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CONTENT

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HYPERTHYROIDISM AND THYROID STORM

What happens when thyroid hormones start to get wild?

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The medical spectrum of entities under the term thyrotoxicosis are considered as clinical conditions with inadequate and increased levels of thyroid hormones (total and/or free fractions), with consecutive inappropriate thyroid hormone actions at cellular level and with diverse etiological background and various different clinical manifestations. The selected medical term hyperthyroidism is considered as one form of thyrotoxicosis which results from increased production and consecutive release of thyroid hormones from the thyroid gland.

Hyperthyroidism can possibly occur if the thyroid gland produces increased levels of thyroid hormones (primary hyperthyroidism), or if it is under excessive stimulation with TSH (secondary hyperthyroidism) or TRH (tertiary hyperthyroidism). Another cause for hyperthyroidism could be the autonomous production of excessive levels of thyroid hormones or passive release of prefomed amounts due to thyroid gland destruction from autoimmune, infectious, chemical, or mechanical ethiology. Rare cases of extra thyroidal sources of increased thyroid hormone levels might be either endogenous such as (struma ovarii, metastatic functional differentiated thyroid carcinomas) or exogenous (medication intake known as factitious thyrotoxicosis).

According to the severity level, hyperthyroidism could generally be considered as overt (clinical) or subclinical. Clinical or overt hyperthyroidism usually is defined with biochemically undetectable TSH serum levels with elevated levels of total or free triiodothyronine (T3) and / or total or free thyroxine values (T4). The subclinical variant of hyperthyroidism is defined with biochemically low or undetectable serum TSH levels and values within the normal reference range for both the T3 / fT3 and / or T4 / fT4.

Primary endogenous hyperthyroidism is usually due to autoimmune Grave's disease (GD) or autonomous nodular thyroid disease (AFTA or multi nodular toxic goiter). GD belongs to the autoimmune spectrum of thyroid disorders in which thyrotropin receptor antibodies (TRAb / TSI – stimulating imunoglobuline) stimulate the TSH receptor, mimicking TSH prolonged action and thus increasing the thyroid hormone production. Autonomous thyroid hormone production in AFTA or multi nodular toxic goiter is frequently caused by somatic mutations of genes that regulate thyroid gland growth and hormone synthesis. Exogenous administration or intake of pharmacologic and / or supra pharmacologic amounts of iodine to such patients may result in iodine-induced hyperthyroidism (1).

Not so frequent and also less common causes of hyperthyroidism are the entities of Hashimoto (in the initial phase), painless and subacute thyroiditis, characterised with inflammation of the thyroid tissue and consecutive release of preformed hormones into the circulation. The initial

phase of Hashimoto thyroiditis can sometimes be named as "hashi-toxicosis" and is due to lymphocitic infiltration and antibody (aTPO – anti peroxidise and aTG – anti thyroglobulin) destruction of the thyroid gland. Painless thyroiditis could occur during lithium (2), cytokine (e.g., interferon-α), or tyrosine kinase inhibitor therapy (3). In the post partum period it could be referred to as postpartum thyroiditis but most often it is associated with concomitant Hashimoto autoimmune thyroiditis. A painless destructive thyroiditis (not usually lymphocytic) occurs in 5% – 10% of amiodarone treated patients (4). The initial thyrotoxic phase of the subacute thyroiditis is thought to be most probably caused by viral infection (definite ethiology is still unclear) and is characterized by elevated sedimentation rate, fever and considerable thyroid pain.

Thyroid storm

Thyroid storm is considered as a very rare, but at the same time, a very serious complication of patients with hyperthyroidism. The condition presents with immense increase of T3/fT3 and T4/fT4 circulating levels, or usually both, with overt hyperthyroid state, concomitant hyperthermia, "malignant" tachycardia, arrhythmia and hypertension. Such rapid onset of clinical signs and symptoms are usually life threatening, with documented mortality rate between 10% and 30% if not diagnosed on time and appropriately treated (5). Taking into consideration the severity of the clinical presentation, the thyroid storm could be classified into 2 separate stages: the initial or early stage (termed also as impending storm) and the consecutive crisis (termed as the actual thyroid storm). Up to date, the scientific community has no worldwide accepted diagnostic criteria for the initial impending storm. Usually, the Burch and Wartofsky's Point Scale is considered to be applicable (6). Extreme caution and attention is mandatory in case of aggravation of the basic hyperthyroidisam clinical presentation (increase in body temperature 38 °C to 39 °C, alteration of the cardiac frequency 120 to 159 beats/min, concomitant sweating, nausea, irritability). The initial impending storm is usually reversible, if diagnosed properly and treated adequately. On the other hand, if the clinical signs and symptoms worsen, the diagnosis of thyroid storm should be immediately considered.

Several factors have been identified as precipitating for the thyroid storm development such as thyroid or non thyroid surgery, poly trauma, pregnancy and systemic infection, preferably in patients with undiagnosed and / or untreated hyperthyroid state (7) For patients who are scheduled for surgical treatment, the classical presentation of clinical signs and symptoms of thyroid storm could be atypical due to the effects of anesthetic drugs. However, a sudden notable change in the hemodynamic parameters such as increase of blood pressure or heart rate frequency, especially when it is not in correlation with the anesthetic phase, the initial phase of thyroid storm should always be taken into consideration. At the same time, similar hyper metabolic conditions should be excluded, such as possible malignant hyperthermia development (MH). It is imperative to initiate thyroid storm treatment as soon as possible, most appropriate in the initial impending stage, taking into consideration the current percentage of the mortality rate in cases of misdiagnose or prolonged treatment initiation.

In order to avoid or at least minimize the possibility of thyroid storm development during anesthesia, it is obligatory to examine the thyroid function in every patient prior to either thyroid or non thyroid surgical intervention. In patients who are previously diagnosed with hyperthyroidism or thyrotoxicosis, antithyroid drugs (propylthiouracil or metimazole), together with saturated solution of potassium iodide and / or b-blockers, should be preoperatively administered in order to maintain stabile hormone levels and stabile hemodynamic parameters. Should initial signs or symptoms of thyroid storm development be detected, additional multimodality treatment options have to be available, including corticosteroid therapy, abundant oxygen, volume resuscitation, effective temperature control with antipyretics or cooling blankets, and correction of electrolyte imbalance (8,9). Possible administration of b-blockers, should be considered in patients with concomitant myocardial ischemia, congestive heart failure, or atrial arrhythmias. If thyroid storm manifestations are obvious, the most applicable option for use is Esmolol into i.v. pump 50–100 μg/kg/min. Anticoagulant therapy could be taken into consideration for patients with previous or actual atrial fibrillation event (10). Anesthetic drugs that might induce or excite the sympathetic nerves and release histamine should be avoided.

