnant groups of certain parameters were tested with Kruskal-Wallis Anova (H/p). In assessing the predictive values of certain parameters for preterm delivery and birth of babies small for gestational age and birth weight of a child <2500 grams, Logistic regression analysis (Wald, Exp (B), 95.0% CI for Exp (B), p). The significance is determined by p <0.05.

Results

Out of the 110 pregnant women enrolled in the study, 78% was with normal weight born fetus at term, preterm birth – 14% and SGA births – 8%.

The women in the SGA group are statistical younger than women in the other 2 groups, which was statistically significant. There was no significant difference in the level of education and family socio-economic situation. Maternal age of the study population is shown in Table 1.

Table 1. *Maternal age of the study population (n=110)*

	Group I (n = 86)	**Group II** (n = 15)	**Group III** (n = 9)	**P**
Maternal age ± SD	29.9 ± 4.5	29.9 ± 5.2	27.6 ± 4.5	p>0.05

Group I – women delivered at term and baby weighted more than 2500 gr,
Group II-women with preterm birth,
Group III – women delivered SGA baby.

There was significant difference in BMI between the Groups as shown in Table 2.

Table 2. *BMI in pregnancy*
Multiple Comparisons p values

Group	II R:52.06	III R:41.50	I R:63.85
II		0.68	0.24
III	0.68		**0.02**
I	0.24	**0.02**	

The level of CRP shows statistically significant difference between the groups, as shown in Table 3.

Table 3. *CRP in the first and in the third trimester*

CRP level	**GroupI**	**GroupII**	**Group III**	**P**
in first trimester ± sd	3.58 ± 1.22	4.94 ± 2.13	4.93 ± 1.90	p=0.006
in third trimester ± sd	4.40 ± 2.51	5.73 ± 3.26	5.45 ± 1.64	p=0.001

p – Pearson Chi-Square.

In determining the predictive values of antenatal the first trimester CRP and the third trimester CRP for preterm delivery, the enter method was used. The global accuracy of this model for predicting preterm delivery is 70.00%. The sensitivity is 34.80% and the specificity is 91.90%. The third trimester CRP (Wald=4.58 / p<0.05 (p = 0.03)), had a greater impact on a preterm delivery, than the CRP in the first trimester (Wald=2.31/ p>0.05).

Pregnant women who have increased CRP values by 7.76 times (Exp (B) = 7.76) in the third trimester are more likely to have preterm delivery than pregnant women who have normal CRP values. The impact of maternal CRP is significant (95.0% CI: 1.19-50.65/ p<0.05) (Table 4).

Table 4. *Predictive value of CRP for preterm delivery*

CRP Step 1[a]	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
CRP first trimester(1)	- 1.21	.80	2.31	1	.13	.30	.06	1.42
CRP third trimester(1)	2.05	.96	4.58	1	.03	7.76	1.19	50.65
Constant	- 2.02	.68	8.97	1	.00	.13		

In determining the predictive values of CRP level for SGA babies the enter method was used. The global accuracy of this model for predicting SGA is 65.00%.

Pregnant women who have increased CRP values by 2.30 times (Exp (B) = 2.30) in the third trimester are more likely to give birth to SGA babies than pregnant women who have normal CRP values. The impact of maternal CRP was not significant (95.0% CI: 0.38-13.74 / p>0.05) (Table 5).

Table 5. *Predictive value of CRP for SGA*

CRP Step 1a	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
CRPfirst trimester (1)	-.11	.71	.02	1	.88	.90	.22	3.63
CRPthird trimester (1)	.83	.91	.83	1	.36	2.30	.38	13.74
Constant	-.81	.49	2.75	1	.10	.45		

Discussion

Results from our study showed that antenatal maternal serum CRP levels in the third trimester of pregnancy are useful predictor of adverse pregnancy outcomes. This statement is seen in other studies that measured the antenatal maternal serum CRP levels inpregnancy (7, 8, 9). A study from Grgic and all, and a study by Shahshahan and all, reported a significant elevated CRP level in patients with preterm delivery (12,13). The other study reported no significant difference in serum CRP levels measured between the preterm and term deliveries (14,15). Our results indicate that elevated CRPlevels during the third trimester of pregnancy lead to increased risk for preterm delivery and fetal growth restriction.

Pathophysiologic mechanisms which may occur during pregnancy, like maternal low-grade systemic inflammation, shown by elevated CRP levels, may result in placental hypo perfusion, or may activate pathway of preterm labor. Elevated CRP in preterm labor is a result of upregulated

secretion of cytokines. Gibbs et al. reported association between infection, low-grade inflammation and adverse pregnancy outcomes (16). Maternal infection directly, and low-grade inflammation through inflammatory mediators indirectly, have potential to damage the fetus (17). In a study of Lindner and all, umbilical cord blood was analyzed for presence of fetal immunoglobulin M antibody against oral anaerobic bacteria and levels of inflammatory markers. The results showed that the presence of antibody and inflammatory markers significantly increased risk for adverse obstetrics outcome (18).

Other inflammatory markers in maternal blood, have also been used for detecting pregnancy complication with different success rates (19,20). Among these markers, Asadi *et al*. reported that maternal serum CRP level was found to be the most accurate predictor for adverse pregnancy outcomes (21).

Today is known that inflammation increases early in pregnancy due to implantation, and then reduces during the second trimester. Even a little increase in the degree of systemic inflammation, as shown in our study with CRP elevation, can represent an additional risk for pregnancy complications (22,23). In study of Silverbeg and all, women who had a preterm delivery or SGA baby showed an increased risk for premature cardiac disease or death, suggesting a possible correlation between the inflammation during the gestation and the inflammatory condition in the women life, which lead to cardiovascular disease (24).

The potential explanations on different results from studies in the literature might be the different inclusion and exclusion criteria of the study populations and a time period for blood collection and CRP measurement. Our finding suggests that inflammatory process can be present from early pregnancy, but elevated levels of CRP in the third trimester arethe most predictive factor for preterm birth. In our study, the differences between mean CRP levels in the groupswerestatistically significant in the first and in the third trimester. However, predictive value of elevated CRP was statistically significant only for preterm delivery, and only in the third trimester. We showed a predictive value of elevated CRP levels during pregnancy for birth of SGA baby, but this association was not statistically significant. Previous studies on SGA neonates showed inconsistencies on the association of elevated CRP levels and SGA baby (25,26). In a study by Vecchie and all, it had been reported that CRP serum levels at midpregnancy were significantly higher in the group with pregnancy adverse outcomes (10).

Conclusion

The question is to what extent maternal low-grade inflammation affects the pregnancy's outcome. We observed a positive association between serum CRP levels and adverse pregnancy outcomes, but CRP is a nonspecific marker which can produce some biasness. In our study maternal low-grade inflammation, was associated to adverse pregnancy outcomes, mainly with preterm delivery. Further studies need to explore the pathophysiological mechanisms and causalityof this observation.

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CASE REPORT UDK: 618.11-006.2-053.6

LARGE OVARIAN ENDOMETRIOMA IN 26-YEARS-OLD PATIENT

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ABSTRACT

Background: One of the most common benign gynecological disease that occurs in women of reproductive age is endometriosis. Endometriosis can be manifested in three main types, from superficial to deep infiltrating endometriosis and ovarian endometriomas. Ovarian endometriomas are ovarian cyst with diameter smaller than 5 cm to maximum of 10 cm. We report an unusual case of an extremely large endometriotic cyst with minimal symptomatology in young woman.

Case report: A 26-years-old nulliparous woman, presented at our hospital with an increase of her abdominal girth and abdominal fullness that had gradually worsened over approximately two years. She had regular period, without dysmenorrhea, and she noticed progressive weight lost. At the examination, abdominal wall was severely distended, but painless on palpation. CT on abdomen and pelvis demonstrated a large abdominal cystic mass approximate 400 × 254 mm with solid part in cyst measuring 15 cm, compressing the surrounding organs. Serum CA 125 level was 600U/ml. Exploratory laparotomy was performed. There was a huge left ovarian cyst filled with chocolate fluid (11kg weight). The right ovary looked completely normal, such as visceral peritoneum and bowel looked free from deposits. The histopathological diagnosis confirmed an ovarian endometrioma. Postoperative recovery was without adverse events. After a 24-months follow-up period, the patient showed no recurrence of the endometrioma and Ca 125 level in normal range.

Conclusion: We present a rare case of exceptionally large endometrioma (11 kg) in young patient. This case was diagnostic dilemma – a huge ovarian cyst that was actually a large endometrioma, which is extremely rare. So, we must consider this possibility in the patient with large ovarian cyst.

Key Words: *26-years-old woman, laparotomy, large endometrioma.*

Introduction

Endometriosis is a chronic inflammatory disease with a prevalence of 10-12% in reproductive women (1), and up to 50% in infertile women (2). Endometriosis can be manifested in three main types, from superficial to deep infiltrating endometriosis and ovarian endometriomas(3). Ovarian endometriomas are the most common form of this disease measuring less than 10 cm in diameter (4). Many hypotheses of endometriosis occurrence are circulating today, but none of them has the whole answer. The symptoms of endometriosis are dysmenorrhea, dyspareunia, subfertility and pelvic masses. Endometriosis is the most common cause of chronic pelvic pain in women (5). In this paper, we are presenting the case of a young patient with extremely large endometriotic cyst measuring 40 cm in its largest diameter. The large endometrioma manifested clinically as a cystic tumor causing abdominal distention and compression of adjacent organs. The primary objective in diagnosis of an abdominal mass is identifying the organ of origin, which may prove a significant challenge preoperatively (6). This is important because it will dictate the specialists involved, the diagnostic and surgical management preoperatively and postoperatively.

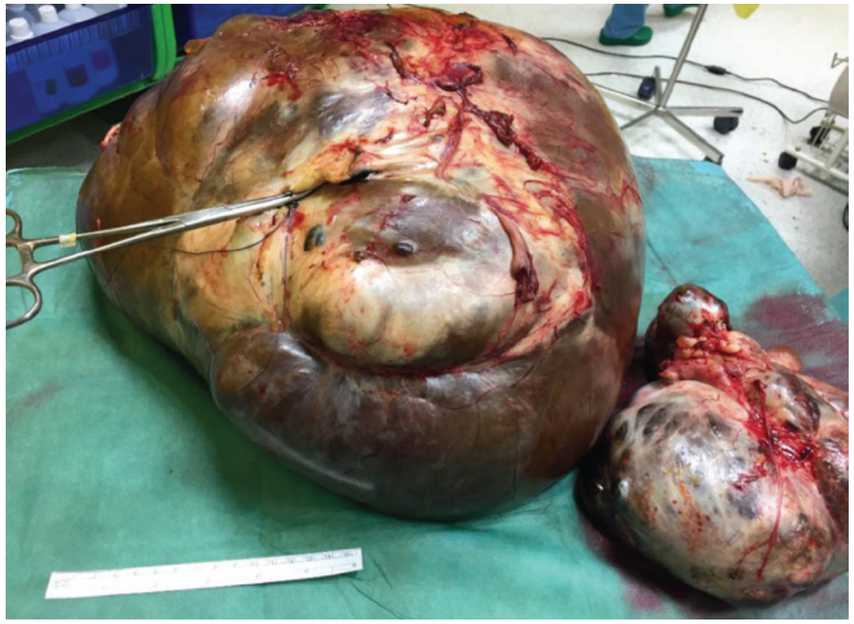
Case Report

A 26-years-old woman visited our hospital complaining of distended abdomen, abdominal fullness and progressive weight lost. She had experienced menarche at 14 years of age and regular menstruation since. She had no symptoms of dysmenorrhea, dyspareunia, abdominal pain or abnormal uterine bleeding. On presentation, the patient was with normal vital parameters. She was afebrile with normal oxygen saturation. Her abdomen was distended, but painless on palpation. Her abdominal circumference was 99 cm. Physical examination palpable abdominal mass all up to the xiphoid process with regular contours and had a cystic to rubbery consistency. There was no tenderness or rebound tenderness. The laboratory tests were unremarkable except for mild anemia. A computed tomography scan of the abdomen showed a large cystic occupying mass measuring 40 × 25 cm with solid part in cyst measuring 15 cm. The cyst occupied the most of the abdomen from the substernal to suprapubic regions and caused posteriorly displaced intestines. The uterus was normal in size and without any structural abnormalities. There was no abdominal organ invasion or ascites. The pelvic and para-aortic lymph nodes were not enlarged. The radiologic differential diagnosis was ovarian cancer or benign serous or mucinous cystadenoma of the ovary.

Based on these radiologic findings, the decision was made to preform operation by open laparotomy. Preoperative blood work demonstrated an elevated CA-125 of 600, normal range of CA-19-9 and CEA. Because of the patient's age and desire to retain fertility, the patient was not consented for hysterectomy. Preoperative discussion included the possibility of performing a second surgery if needed based on findings from the initial surgery. Explorative laparotomy was done and a large left ovarian cyst was found, with cystically transformed left

ovary and another 20 cm cyst on the same ovary. Ovarian Cysts was with fine borders, solid component and chocolate fluid. The uterus and right ovary were unremarkable. There was no ascitic fluid. Then, left adnexectomy was performed. Gross examination showed large cyst measuring 40 cm in its longitudinal diameter, weighting 11 kg, and a smaller cyst along with a cyst-transformed left ovary.