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SPONTANEOUS PERIRENAL URINOMA: RARE COMPLICATION OF CALCULI IN THE URETEROPELVIC JUNCTION IN ADULTS

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ABSTRACT

Urinoma, defined as a collection of extravasated urine in the perirenal or paraureteral space, is caused by obstructive and non-obstructive pathologies. Trauma is the most common cause in adults for urinoma. Ureteral stones is a rare condition and least common reason in the pathologies of urinoma. It mimics the symptoms of ureteral stone. There are two types of urinoma, which are encapsulated collection of extravasated urine in the subcapsular space, called subcapsular urinoma and extravasated urine in the perirenal space, called perirenal urinoma. MDCT native series and contrast material- enhanced computed tomography, with delayed series and 3D volume rendering images is the best modality to detect the urinoma. We present a case of calculi in the ureteropelvic junction leading to perirenal urinoma formation in the 69 years old female patient, present with pain in right flank region, accompanying with nausea, vomiting and fever. Least few month patient used non steroid anti-inflammatory drug (NSAID) for chronic pain relive.

Keywords: calculi in the ureteropelvic junction, MDCT, NSAID, spontaneous perirenal urinoma.

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CONFLICT OF INTERESTS: None declared

Introduction

Perirenal urine extravasation, also known as urinoma, refers to an encapsulated urine extravasates in the subcapsular space, called subcapsular urinoma or as a free fluid collection in the perirenal space, called perirenal urinoma (1). It occurs most commonly following renal trauma, endoscopic surgical procedures and in rare cases, perirenal urinoma caused by ureteral obstruction from calculi (ureteral stone) or induced by NSAID-associated interstitial nephritis (2). These urinomas can be unilateral or bilateral. Some of them are symptomatic or asymptomatic. Spontaneous urinoma is rare and detected only when flank pain has developed. Acute interstitial nephritis caused by NSAID drug is a rarely reported etiology of spontaneous urinoma, and there is no consensus on the management of this type of urinoma (3). Some patient showed impaired renal function in the kidney ipsilateral to the urinoma. Some authors proved that there was no difference in renal function in patient with urinoma. Wells at all showed pop-off mechanism of urinoma which significantly protects global renal function in a long term. Urinomas may be occult initially and may lead to complications such as electrolyte imbalances and abscess formation, if it is not promptly diagnosed and appropriately managed (4). Radiologist play a key role in diagnosing urine leaks and determining their cause and extend. Diagnostic imaging as MDCT plays a crucial role in promptly identifying these leaks and determining their cause and extend. In some cases, the role of the radiologist ends with diagnosis and patient treated conservatively or surgically. In other cases interventional radiology and imaging-guided procedures play a crucial role in the management of these condition.

Case report

We report a case of a 69 years old female patient who came at the emergency department in University Clinic of Surgery, with chief complaints of right-sided flank pain for 3 days, nausea, vomiting and fever, without known history of calculi before. She used NSAID drug for chronic pain relive for the last few months. The patient did not use tobacco products, alcohol or abused drugs. On physical examination temperature was 37.9 °C, pulse 72, blood pressure 146/95 mmHg, abdomen was soft, tenderness in right lumbar region was present. Laboratory studies showed: Haemoglobin 12,6 g/dl; Leukocytes 10,5; granulocytes 76,9%; sodium 138 mEq/L; potassium 4,2mEq/L; glucose 5,1 mmol/l; serum creatinine 76 μmol/l; serum.urea 7,3 mmol/l; CRP 61,7. Urine analysis showed: 4-6 erythrocytes in the urine; 20-25 Leukocytes; bacteria positive+. Urgent MDCT investigation was requested. MDCT was performed: unenhanced MDCT to investigate suspected renal colic (Fig. 1) and after continued with contrast administration in 3 phases. MDCT allows detection of tiny calculisized 5 × 7 mm in the right UP junction, unilateral renal enlargement with hydronephrosis Gr. II, associated with fluid – lake effusion surrounding the renal pelvis, UP junction and proximal right ureter. The right sided perirenal fluid extravasation became strongly hyperdense in the excretory phase corresponding to extravasated urine, allowing diagnosis of perirenal urinoma. Large extravasated collection was noted on delayed

phase, in the perirenal spaces and extending along psoas muscle inferiorly. Collection was seen communicating with defect in the proximal ureter at level of the UP junction. (Fig. 2)

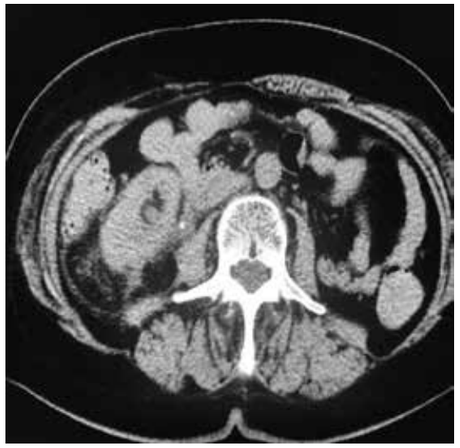

Fig. 1

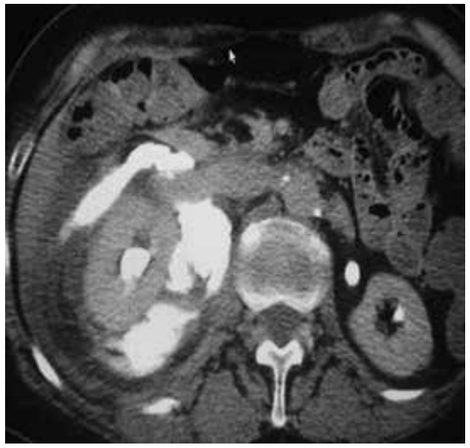

Fig. 2

We used 3D volume rendering images which allowed visualisation of size and shape of the urinoma, with spatial relationship to the kidney, pelvis and proximal ureter. (Fig. 3, Fig. 4) The findings were interpreted as consistent with the perirenal urinoma secondary to the obstructive right ureteric calculus. The patient then went to surgery for percutaneous nephrostomy and endoscopic stone removal. Antibiotics therapy were prescribed.