Picture 1. *Large endometrioma from 26-years-old-patient*



Gross pathology of the large ovarian cyst demonstrated a smooth-walled tan-pink lesion measuring 40.0cm × 36.0cm × 30.0cm containing serosanguineous fluid. Pathologic examination of the cyst wall showed endometrial glands and stroma, with focal hemorrhage, hemosiderin deposition and fibrosis. Immunohistochemical stains and thin layer of CD 10+ cells supported this finding. There was no evidence of carcinoma cell in this specimen. The small cyst was with the same histopathological characteristics, endometrial glands and stroma with focal hemorrhage and fibrosis being supported by ovarian tissue.

The patient carried no preoperative diagnosis of endometriosis, and beyond the endometriotic cysts, there were no additional endometriotic deposits visualized on open laparotomy. The patient stayed in our hospital 5 days and her postoperative recovery was without adverse events. Follow-up ultrasound imaging and medical management (oral estrogen-progesterone pills) were recommenced to monitor for disease recurrence. On the last gynecological follow-up 2 years after surgery, the patient was free from disease, and without using the oral hormonal therapy.

Discussion

Ovarian endometrioma is the most common form of endometriosis. Approximately 40% of women with endometriosis have ovarian endometrioma. The size of ovarian endometrioma usually ranging from 3-6 cm, to maximum 12 cm. Huge ovarian endometriomas are extremely rare, only a few cases being described (7, 8), and the largest endometrioma described in the literature is an endometrioma weighting 64 kg (9). However, nearly all papers with endometriomas reported much smaller dimension of endometriotic cyst, and therefore in our case we had low clinical suspicion that this mass represented an endometrioma preoperatively. There are very few reports of large endometrium like this one presented by Sakpal et al. (9) and we were unable to find any other cases of endometriomas approaching the size observed in our patient. Ten centimeters is generally accepted like large endometrioma, far less than the size of the mass observed in this patient. In this case endometriotic cysts was so big that filled all of the abdominal cavity and presented only with distended abdomen and significant weight loss. The significant weight lost may have been the result of loss of appetite and abdominal discomfort caused by the cyst. In this case, pre-operatively it was difficult to establish diagnosis whether this was a benign or malignant tumor. The patient's significant weight loss, the presence of a solid component according to radiographic examination, high elevated levels of CA-125 led us to a diagnosis of ovarian malignancy. This is similar to the report by Bast et al (10).

From a radiological perspective, the image interpretation was severely compromised, from the distorted normal anatomy and huge abdominal cyst. Imaging with MRI, may have aided in preoperative diagnosis; however, the patient refused this imaging modality. Serum CA-125 have been evaluated for diagnosing ovarian malignant tumors. However, CA-125 levels seem to be slightly elevated in endometrioma. In our patient serum CA-125 was 600.

The age of patient is important factor when considering treatment options. In young patient with suspicious ovarian malignancy, intraoperative frozen section histological analysis may be appropriate. In the time of surgery, the gross specimen looked like benign disease, with normal uterus and right ovary, without endometrial deposits on intestine, so we did not perform frozen section histological analysis. The pathological diagnosis was large endometriotic cysts on left ovary.

Clinical symptoms of endometriosis depend on stage and anatomic localization of the disease. The common symptoms are dysmenorrhea, dyspareunia, abnormal uterine bleeding, chronic pelvic pain, and subfertility. However, the patient with endometriosis may be asymptomatic (11, 12). In our case, the patient had only abdominal distension, abdominal fullness and weight lost in the past months. This case was diagnostic dilemma, a huge ovarian cyst that was actually a large endometrioma, which is extremely rare. So, we must consider this possibility in the case of large ovarian cyst.

Published study contend that, long-term follow-up until 5 years after surgery is appropriate, because there is a risk of recurrence, and high increase risk of ovarian cancer among women with ovarian endometriosis (13, 14). Appropriate individual treatment is very important in women with endometriosis, especially in case like ours.

Conclusion

Although endometriosis is a relatively well-known clinical entity, its manifestations are versatile and may be diagnostic dilemma to many clinicians. Here, we present a case of one of the largest endometrioma identified to date. Preoperative imaging demonstrated a large, space occupying mass thought to be a benign serous cystadenoma or carcinoma of the ovary. These cases highlight the importance of a broad differential diagnosis, which includes endometrioma for large abdominal cyst in women of childbearing age. Good patient counseling about the therapeutic option, postoperative follow up and of course preservation of fertility, especially in young patients like ours is of paramount importance.

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ORIGINAL ARTICLE UDK: 616.346.2-002-089.873:[616.98:578.834(497.7)"2020/2021"

ANALYZING OF EMERGENCY APPENDICITIS ADMISSIONS DURING THE COVID-19 LOCK-DOWN IN AN EMERGENCY SURGICAL CORONA CENTER

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ABSTRACT

Background: COVID-19 pandemic restrictive measures and the fear of the disease, made a lot of changes in correlation to other actual illnesses. In particular, acute appendicitis as a medical emergency that need fast evaluation and surgery, but still some other medical and non-medical factors influenced its emergency treatment during COVID-19. These factors may also indirectly influence the patients' outcome.

Aim: This study was aimed to evaluate the clinical patterns and outcome of patients who underwent surgery for acute appendicitis during the pandemics.

Materials and Methods: In a retrospective manner, data from all patients admitted and surgically treated for acute appendicitis in the General City Hospital "8th of September" (surgical COVID – 19 center in Macedonia) during the period from March 2020 to April 2021, was obtained. Patients according to their PCRs were divided in three groups: COVID-19 negative, COVID-19 positive and post – COVID-19 group. In all patients we analyzed: the type of surgery done, duration of COVID-19 symptoms, duration of surgery, pathohistological findings, need and duration for ICU treatment, hospital stay and mortality.

Results: During this period a total of 52 patients underwent appendectomy. Significantly large number of patients underwent open appendectomy. The pathohistological findings showed significantly higher number of perforated appendixes in all groups. Patients from the COVID-19 positive and post-COVID-19 group had longer ICU stay and mortality.

Conclusion: Our study analyses showed that during COVID-19 pandemics in our center, patients with appendicitis had higher incidence of perforated appendix, longer length of hospital stay and increased rate of complications.