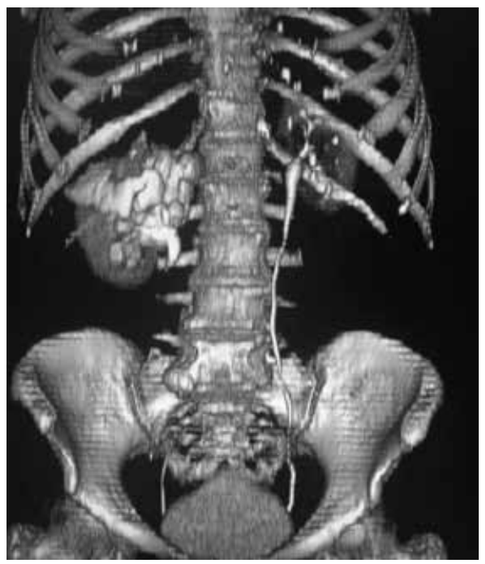

Fig. 3

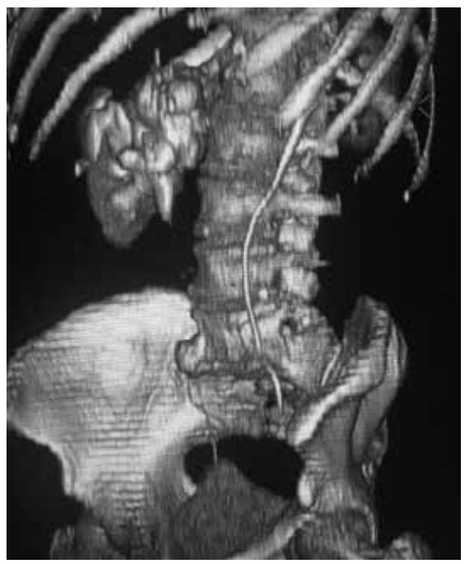

Fig. 4

Discussion

Urinoma are rare condition in all its causes. Trauma of the urinary system is the most recognized cause in adults. Obstructive cause like ureteral calculi are less likely seen manifestations as urinoma. The mechanism by which urinoma is formed, due to obstruction from ureter calculi, are very rare. Calculi causes rise in the intrapelvic pressures, pielosinus backflow of the urine and subsequent rupture of the caliceal fornices, which result in the extravasation of urine. Most commonly urine leaks into the subcapsular space or into the perirenal space within Gerota's fascia. In extensive extravasation, urine may travel superiorly, inferiorly, through lymphatic vessels or may cross the midline (5). Urinoma may extend superiorly, through aortic hiatus into the mediastinum and trough the diaphragm into the pleural spaceor extend inferiorly along the m. ileopsoas compartment, below the inguinal ligament to the soft tissues of the pelvis, perineum, thighs, buttocks. Sometimes a urine leak may extend into the intraperitoneal cavity and surround bowel loops, causing urinary ascites (6). Intraperiotoneal urine leak are usually a result of penetrating or iatrogenic injury. Renal urine leaks may also be a result of transmitted back pressure caused from obstruction of the genitourinary system: pelvic mass, pregnancy, retroperitoneal fibrosis, bladder outlet obstruction or posterior urethral valves. Iatrogenic injury during surgical or percutaneous and endoscopic procedures are an uncommon cause of renal injury (7, 8). There are only few reports in the literature with stone-related urinoma, with typical symptoms of the patient resembles that a ureteral stone itself. Most of the patient complains of nausea, vomiting, flank pain, fever, abdominal pain. Uroanalysis can show haematuria and pyuria (9). Urinomas may be occult in the initial phases and may manifest with delayed complications such hydronephrosis, electrolyte imbalances, paralytic ileus and abscess formation. Diagnostic imaging plays a crucial role in diagnosis of urinoma. MDCT is gold standard in diagnostic imaging procedures. CT protocols in the patients, involve scanning the abdomen and pelvis prior to and following the intravenous administration of 100-150 ml of contrast material. Delayed phase images obtained 7-20 minutes after contrast material injection are the key for demonstrating a urine leak because iodinated urine increased the attenuation of the urinoma and value of HU units over time. Sagittal and coronal three-dimensional reformatted MDCT images with 3D volume rendering can be very useful and help further define the extent of urinoma to the perirenal space (10). In the patient who cannot receive intravenous contrast material, or have allergic reaction to the contrast material, or have a renal transplant, scintigraphy plays a vital role in diagnosis of urine leaks (11). The initial management of an urinoma may be conservative with antibiotic therapy or percutaneous drainage, but if the size of urinoma does not decrease with conservative therapy after few days, the patient needs a surgical intervention, endoscopic procedures for stone removal or an ureteral stent placement needs to be done (12).

Conclusion

Urinoma is a serious entity that need prompt diagnosis and adequate management of this condition. If urinoma is not detected in time, it could cause serious complications as electrolyte

imbalanced, abscess formation, paralytic ileus, sepsis. Radiologist play a key role in diagnosing urine leaks and determining their cause and extend. MDCT provides confident differentiation from other urinary and extra-urinary conditions. MDCT is the gold standard and it is able to demonstrate the relationship between the urinoma and the kidney, the ureter, and fascial planes much better than ultrasonography or iv urography. In some instances the role of the radiologist ends with diagnosis of urine leaks, after which patients are being treated conservatively or surgically. In many other cases, imaging-guided interventions play very important role in the management of the urine leaks.

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АПСТРАКТ:

Уриномот се дефинира како колекција од екстравазација на урина во перирenалниот или парауретералниот простор, предизвикана од опструктивна или неопструктивна причина. Траумата на бубрегот е најчеста причина за појава на урином кај возрасни. Конкрементите во уретерот се ретка причина за појава на уриномот и може да имитираат повеќе состојби меѓу кои и состојбата на уретеролитијаза. Постојат два типа на перирenални уриноми: инкапсулирана колекција на екстравазат на урина во субкапсуларниот простор - субкапсуларен урином и екстравазација на урина во перирenалниот простор - перирenален урином. Компјутерската томографија: неконтрастна серија и постконтрастната КТ урографија со доцна урографска фаза и 3Д реконструктивни прикази, се метод на избор при детектирањето на уриномот. Презентираме случај на 69 годишен пациент, од женски пол, со симптоми на болка во десна лумбална регија, придружени со гадење, повраќање и треска. Во последните неколку месеци пациентката повремено користела и нестероидни антиинфламаторни лекови (НАИЛ) за намалување на хронична болка. Кај пациентката е направен МДКТ преглед на абдомен и уротракт, нативна серија и серии по интравенска апликација на контраст и е поставена дијагноза на перирenален урином, причинет од конкремент во десниот уретер во ниво на уретеропелвичниот сегмент. Во литературата се опишани само неколку состојби на перирenален урином предизвикани од зголемен интрауретерен притисок заради постоење на конкремент.

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FAST TRACK SURGERY PROTOCOL FOR TOTAL JOINT ARTHROPLASTY

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ABSTRACT

Background and objectives: Safe and effective clinical pathway is needed for the growing numbers of patients for joint arthroplasty in our hospital. Our primary objective was to determine whether implementing a new protocol can reduce length of hospital stay of the patients for total hip or knee arthroplasty while maintaining patient safety, without increasing perioperative complications.

Methods: In this retrospective-prospective study, 61 patients for total hip or knee arthroplasty, are treated according to the new multidisciplinary protocol (prospectively) and compared to 61 patients treated with a standard one (retrospectively).

The new protocol emphasizes preoperative patient education, postoperative multimodal analgesia, pre and postoperative use of tranexamic acid, early mobilization and rehabilitation. The primary outcome was the number of hospital days. Secondary outcomes were concerned with patient safety and involved evaluating postoperative side effects, complications, number of blood transfusions and pain scores.

Results: The number of hospital days was reduced for the patients in the new protocol compared with the standard protocol. There was a statistically significant difference with the pain scores in favor of the new protocol in all six measurement times. Significantly more patients received blood transfusion intra and postoperatively with the standard protocol compared to the patients in the fast track protocol. There was no significant difference between the two groups in the rate and severity of complications.

Conclusion: Multidisciplinary approach in forming a clinical pathway in total joint arthroplasty reduces length of hospital stay without increasing the complication rate.

Key words: fast track protocol, total joint arthroplasty.

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Introduction

Fast track surgery is a multimodal approach which is composed of multiple individual elements of patient care designed to achieve earlier discharge from the hospital (1). This clinical pathway encompasses preoperative patient selection, education of the patients, multimodal postoperative analgesia and early patient rehabilitation and mobilization. Enhanced recovery after surgery or fast track surgery is implemented in different kind of surgery, as well as for total joint arthroplasty. These programs are associated with a reduction of cost of care and length of hospital stay, incidence of complications, without an increase in readmissions or adverse events (2-5).

We wanted to see whether we can implement a similar kind of program and whether this program will work in our hospital.

Patients and methods

We decided to start an implementation of this new multidisciplinary protocol, for the patients with total hip or knee endoprothesis in our hospital. We set up patient criteria for enrolment in this program, which are listed in Table1. Whoever met the eligibility criteria from the day we decided to implement this protocol was enrolled in the study.

Table 1 New joint program patient eligibility criteria

Primary hip or knee replacement
Age ≤ 85
ASA I – III
BMI ≤ 45
Normal hematocrit
No rheumatoid arthritis
No history of pulmonary embolism or DVT within the last six months
Functional strength of upper extremity
Suitable home layout and design
Adequate home support (responsible adult to assist the patient at home)

ASA- American society of Anesthesiologists;
BMI- Body Mass Index DVT–deep venous thrombosis

One of the reviewers analyzed 61 medical charts retrospectively, before the implementation of the new protocol from the patients who met the same eligibility criteria as the patients for the new protocol. The data that were abstracted were demographic and clinical variables including age, sex, body mass index (BMI), ASA status, comorbidities, surgical procedure, type of anesthesia, intraoperative and postoperative blood transfusion, nausea and vomiting, other complications, length of hospital stay and pain scores with Visual Analogue Scale.

New protocol

The new protocol was designed as an evidence based approach to perioperative care by a multidisciplinary team. The preparation of the patient started as soon as we saw that he met the enrolment criteria with an enhanced preoperative education (oral and written). The education was about the surgery, anesthesia, hospital stay and what is expected from the patient perioperativly, with a single purpose to familiarize the patient with the procedure, so he can receive true and realistic information about it. The type of anesthesia was left to the discretion of the attending anesthesiologist, but the postoperative analgesia was determined. It included Ketonal 100 mg. two times 24 hours i.v and Tramadol 50 or 100 mg.i.v.3 times 24 hours for the first two postoperative days, and after that Ibuprofen 400 mg. 2 times 24 hours per os and Paracetamol 500 mg. 4 times 24 hours per os. The decision to place a urinary catheter was left to the surgeon and the anesthesiologist in the operating room, but even if it was placed, it was taken out the next day. Perioperativly we used the antifibrinolitic tranexemic acid 1,0 gr. 30 min. before surgery and 1,0 gr. 3 hours after surgery. Physical therapy was started on postoperative day 0 with a verticalization of the patients, sitting to standing position, with a progressive walking 5 to 10 m. on the next day with the help of a physiotherapist and walking aid. The patients were counseled to breathe deeply every 30 min., ankle pumping, static quadriceps and buttock exercises. Patients were encouraged to eat and take fluids regularly. Patients were discharged home when they met the following criteria: pain managed with oral medication, normal vital signs, no sign of infection or bleeding, appropriate oral intake without nausea and vomiting, stable hemoglobin, able to perform self-care, independent in bed mobility and transfers, walking 20 m. with walking aid and patient readiness to leave the hospital.

Standard protocol

The standard protocol included limited preoperative education, no standardized postoperative multimodal analgesia, placed urinary catheter in every patient, no antifibrinolitic and no standard physical therapy.

Results:

Table 2 Patient characteristics

	Standard protocol	New protocol	p value
Age, mean (SD)	63.49±10.62	61.68±10.12	p=0.34
Gender, %			p=0.58
Male	22 (36.23%)	26 (42.6%)	
Female	39 (63.77%)	35 (57.4%)	
ASA status, %			p= 0.21
I	2 (3.28%)	3 (4.92%)	
II	40 (65.57%)	38 (62.29%)	
III	19 (31.19%)	20 (32.79%)	
Weight, mean(SD)	82.79±16.45	85.15±16.96	p= 0.43
Height, mean (SD)	166.25±12.04	167.49±9.05	p= 0.52
BMI, mean (SD)	29.91±5.27	29.98±5.52	p= 0.07
Type of surgery			p= 0.55
Hip arthroplasty	45 (73.77%)	41 (67.21%)	
Knee arthroplasty	16 (26.23%)	20 (32.79%)	

SD- standard deviation, ASA- American Society of Anesthesiologists, BMI-Body Mass Index

Table 3 Patient comorbidities

	Standard protocol	New protocol	p value
Cardiac disease	11 (18.03%)	12 (19.67%)	p=0.82
Hypertension	44 (72.13%)	46 (75.41%)	p=0.84
COPD	6 (9.84%)	7 (11.4%)	p=0.77
DM insulin dependent	5 (8.2%)	1 (1.64%)	p=0.21
DM insulin independent	1 (1.64%)	3 (4.92%)	p=0.62
Renal disease	0	0	

COPD-chronic obstructive pulmonary disease; DM- diabetes mellitus

Table 4 Type of anesthesia

	Standard protocol	New protocol	p value
General anesthesia	15 (24.59%)	20 (32.79%)	p=0.42
Spinal anesthesia	46 (75.41%)	41 (67.21%)	

Table 2, 3 and 4 are showing demographic characteristics, comorbidities and type of anesthesia,where no significant difference was found between the two groups.

Table 5 Transfusion of blood, nausea and vomiting

	Standard protocol	New protocol	p value
Blood transfusion			
• intraoperative	8 (13.12%)	1 (1.64%)	p = 0.032
• postoperative	10 (16.39%)	1 (1.64%)	p = 0.008
Nausea and vomiting			
• Operative day	7 (11.47%)	9 (14.75%)	p= 0.79
• First postoperative day	1 (1.64%)	/	/
• Second postoperative day	/	/	/

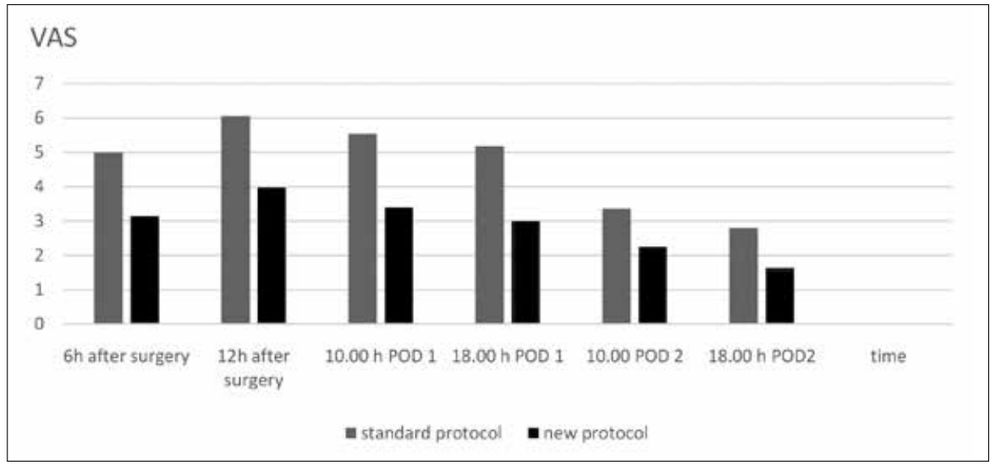
Table 5 shows that there is a statisticallysignificant higher rate of blood transfusion among the patients who did not receive tranexemic acid, compared to the patients that received tranexemic acid). The second part shows that there is no difference between the groups considering the incidence of nausea and vomiting.