Key Words: *appendicitis, COVID, surgery, treatment.*

Introduction

As it is known, World Health Organization, in March 2020, declared a pandemic of Coronavirus Disease 2019 (COVID-19) caused by (SARS-CoV-2) – severe acute respiratory syndrome coronavirus 2 (1).

As soon as pandemic was declared, every country started to introduce different restrictions in regard of the grouping, social distancing, public gathering, movement limitations, in order to find control and stop the virus spread. Lockdown was established in different countries around the world and Macedonia was one of them.

The measurements as lockdown and quarantine, led to reduction of virus spread and in that period, reports confirmed that overall emergency admissions and hospitalization due to different non-COVID-19 diseases was significantly lowered and reduced. This was also a case in our country (2).

In this manner, it was noticed that one of the most frequent emergency states, like acute appendicitis was a condition that, on one hand, admissions were significantly lowered in the emergency centers, while on the other hand, the severity of the findings in the admitted patients were worse (3,4).

Appendicitis, in its acute state, has classical presentation in almost half of the patients. However, misdiagnosis can happen and unfortunately it has direct correlation to increased morbidity and mortality (4,5). Before the pandemics, laparoscopic appendectomy was a generally preferred and advised surgical approach in acute appendicitis. This was due to literature facts that patients in whom this surgical technique was used, show less postoperative complications, less needs for analgesia, faster recovery, early mobilization, shorter length of hospital stays, when compared to patients who underwent classical open primary appendectomy (6,7,8,9,10).

During the pandemics, for surgeons working in surgical COVID-19 centers, several guidelines were published. Thereby, pathways for acute emergency, as well as elective surgery emphasized and recommended that in COVID-19 settings, a special causation and advice for doing an open surgery rather than laparoscopic one will lower and minimize the risks of aerosol formation, spread during the deflating of pneumoperitoneum and lower the production of dime and smoke which occurs with laparoscopic cautery and other devices used in all types of surgery. Therefore, in the early setting of the COVID-19 pandemic, surgical practice and management has changed for all patients with acute appendicitis, as guidelines gave priority to non-operative management and open appendicectomy, as well in all cases where operative treatment was indicated (8,9,10). These guidelines were also adopted in the General City Hospital "8th of September", the only COVID – 19 surgical center in Macedonia.

When talking about the restrictions – "stay at home" and emergency admitting of acute appendicitis, literature reveals that several studies confirmed that patients infected with SARS-CoV-2 infection, demonstrate bowel abnormalities (11). Furthermore, close relationship between COVID-19 and appendicitis, as well as patients that are presented with appendicitis symptoms are

confirmed (12,13). This may be considered in two different ways. The first one is the assumption that the "stay at home" restrictions will end up with less patients who come to emergency (who have appendicitis symptoms), while the second way is, that patients who do come to emergency, may have a delayed diagnosis and upcoming complications no matter if they are positive on SARS-CoV-2 with symptoms, asymptomatic or negative (14-19).

Therefore, the aim of this study was to analyze the data of patients who came with appendicitis in the emergency department during the COVID-19 lockdown and after, and to analyze the surgical findings, analyze surgical procedures, outcomes, and general clinical findings in those patients. Additionally, all these clinical parameters were compared in patients in regard of the positive, negative and post-COVID infection.

Materials and Methods

This was a retrospective study, that included data from all patients that were admitted and treated for appendicitis from 1st of March 2020 to 1st of April 2021, in the General City Hospital "8th of September" (official surgical COVID center in Macedonia). All data was collected from the integrated hospital informational system (HIS) after the hospital approval for the study.

The study included all adult patients diagnosed with acute appendicular pain who underwent surgery. The study excluded all patients whose clinical picture and examination indicated appendicular suffering, but intraoperatively Chron's disease, partial ischemia of the cecum, perforated ovarian cyst was found.

Based on the obtained PCR test, patients were divided into three groups: COVID-19 negative group – (COVID-19-); COVID-19 positive group (COVID-19 positive) and post-COVID-19 infection group – (postCOVID-19).

For all patients, we analyzed demographic data and clinical data: type of surgery done, duration of COVID symptoms (for positive and post COVID groups), comorbidity present, duration of surgery, pathohistological findings, need for ICU addition, duration of ICU treatment, duration of onward stay and mortality.

The collected data were put in a computer done database. Then a descriptive analysis and comparison was made between the groups themselves to determine a significant difference. The data were statistically processed with the IBM SPSS program where Independent – Samples t-test with $p=<0.05$ was used as a statistical formula.

Results

According the inclusion criteria, study included total number of 52 patients, out of whom 40 were in the COVID – 19 negative group, 6 in the COVID – 19 positive group and 6 in the post-COVID – 19 group. Summary data are shown in Table 1.

As for the group analyses, COVID – 19 negative group, included 40 patients (12 female and 28 male) with average age of 33 years. In 33 patients open appendectomy was done, while in 7 patents laparoscopic one. The surgery lasted less than 60 minutes in 22 patients, between 61-120 minutes in 15 patients and more than 121 minutes in three patients. Pathohistological, 3 patients had catarrhal, 7patients had phlegmonous, 6 patients had gangrenous and 24 patients had perforated appendicitis. Intraoperatively, local peritonitis was present in 15 patients, diffuse peritonitis in 2, abscess formation in 14, while in 9 patients there was no surrounding inflammation. 18 patients were admitted to ICU for less than three days. The ward hospitalization was less than three days in 10 patients and in 30 – more than 3 – maximum up to 10 days. Data is shown in Table 1.

Table 1. *Demographic and clinical data of the patients*

Variables	COVID19-	COVID19+	postCOVID19
Total number	40	6	6
Gender			
male	28	5	4
female	12	1	2
Age	33	40	44,5
Comorbidies			
1 comorbidies	3	1	0
2 comorbidies	1	1	1
> 3 comorbidies	0	1	1
No comorbidies	36	3	4
Clinical presentation for COVID19+ (only for positive and postCOVID19 patients)			
Asymptomatic	0	1	0
Mild	0	0	3
Moderate	0	5	3
Severe	0	0	0
Critical	0	0	0
Time after infection (only for suffered patients)			
< 1 month	0	0	5
1-2 month	0	0	1
> 2months	0	0	0
Surgical technique			
open	33	6	6
laparoscopic	7	0	0
Duration of operation			
< 60 min	22	3	1
61min to 120 min	15	2	3
> 120 min	3	1	2
PH findings			
catarrhalis	3	0	0
phlegmonose	7	1	1
gangrenous	6	0	1
perforate	24	5	4
Intraoperative findings			
Local peritonitis	15	3	3
Diffuse peritonitis	2	0	0
Abscessus	14	2	3
No findings	9	1	0
ICU stay			
Yes	18	5	5
No	22	1	1
ICU stay days			
< 3 days	18	4	3
4-10 days	0	1	2
>11 days	0	0	0
Department stay			
< 3 days	10	1	1
4-10 days	30	5	5
> 11 days	0	0	0
Mortality			
Alive	40	5	6
Deaths	0	1	0

COVID-19 positive group included 6 patients. Three patients have no comorbidities. Regarding the symptoms for COVID – 19, 5 patients had moderate clinical symptoms, while

one patient was asymptomatic. In all patients open appendectomy was done. 5 patients had perforated, while one had phlegmonous appendicitis. Intra-operative local peritonitis was seen in three patients. 5 patients needed ICU postoperatively, 4 of them less than 3 days and one patient needed longer stay and had fatal outcome. Data are shown in Table 1.