Table 6 Length of hospital stay (number of days)

Standard protocol	New protocol	p value
9.19±1.99	7.065±3.51	p<0.01

Table 6 shows the primary outcome of this study, where we can see that there is a statistically significant earlier discharge home (2days) in the new protocol patient group.

Figure 1 Pain scores according to Visual Analogue Scale (VAS)



POD 1 (first postoperative day); POD 2 (second postoperative day)

Figure 1shows that there are lower pain scores in the new protocol group with a multimodal analgesia program compared to the standard one.

Discussion

The implementation of these protocols is always faced with many difficulties, starting with the medical personnel itself, because these programs are associated with more work and engagement from the personnel. Every change is usually hard, even if it brings positive things. The patients usually feel very safe in the hospital, and leaving the hospital is sometimes disturbing for them. And sometimes there are realistic problems, such as having no help at home, architectonical issues (stairs, floors, no elevator, bathroom on different level), and bad preoperative patient condition with many comorbidities. It is showed that increasing age, American Society of Anesthesiologists (ASA) physical status, preoperative use of walking aids, low preoperative hemoglobin, and patients living alone were associated with an increased length of stay (6, 7).

The development of this new protocol was a novel thing for our hospital, so we decided not to bring many new and drastically different principals of work, because it is important to change things, but maybe more important is to sustain these changes if they show good results. Preoperative education of the patient has an influence on the psychological state of the patient, getting to know the real aspects of the operation itself, as well as the postoperative time. Patients need to know that they will have certain level of pain, but this should not stop them from actively having part in mobilization and rehabilitation, taking care of themselves and taking food and liquids. That means they should have an active role in the healing process. One review study showed that preoperative education decreases the level of anxiousness among patients, but does not reduce hospital length of stay (8, 9).

There are many modalities of postoperative analgesia. There is multimodal systemic analgesia, intrathecal opioids, local infiltration analgesia, single shot or continues peripheral nerve blocks and epidural analgesia (10-12). What is used depends on drugs availability, education of the anesthesiologist for the technique, tradition in the hospital, the patient itself and the preferences of the surgeon also. That is why we descided to use multimodal sistemic analgesia with medecine we use in our every day practise. One metaanalisys shows safety and effectiveness in intravenous tranexemic acid in decreasing intraoperative and postoperative bleeding in orthopedic patients (13). In our study we also saw significant decrease of blood transfusion with the use of tranexemic acid. Placing a urinary catheter is an old habit that needs to be changed. Increased risk of intrahospital infections and decreased mobility of the patients are one of the reasons for that. The study of Loftus showed the connection of decreasing length of hospital stay with avoiding the use of urinary catheter in patients (14). Out of 122 patients, only one had a serious complication, luxation of the femoral part hip endoprothesis and that patient belonged to the standard protocol group.

Our study has several limitations which are important to recognize. The retrospective nature of this study relies both on the completeness of the patient chart as well as on the legibility of the handwritten records, not to mention consistency across nurses with regard to documentation of an event. When we collected the data retrospectively, we looked forpatients who would have met the new protocol criteria, but sometimes we could not get all the information from the data (for example, did they have help home). We did not do the discharge according to criteria, we just made a note whether the patient fulfilled the criteria. In all 61 patient they were fulfilled on the day of discharge, and sometimes even earlier. But we did not want to force the surgeon to discharge them in order to receive better results. This way we thought we would make more realistic comparison with the patients in the standard protocol when we did not have the discharge criteria.

The decrease from 9 to 7 days, compared to world experience is not a lot, but maybe more important is the development of closer relationship between the different profiles of medical personnel (anesthesiologist, surgeon, physiatrist, nutritionist, nurseetc.) and more important that this multidisciplinary approach brings results and opens a door for further improvement[15].

Conclusion

Fast track surgery protocol for total joint arthroplasty is a multimodal multidisciplinary protocolthat shows success in the patient results (decrease in hospital length of stay, lower pain scores, lower number of blood transfusion) as well as in its applicability and practical implementation for a long run. Of course there is a need for further improvement in every aspect of the protocol in the future.

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STEVEN-JOHNSON SYNDROME AND ANESTHESIA

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ABSTRACT

Steven Johns Syndrome (SJS) is a rear disease that affects skin, mucosal membranes and leads to severe systemic manifestation as a result of delayed hypersensitivity to different factors. Even thought, the syndrome is rare, it has high mortality rates and survivors often develop long term sequels. Several aspects of the disorder during the acute and chronical phase are reported as challenging from anesthesia aspects but unfortunately no clear anesthesia guidelines for these patients have been published yet. We present a successful anesthesia management in a SJS survivor patient undergoing general anesthesia and discuss some of the literature reports.

Conflict of interest: Denied

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Case Report

A 53-year-old patient, weighted 78 kg was presented for thyroid goiter removal at the clinic for Thoracic surgery.

At the pre-anesthesiologic assessment patient gave a data that she was diagnosed with Steven-Johnson Syndrome (7 years ago), after taken Penicillin for strep throat. At that time, she had systemic manifestations with inability to swallow, severe mouth and throat ulcers, epidermal lesions on the arms, vagina, eyes ulcers, increased temperature and was hospitalized and symptomatically treated for 15 days. No documentation was available (no possibility for us to find the documentation, no computerized data at that time and patient lost documentation) so we only leaned to anamnestic information from the patient.

At the present history, patient had blindness on one eye and epidermolysis on the other eye (no ability to watch on light), psychological depression confirmed (treated) and chronic bronchitis, treated with bronchodilators chronic therapy. Laboratory findings and ECG were normal, and x-ray confirmed chronic broncho-vascular changes. Patient had visible mouth ulcers, no visible ulcers on the oral mucosa, small restriction on mouth opening due to pain of the ulcers, Mallampati score of 1, good neck mobility and visible scars on the arms and the trunk.

In consultation with dermato-venerology department (due to her SJS) we processed the patient to do immunological assay and allergy tests (for anesthetics and antibiotics) and further preoperative preparation at the dermatology clinic. Immunological assays for anesthetics were negative (penicillin and cephalosporins were noted as contraindicated) and only antihistamines as preoperative preparation were recommended.

After the preoperative consultation was made the surgery was scheduled. 3 days prior to surgery, patient was hospitalized and received chloropyramine, corticosteroids and gastric protection as addition to her chronic therapy.

On the day of the surgery the same protocol was followed and after the premedication patient was send totheoperating theatre (OT). In OT, because the patient had already anintravenous line on the dorsal part of the arm, only the standard monitoring was placed. The vital signs were checked, and they were as follow: BP 140/90 mmHg, HR90bp/min, SpO_2 of 95%, and were routinely followed every 5 minutes during the surgery.