Post COVID – 19group included 6 patients. 5 patients had COVID-19 one month before the acute appendicitis. In all patients, clinical manifestations of COVID-19 were moderate to mild. Open appendectomy was done in all patients. Pathohistological, phlegmonous, gangrenous and perforated appendicitis where found. Intraoperatively half of the patients had local peritonitis and half had abscess collection. ICU treatment was needed in 3 patients for less than 3 days. No fatal outcome was noted in this group. Data are shown in Table 1.

Multi Variate Analysis between the Groups

Duration of the surgery (in minutes), pathohistological finding (catarrhal, gangrenous, phlegmonous or perforated appendicitis), intraoperative finding and duration of onward hospitalization showed no significant difference between the COVID-19 negative and COVID-19 positive group. However, the need for ICU stay, length of ICU stay was significantly higher in COVID-19 positive group. The same pattern was noticed in between the COVID – 19 negative group and Post COVID group. A multivariate analysis between the groups is shown in Table 2.

Table 2. *Multivariate analysis between the groups*

Variable	COVID19- / COVID19+ significantly
Duration of operation	0.461
PH findings	0.161
Intraoperative findings	0.781
ICU stay	0.000
ICU stay days	0.000
Department stay	0.331
Mortality	0.000

Table N.2 – Significant difference between COVID19 negative group and COVID19 positive group

Variable	COVID19+ / postCOVID19 significantly
Duration of operation	0.646
PH findings	0.698
Intraoperative findings	0.290
ICU stay	1.000
ICU stay days	0.897
Department stay	1.000
Mortality	0.031

Table N.3 – Significant difference between COVID19 positive group and postCOVID19 group

Variable	COVID19- / postCOVID19 significantly
Duration of operation	0.862
PH findings	0.348
Intraoperative findings	0.563
ICU stay	0.000
ICU stay days	0.000
Department stay	0.331
Mortality	NaN

Table N.4 – Significant difference between COVID19 negative group and postCOVID19 group

Discussion

The pathophysiology of appendicitis is not fully understood, though it is believed that the natural history begins as inflammation and it progresses to localized ischemia, then perforation, and finally abscess. It is hypothesized that appendicitis likely begins by some sort of obstruction occurring at the appendiceal orifice like lymphoid hyperplasia, infection, fecalith or tumor. This obstruction leads to an increase in intraluminal pressure and subsequent small vessel occlusion and lymphatic stasis. The appendix continues to distend, worsening the lymphatic and vascular compromise until the wall becomes ischemic and necrotic and ultimately perforates (8).

Accordingly, the longer patients wait to go to the hospital, the higher the likelihood of perforation is. This has a very tin connection and can be transformed to the time lost for patients going in emergency room with appendicular symptoms during the COVID-19, especially during “stay at home” time of quarantine. However, our study even though, does not evaluate a pathohistological finding for appendicitis during non-covid era, and shows that mainly patients who were operated during covid era, showed increased levels of appendicular perforation and worst local and general findings.

The same was confirmed in previous papers that discuss how prehospital delay is associated to higher rates of perforation (7). This study has revealed that there were more patients with perforated appendicitis during COVID-19 quarantine compared to with the same time period of the previous years. This leads to a conclusion that due to the quarantine restrictions and the global fear of infecting with COVID-19 virus, emergencies states were consciously delayed by the patients. Taking in consideration, acuteness of the appendicitis, patients presenting late to the hospital (later than 24hrs after the onset of symptoms) are at higher risk of suffering worse prognosis and outcome (7).

When discussing a progressive pathohistological appendicitis finding, we cannot forget the fact that abdominal imaging in COVID-19 patients have demonstrated that during the infection, different bowel abnormalities are present (11). The relationship between the upper respiratory viral diseases and appendicitis have been earlier confirmed (12). Mohamed A et al. in a case report, presented a case of patient with typical clinical signs of acute appendicitis, who did not had appendicitis, but was COVID-19 (13). Therefore, we can say that the COVID-19 impacts the acute appendicitis on several levels like delayed getting to emergency department, mixed symptoms, causing bowel abnormalities. Overall, our study confirmed that positive patients who have surgery for appendicitis have increased need for ICU and higher mortality rates. This seems to be logic since it is familiar that patients which have asymptomatic SARS-CoV-2 infection, who are undergoing emergency or elective surgeries are exposed to respiratory-related complications and high mortality (17).

In context of surgery done, our study confirmed that COVID-19 positive patients generally undergo open appendectomy in accordance to the global guidelines adopted. However, guidelines do advice non operative treatment when it is possible, which with our study we strongly disagree since this “non-operative” strategy is bad for patients and their outcome in context of morbidity and mortality.

Therefore, understanding the trends of disease processes such as appendicitis on one hand, and the interference of the COVID-19 on the other hand, is imperative from several aspects. First of all from, aspect of patient – patients should not been encouraged to stay at home when their health is compromised. Second, from the aspect of public health-some gained knowledge that lies between COVID-19 and appendicitis might be a good preparing pattern for the next public health crisis. The public health benefits from staying home in an attempt to reduce pandemic spread, but in exchange for one's personal health may actually increase health care costs and increase morbidity, as treating an advanced illness becomes more difficult and costly. Additionally, patients must be educated to put aside their fears and strongly support their need to seek appropriate care in a timely manner.

Limitations and Recommendations

There are several shortcomings of the article that the authors could identify. The retrospective nature of the data may introduce selection bias for cases with acute appendicitis. The limited sample size from a single institution challenges the ability to generate robust estimates on the rate of perforation. The ability to identify a complete 30-days postoperative complication rate was limited by lack of follow-up due to quarantine, and the fact that the data were collected and analyzed less than 30 days since the "safer at home" recommendation was lifted. The number of patients in the groups were not equal. Thus, only in hospital, complications were included. Further, neither patients' personal perception of COVID-19 nor their willingness to seek medical evaluation was assessed. Nevertheless, the strength of this current series resides in the fact that this is one of the first surgical series to evaluate outcomes of an acute surgical pathology during the global pandemic.

However, this study has some advantages. To our knowledge, this is the only study that shows the data of the appendicitis treatment in surgical center in Macedonia. Additionally, this study may be a trigger for other medical and public health studies during the era of COVID that might be particular used in different health systems as a guidelines and recommendations.

Conclusion

From this study it can be concluded that patients who are infected with COVID-19 and those who have recently had the infection, have a greater presentation of perforated appendix, need for ICU treatment, as well as a longer duration of treatment and hospital stay, increased number of intraoperative and postoperative complications and mortality, compared to patients who are COVID-19 negative.

In future, it is recommended to perform a new study in order to see how long after COVID-19 infection the need for ICU treatment will be equalized in patients who have not had COVID-19 infection.

Conflict of interest: none

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CHONDROSARCOMA OF THE LARYNX – INCIDENTAL FINDING DUE TO REGULAR CHECK-UP OF A HYPOTHYROID PATIENT

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ABSTRACT

Introduction: Chondrosarcoma (CS) of the head and neck is a rare pathology (2 – 5%), mainly located in the maxilla, but other parts of the skull may be typical localization as well.

Case outline: We present a case of a 61-years-old female patient diagnosed with hypothyroidism and prevailing aphonia, treated with antibiotic and anti-inflammatory therapy for four years. Ultrasound showed small volume of the thyroid gland with hypoechoic inhomogeneous structure. Due to the hoarseness in patient, computer tomography (CT) was indicated. CT showed calcified tumefaction in the region of the left hypopharynx, stenosis of the trachea in length of 23 mm, with distally post stenotic dilatation of the trachea. Therefore, patient was referred for treatment at the Clinic of Otorhinolaryngology where total laryngectomy was done. Histopathological low-grade chondrosarcoma was confirmed.

Conclusion: Low-grade chondrosarcoma of the larynx, although is a rare diagnosis, it has a good prognosis. In conclusion to our case, we can say that this diagnosis might be suspected when patients complain of hoarseness, even in patients with hypothyroidism and atrophic thyroid gland.

Key Words: *aphonia, chondrosarcoma, hypothyroidism, laryngectomy, ultrasound.*

Introduction

Chondrosarcoma (CS) of the head and neck is a rare pathological finding. Literature report incidence from 2 – 5%, mainly located in the maxilla, but other parts of the skull may be additionally involved as well. Approximately, 0.07% – 0.2% of the cases arise from the larynx, with frequent localization (80%) in the posterior lamina's internal surface of the cricoid. In around 20% of the cases, atypical location is found in the thyroid cartilage, especially the inferolateral wall, followed by the arytenoid cartilage. However, the most rear sites to arouse and localize are vocal cords, hyoid bone or epiglottis (1). Chondrosarcoma (CS) of the head and neck depending on the tumor growth and location, may be presented with different clinical signs like dyspnea, dysphagia, hoarseness, even airway obstruction with or without stridor or pain. Due to cricoarytenoid articulation vocal cord stiffness may be found which lead to stridor and harness, but in this case recurrent nerve is without lesion (2). Depending on the extension and histological grade of the tumor, treatment include partial or total laryngectomy. The prognosis for low-grade CS is usually good (3).

Case Report

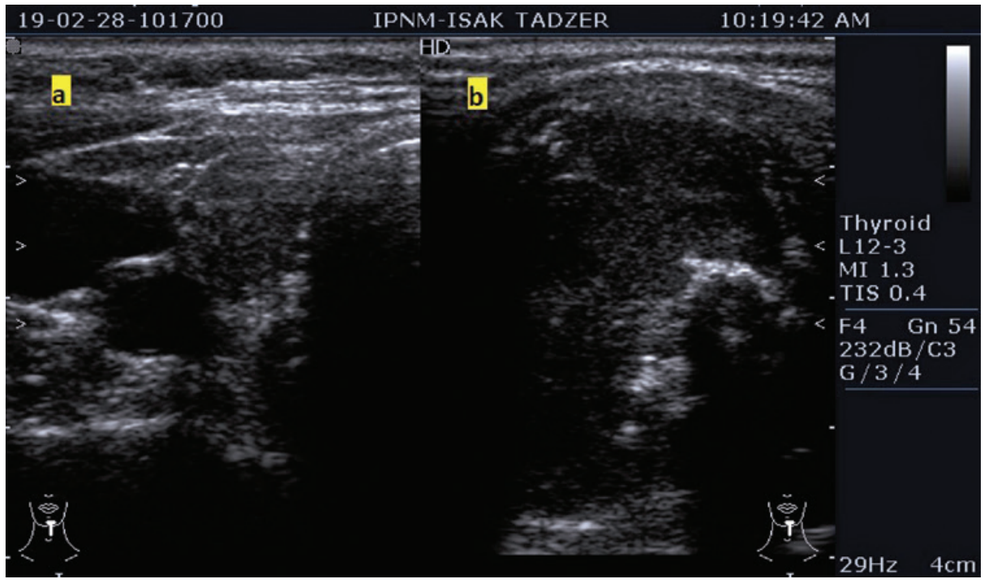
For presenting this case, inform consent was obtained.

We present a case of a 61-years-old female patient with diagnosis of hypothyroidism, admitted for a thyroid check-up at our Thyroid Department in 2018. From the anamnesis, patient was diagnosed with hypothyroidism four years ago (2014), with starting laboratory test presented as follows: FT4=0.64 pmol/L (normal range: 1.4 – 4.2 pmol/L), TSH=20.2uIU/mL (normal range: 0.4 – 4 uIU/mL). Since then, patient was treated and controlled at the secondary health institutions for several years and this was the first time she came to the Institute of Pathophysiology.

At the moment of the check-up, the patient was euthyroid, with normal levels of thyroid hormone, but she had severe hoarseness and aphonia. From the medical history, we revealed that the symptoms of aphonia and hoarseness were present for longer than four years. Due to these symptoms, the patient visited ear, nose and throat (ENT) specialist back in 2015 and stroboscopic finding of vocal cords paresis was confirmed (adduction of the left vocal cord). Allergy tests were negative and she was officially diagnosed with spasmic dysphonia and paralysis, chronic laryngitis and lesion of the right recurrent nerve. After that exam, the patient has been on chronic therapy with antihistamines, non-steroid anti-inflammatory drugs and corticosteroid therapy.