The patient received O2 as pre-oxygenation for 3 minutes. The induction in anesthesia was performed with 2.5 mg of Apaurin, 150 micg of Fentanyl and 120 mg of propofol. Mask ventilation was gentle and satisfactory. To facilitate the intubation 50 mg of Rocuronium was given. Videolaryngoscope and bronchoscope were prepared. Intubation was smooth, on first attempt and no bleeding or ulcers were found. Anesthesia was maintained with propofol continuous infusion and fentanyl as needed and no additional doses of relaxant was given. Patient was ventilated on Pressure Control Volume Guaranteed (PCVG) mode with tidal volume of 6 ml/kg to $EtCO_2$ 30-40 mmHg.

Patient was carefully placed in position with extended neck with carful pads adding. Surgery went uneventful, no hemodynamic instability or bleeding occurred, and lasted for 45 minutes.

Waking up from anesthesia was smooth and after all criteria for extubating were fulfilled, decision for extubating in the OT was made successfully. No complications occurred in the postoperative course.

A week after the surgery patient was discharged in good condition.

Discussion

We present a successful management in patient with SJS undergoing general anesthesia and discuss several aspects that are debated in the literature. Literature that discusses anesthetic consideration in patients with SJS is very scattered. It is based mainly on anesthetic management in the acute phase of the disease and mainly on individual case reports. Therefor no randomized control trials are present, and no specific guidelines are present.

Steven -Johnson Syndrome is SJS is rear skin and mucosal membranes disorder that is characterized with moderate to severe skin lesions that have tendency to be recurrent and symmetrically exposed (1). The acute phase of the disease, when this skin and mucosal exfoliative process starts developing (is commonly compared to second degree of burns) is life-threatening and always follows after prodromal phase (flu -like symptoms) (2). Its occurrence is reported with the incidence of 1 to 6 per million peopleand mortality rate from 3% to 18% (2).

In the literature, the disease can be found with different taxonomy, but most usually as SJS or Toxic Epidermal Necrolysis (TEN). SJS and TEN are two different phenotypes of the same mucocutaneous reaction and are differentiated one from another in correspondence to the percentage of the epidermal separation observed. If less of the 30% of the skin is involved, we talk about SJS otherwise for TEN (3).

Pathophysiology underlying this disease is delayed hypersensitivity to several factors like drugs (antibiotics, anticonvulsant drugs, allopurinol, barbiturates and sedatives), infection (systemic with different viruses or bacteria reported, or in immune deficient patients) andrecently genetic susceptibility is reported (humanleucocyte antigen Bx1520) (3). When hypersensitivity to mention factors occur a burst of histamine is exposed and massive mastocyte degradation mainly targeted to the biggest organs like skin and mucosal membranes occurs (4). Even though the pathophysiology of the disease is known no specific treatment is delegated. Mainly treatments advocated are supportive, sensitivity inhibition (steroids and antihistamines) and symptomatic targeted (4).

From anesthesiologic point of view, this disease is commonly challenging due to many obstacles. Starting from simple monitoring, the question is what type of anesthesia to be chosen (as safest), how to manage anesthesia, which ventilation modes to choose and the hemodynamic challenges.

Monitoring in acute phase is challenging due to lot of skin exposed and exfoliated. Reports show that simple ECG and blood pressure cuff should be put on places where intact skin is found with supportive pads. Intravenous line is another topic discussed due to same circumstances

(5,6). Overthought no literature supports anesthetically management in SJS acute phase survivor the same issues can be reflected in these patients due to the scars present and thin and sensitive skin features.

Another anesthesiologic challenge is hypersensitivity. What is certain is that most of the anesthetic drugs produce histamine relies that probably may trigger new recurrent reactions. Drugs like glycopyrrolate, midazolam, fentanyl and neostigmine are argued as possible triggers, so immunological assessments to anesthetics should be done (7).

Anesthetic implications of impossible or difficult mask ventilation due to skin involved and mouth ulcers as well as difficult intubation with possibility of mucosal lining bleeding, edema and pushing down debris intothe lungs is another spot that needs special attention.

Mechanical ventilation and possibility of pulmonal bulbs bursting is debated so low tidal volumes are recommended (7).

In the acute phase of the disease another thing to be worried is hemodynamic stability due to large fluid needed (second degree of burns features) and electrolyte deficit.

To our knowledge no management of a patient survivor has been reported yet. When speaking of our patient, she had typical features of SJS survival, with present scars on the extremities and the trunk, mouth ulcers but without acute epidermolysis and epidermis exposed. Therefore, hemodynamic instability due to fluid lost was not our issue. Hypersensitivity to drugs was tested and antihistamine and steroid therapy was introduced to minimize the chances for reaction.

Due to the type of the surgery (thyroid surgery), general anesthesia with endotracheal intubation was the anesthesia of our choice. Monitoring wasan issue in terms of blood measurement cuff (due to scars), so we put small soft pads before cuff application.

Fortunately, in our patient no lip lining adhesions were present, just small lip ulcers so mask ventilation and intubation went smooth (overthought we were prepared for difficult intubation).

Some authors suggest that general anesthesia with intubation is the safest, but most of the cases reported are toward ketamine anesthesia and no manipulation of the airway (7,8). However, these features may not be directly reflected from the acute phase patient to survivor. Extubation was also safe for our patient, although several cases reported prolonged mechanical ventilation in acute phase patients (7).

For our patient most of the things went uneventful, to our luck, but all the consideration regarding the disease were taking intoaccount.

Conclusion

The importance of this case exposes anesthesiologists' obstacles in patients with SJS. However, someobstaclesin SJS survivor and acute phase patients do not reflect in totally. We have shown that the decision to what type of anesthesia to be given was made on the basis of acquired knowledge for this disease and therefor specific features of the disease must be taken into account.

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CONTRIBUTION OF THE DYNAMIC RENAL 99MTC-DTPA SCINTIGRAPHY IN THE DIAGNOSIS AND FUNCTIONAL ASSESSMENT OF THE TWO SEPARATE MOIETIES OF A DUPLEX KIDNEY

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ABSTRACT

Background: Duplicated collecting system is a rare congenital abnormality of the urinary tract. It presents with two separate parts - moieties, with separate ureters, which havean independent function. Usually, it is diagnosed prenatally or it presentsin early childhood and on rare instances in adults. Different diagnostic procedures such as ultrasonography and computed tomography (CT) scans are most commonly used. Nuclear medicine cortical and dynamic renal scintigraphy are methods of great value in cases of diagnostic uncertainty or dilemma.

Aim: To present a case of a patient with duplex kidneydiagnosed in adulthood and to highlight the contribution of the dynamic renal scintigraphy in the diagnosis and functional assessment of thetwo separate moieties.

Casereport: Symptomatology presentedin an adult male patienta few years before with a differential diagnosis for a right upper-pole renal cyst. CT scan introduced a possible diagnosis of the right duplex kidney with two separate ureters arising from both moieties, the upper one being hydronephrotic. Dynamic scintigraphy followed by a diuretic study helped in reaching a final diagnosis by determining the separate function of each of the moieties. Cortical scintigraphy allowed for visualization of the functional parenchyma.