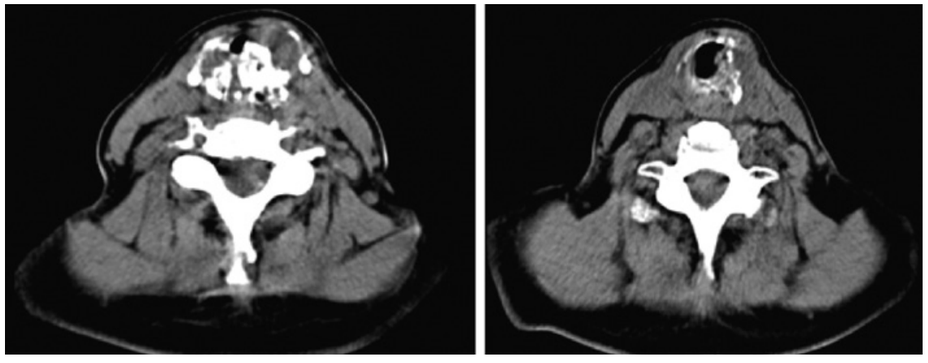
The check-up of the patient continued with ultrasound (US) examination of the thyroid gland. This examination showed atrophic thyroid gland, with hypoechoic non-homogeneous structure, with a presence of rough calcified mass (with d – 25 mm), above the left thyroid lobe, in the left infrahyoid level, laterally from the cricoid articulate and the thyroid cartilage (Figure 1). This US finding together with the aphonia and hoarseness made us go for further investigations like scintigraphy and Fine Needle Aspiration Biopsy (FNAB).

Figure 1. Ultrasound of the right thyroid lobe (a) and the calcified mass in the left hypopharynx (b)



Scintigraphy of the thyroid gland detected small thyroid lobes, without any accumulation in the mass. The FNAB of the calcified mass detected lymphocytes, erythrocytes, neutrophils and macrophages which indicated changes equal to Classification group I. Additionally, in the patient computed tomography (CT) scan with contrast was done. CT showed calcified tumefaction in the region of the left hypopharynx, stenosis of the trachea in length of 23 mm, with distally post stenotic dilatation of the trachea (Figure 2). The lung parenchyma was normal and no mediastinal lymph nodes were seen.

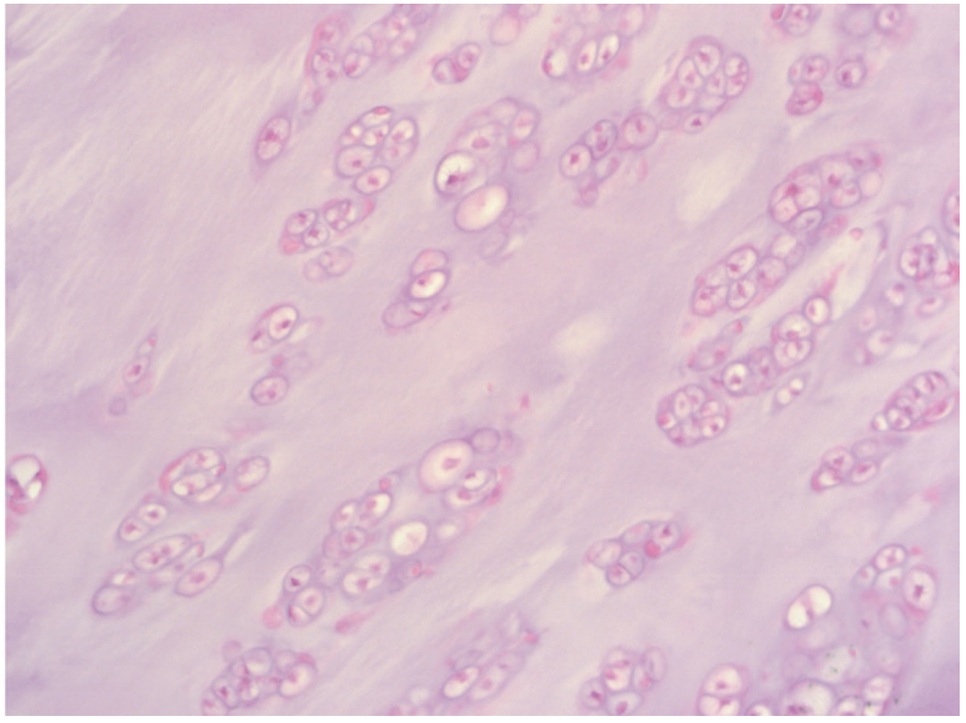
Figure 2. Computed tomography of the neck region showing the tumor.



After the CT results and FNAB patient was referred to the Clinic of Otorhinolaryngology for further treatment. Patient underwent total laryngectomy and partial cervical oesophagectomy

without detection of any lymph nodes intraoperatively. Histopathological report described translucent, blue-gray cut surface of 4×3×2cm sized tumor with negative margins. Histopathology showed irregular shaped lobules of cartilage with varying size and shape. The specimen contained hypocellular and hypercellular areas of hyperchromatic plump nuclei of uniform size with occasionally present binucleated cells. There was low mitotic count with no necrosis and low proliferation index determined by Ki67 immunostaining (<5%), suggesting diagnosis of low-grade chondrosarcoma (Figure 3).

Figure 3. Histopathology of the Chondrosarcoma



Postoperatively no complications occurred. Patient was substituted with Levothyroxine and she is coming for regular check-ups for the thyroid state at the Thyroid Department each year, as well as control check-up at the Oncology Department without any additional therapy.

Discussion

Low grade chondrosarcoma accounts for 95% of these tumors. Usually, it arises from hyaline cartilage. Commonly reported, preferred site for this tumor is the cricoid cartilage in 75% of the cases, followed by the thyroid cartilage (17%), the arytenoid (5%) and epiglottis (2%) (4). Epidemiologically, male predominance is found with a ratio of 3:1 (to as high as 10:1), usually affecting middle to later decades of life (between 40 – 80 years of age), with a peak in the

seventh decade of life. Interesting fact is that the mean age for the diagnosis is coincidence with the maximum cartilage ossification age (2, 5).

The exact pathophysiology is still not clear, but some etiopathogenic hypotheses associated to an abnormal ossification of the cartilages, chronic inflammation, presence of local trauma and metabolic disorders with aging are presumed (6). Ischemic changes in a preexisting chondroma are described as well (7).

We present a case of female patient with hoarseness and aphonia, where during the past years no swallowing or breathing problems existed, where the stroboscopic finding confirmed paresis of vocal cords, but still no CT was indicated or performed for more than four years. Therefore, we can assume that the tumor existed for a longer time (minimum three to four years) before detecting it. We also assumed that this was as a result that when US was performed, only thyroid gland was evaluated, which was nearly hypotrophic. However, taking into consideration the change of the voice, broaden US neck assessment should have been done and maybe the mass would have been seen.