Conclusion: Renal scintigraphy has an important diagnostic role by evaluating the function of the two separate kidney moieties in a duplex kidney condition.

Keywords: duplex kidney, hydronephrosis, scintigraphy,^{99m}Tc-DTPA.

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Introduction

Duplex kidney or duplex ureter (a medical condition also known in the literature as duplicated collecting system) has an incidence of approximately 1% and is among the most common congenital abnormalities of the urinary tract (1,2). A duplex kidney, in fact, is morphologically a single kidney which has an upper and a lower pole called "moieties", each with a separate renal pelvis and each drained by a separate ureter. This condition is usually diagnosed prenatally or in early childhood, but on rare instances, it could initially present in adults, most often with frequent urinary tract infections (UTI), hematuria or flank pain (3).

Starting at the fifth week of the embryonic development, the ureteric bud arises from the mesonephric or Wolffian duct and grows laterally in order to meet the metanephros so that the kidney can form. If in some cases there are two ureteric buds arising from this duct, then the kidney itself and the collecting system, along with the ureter, becomes duplex. Generally, this duplication is classified as complete or partial (4,5). When partial or incomplete duplication occurs, the two branches of the ureter terminate in a single distal ureter, so that the upper and lower kidney polesare typically with normal morphology. In such cases, if ureteral obstruction or vesicoureteral reflux develops then both of the poles will be affected. On the other hand, in case of complete duplication, two separate distal ureteral insertions develop. Usually, the lower-moiety ureter is "normal", meaning it has a normally located ureteral orifice, and the upper ureter inserts medially and inferiorly (Weigert-Meyer rule). Not so rarely, the upper-pole ureter can insert ectopically (into the vagina or perineum in girls, and seminal vesicles or vas deferens in boys). Vesicoureteral reflux (VUR) and ureteral obstruction (either ureteropelvic or ureterovesical junction obstruction) are complications which occur on the lower ureter, and the upper ureter usually present with the aforementioned ectopic insertion as a complication, or by developing a ureterocele (a cystic dilation of the submucosal terminal ureter) (6).

Ureterocele usually causes obstruction, resulting in inconsecutive hydroureter and/or hydronephrosis, with minimal or absent function of the upper pole moiety (3,4). The diagnosisis based on ultrasonography (US) examination and/or contrast-enhanced computed tomography (CT) scan, which can detectthe presence of hydronephrosis, but not so rarely it can be misdiagnosed as a simple renal cyst (7,8). Therefore, when there is uncertainty or a diagnostic dilemma, usually additional imaging is required. Nuclear medicine dynamic renal scintigraphy using radiopharmaceuticals such as^{99m}Tc-mercaptoacetyltriglycine (MAG3) or^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) (which have a tubular secretion clearance and glomerular filtration clearance pathway, respectively), can assess renal blood flow, function and radiotracer clearance of the upper and lower pole moieties. If dilatation of the collecting system (hydronephrosis) and decreased washout of the radiotracer is observed, a further diuretic study accounts for accurate identification of either mechanical obstruction or dilatation without obstruction. Cortical renal scintigraphy, using^{99m}Tc-dimercaptosuccinic acid (DMSA), a radiopharmaceutical which has a stable cortical uptake, produces high-quality images for precise diagnostic assessment of the

reduced parenchymal function of the upper or lower moiety of a duplex kidney. This functional and morphological diagnostic assessment of the separate duplex kidney parts is of great importance for further surgical patient management and postoperative follow up (9, 10).

We present a case with a duplicated collecting system diagnosed in adulthood resulting in consecutive advanced stage hydronephrosis of the upper moiety of a duplex kidney.

Case report

We present a case of a 43 years old male patient, G.G., referred to the Nuclear Medicine department (April 2019), with suspicion of a possible double collecting system of the right kidney. The patient initially (four years earlier, in 2015) presented symptomatology of mild but continuous right flank pain and ultrasonography (US) examination performed at the time was suggestive of a possible right simple renal cyst (40 × 49 mm) at the upper pole of the right kidney with additional detection of several small kidney stones.

At a more recent follow-up due to a regular patient checkup and without the presence of any clinical symptomatology (January 2019) the performed US and CT scan revealed a possible presence of uncertain separation of the upper and lower poles of the right kidney (suspicion of a possible right duplex kidney with clearly defined double collecting system and with dual ureter). It also showed a slight overall enlargement of the right kidney, with the presence of upper hydroureter and consecutive "upper pole" kidney hydronephrosis (most likely due to a presence of VUR), but a completely normal lower portion of the kidney and lower ureter. The left kidney was without any abnormalities. The patient was asymptomatic and laboratory findings were within the reference range (plasma urea concentration of 5.7 mmol/L (2.9-8.2mmol/L) and plasma creatinine levels of 73 μmol/L (50-110 μmol/L)). A differential diagnosis for the right duplex kidney was made, and further imaging was indicated.

Initially, a ^{99m}Tc-DTPA renal dynamic scintigraphy was performed, using the Gates protocol. The patient was well hydrated and no medications were previously used. The two-phase dynamic scan was acquired for a total of 20 minutes, immediately after i.v. bolus tracer injection, in a standard posteroanterior (PA) view (120 short time frames / 4 s in the vascular phase and 10 s in the dynamic phase, with matrix size 64 × 64). In the blood flow phase, asymmetry in tracer activity suggested abnormal (nearly absent) vascularization in the upper pole of the right kidney. Radiopharmaceutical accumulation in this part of the cortex was also decreased (minimal peripheral cortex accumulation was noted indicative for hydronephrosis), and the clearance was delayed, with further prolonged retention, in favor of a dilated collecting system. The regions of interest and time-activity curves are shown inFigure 1 A.

Diuretic renography immediately followed, using F20 furosemide protocol (furosemide intravenously administered 20 minutes after the radiopharmaceutical). A diminished diuretic response was observed, suggesting obstruction with an advanced (grade 4) hydronephrosis of the upper moiety of the right kidney shown in Figure 1B.

On the other hand, the lower pole showed normal tracer accumulation and on-time elimination, giving the right kidney an overall relative function of 41% and a glomerular filtration rate of 43 ml/min.

All three phases of the dynamic DTPA scintigraphy for the left kidney – blood flow, tracer accumulation, and excretion, were within the normal range, with an overall relative function of 59% and a glomerular filtration rate of 61 ml/min (Figure 1 A and 1B).