The essence of this rear case is the fact that CS may be asymptomatic disease for long time, and is usually diagnosed when existing neck mass grows and as time passes, some clinical symptoms may be emphasized in their appearance. The symptoms are polymorphic and depend mostly on the location of the tumor, but the most common symptoms are dyspnea or hoarseness, that indicate larynx involvement. This was confirmed in the study of Thompson L. and Gannon F., where many patients had more than one symptom present, but hoarseness was still the most frequently identified symptom, similar as in our case. Interestingly, in their study, dyspnea was observed in cases where end laryngeal obstruction was found while dysphagia in cases with exolaryngeal growth of the tumor (8).

As for our case, involvement of the subglottis and glottis was confirmed in a female patient, that is rarely confirmed according the literature. Similarly, Elktaibi A. et al reported a case of a 75-years-old male, chronic smoker, who complained of progressive dysphonia, hoarseness, airway obstruction for 6 months and he was diagnosed with well-differentiated grade 1 chondrosarcoma of the larynx, presented on the CT by a large mass (50 × 35 mm) of glottic and subglottic plan lateralized on the left, with severe calcifications, that caused a retraction and narrowing of the laryngeal diameter and destruction of the cricoid cartilage (9).

For evaluation and diagnosis of CS of the larynx, computed tomography with contrast is a standard method. In the case of laryngeal CS, CT discovers “popcorn-like” calcification within the tumor as pathognomonic changes. The tumor may manifest displacement of surrounding structures rather than invasion, due to the slow growing manner of the tumor. (5).

CS arising from the thyroid cartilage is reported in the article of Moerman et al, where 61-years-old male patient was presented with asymptomatic slowly progressive neck swelling. CT provided a 27 × 20 mm mass arising from the outer cortex of the thyroid cartilage anteriorly, with presentation of calcifications and ossifications. In this patient resection of the entire median

part of the thyroid caused a loosing of the anterior commissure and resulted in a significant voice quality change (10).

From the oncological point of view, low-grade CS has a low metastatic potential, and only 10% noticed in CS grade 2 lesions (11). Furthermore, CS are characterized by a low tendency to spread further to regional lymph nodes. Metastasis in the thyroid gland or even primary origin of the CS in the thyroid is very exceptional, but still needs to be taken into consideration as a differential diagnosis in each thyroid mass (12).

Invasion of the thyroid gland invaded by CS was described by several authors (1, 5). Female patient with dedifferentiated chondrosarcoma with metastasis within the thyroid gland, was described by Policarpo M. in 2013. She was presented with a hard, non-painful quickly growing mass in her right thyroid lobe, with compression signs including dyspnea and hoarseness (from the right laryngeal paresis). She underwent a debulking surgery with tracheostomy, but died several days later (5). The case of Pocius L at al. presented well differentiated (G1) laryngeal chondrosarcoma, affecting the left thyroid lobe 23 × 26 × 32 mm, with heterogenic density. Destructive invasion to cartilages and penetration to 18 mm length segment of the trachea (1).

Histologically, characteristic findings of CS demonstrate hyaline cartilage of variable degrees of cellularity, anaplasia, and mitotic index. Cellularity, mitotic activity, and nuclear size are key features in grading and distinguishing benign from malignant tumors (11). Histologically, chondrosarcoma can be classified as grade 1 (small, densely staining nuclei often with multiple nuclei within one lacune), grade 2 (increased cellularity, moderately sized nuclei, low mitotic rate of less than 2 mitoses per HPF (also includes myxoid chondrosarcoma)), or grade 3 (more than two mitoses/HPF, nuclear size generally greater than seen in grade 2, (also includes dedifferentiated chondrosarcoma)), majority being low grade or intermediate grade tumors (13).

The most effective treatment is wide surgical excision as a principal goal, including complete tumor resection as well as the margins of a normal cartilage. There is no clear consensus for therapy because recommendations are based on case reports. No added survival benefit was seen between total and partial laryngectomy. The dedifferentiated variant is known for its poor prognosis (12, 14).

In conclusion to our case, we can say that low-grade chondrosarcoma of the larynx, might be suspected when a patient complains of hoarseness and aphonia for longer period and this might be the case also even in patients with hypothyroidism and atrophic thyroid gland. However, low-grade chondrosarcoma as a rare finding has good prognosis.

We disclose any conflict of interest.

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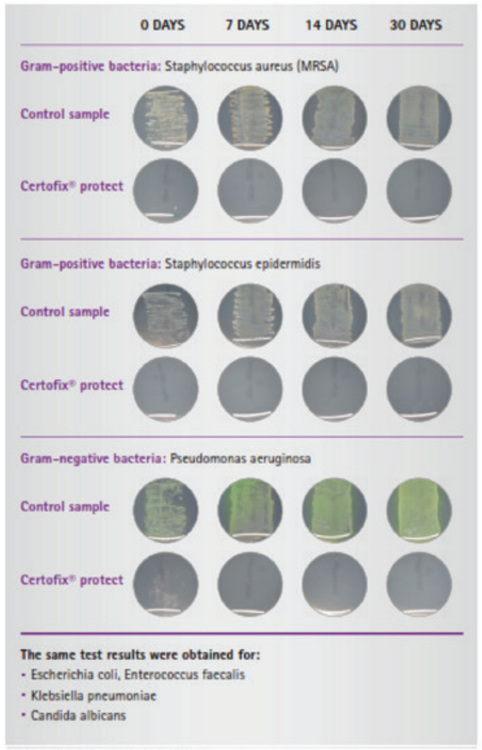

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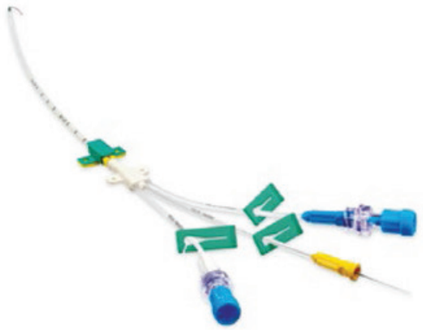

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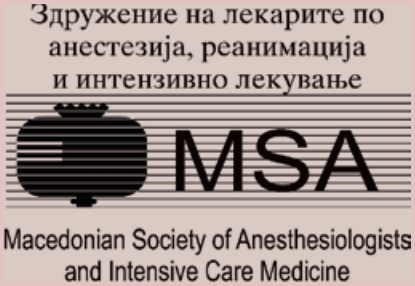
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