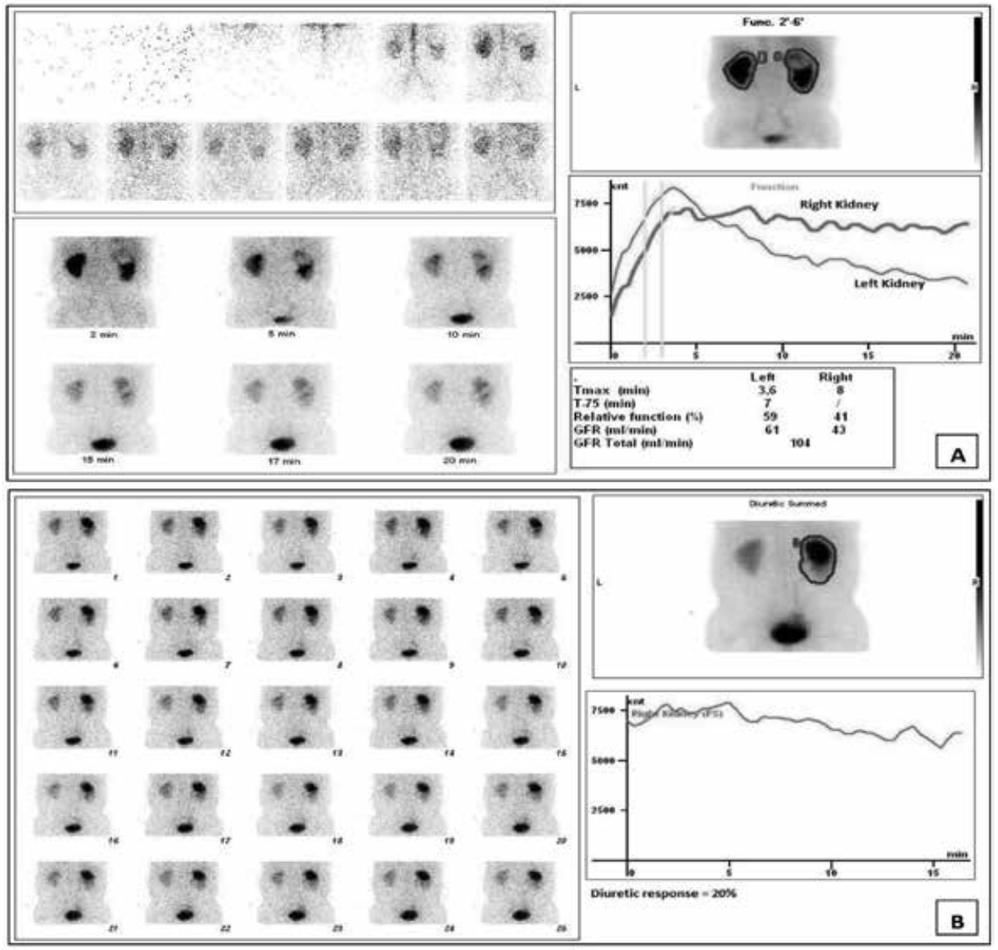

Figure 1.^{99m}Tc-DTPA renal dynamic scintigraphy using the Gates protocol.
1 A) Nearly absent vascularization in the upper pole of the right kidney with decreased radiopharmaceutical accumulation; 1B) Diminished diuretic response suggesting obstruction with an advanced (grade 4) hydronephrosis of the upper moiety of the right kidney;

Separate regions of interest (ROIs) were positioned over the upper and lower pole of the right kidney in the dynamic and in the consecutive diuretic study in order to calculate the separate function and the diuretic response of both moieties. The lower pole showed normal tracer

accumulation, on-time elimination, without any tracer retention. The upper pole presented decreased cortex accumulation, further prolonged tracer retention and diminished diuretic response of 20% in favor of functional renal parenchyma but with uretheral obstruction and advanced grade hydronephrosis. (Figure 2 and 3).

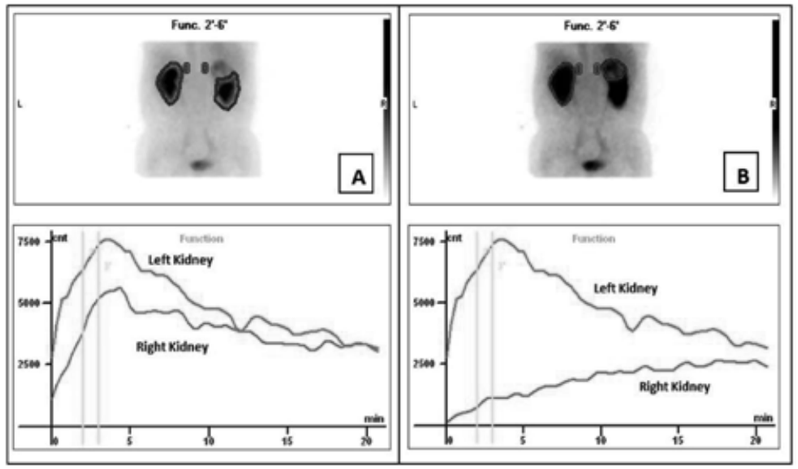

Figure 2. Separate ROIs over the lower and the upper pole of the right kidney versus the ROI over the left kidney in the dynamic phase of ^{99m}Tc-DTPA scintigraphy
2A) Normal tracer accumulation and on-time elimination of the lower right kidney pole;
2B) Decreased cortex accumulation with consecutive delayed and prolonged tracer retention of the upper right kidney pole;

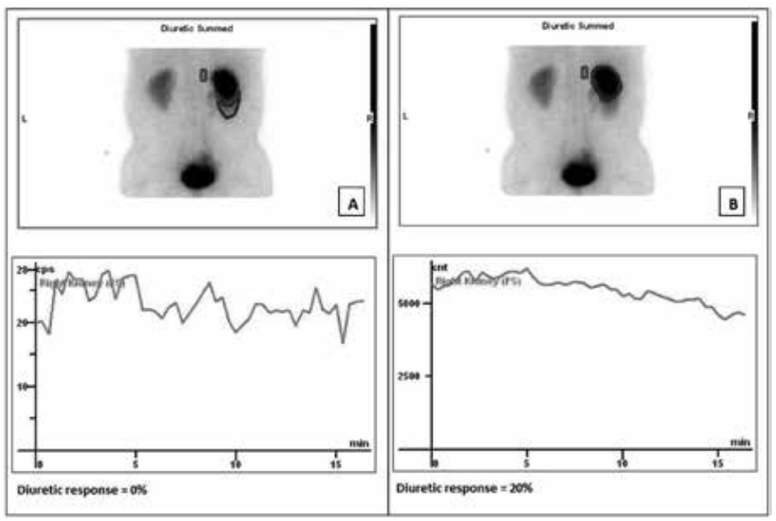

Figure 3. Separate ROIs over the lower and the upper pole of the right kidney in the diuretic phase of ^{99m}Tc-DTPA scintigraphy
3A) No contribution to the diuretic response of the lower right kidney pole due to the absent retention in the dynamic phase;
3B) Diminished diuretic response of the upper right kidney pole of 20% in favor of functional renal parenchyma but with severe uretheral obstruction and advanced grade hydronephrosis;

Cortical renal imaging using 185 MBq/5 mCi of ^{99m}Tc-DMSA to assess the parenchymal function, was also performed. Planar images were acquired 3 hours after tracer injection in PA and AP (anteroposterior) position acquiring 500k counts per view, and additionally in RO (right oblique) and LO (left oblique) positions (100k counts per view). The scan revealed afunctional upper pole of the right kidney with nearly absent tracer uptake (Figure 4).

For both studies, a dual-head gamma camera Mediso DHV Nucline Spirit, equipped witha parallel hole, low-energy general-purpose (LEGP) collimator, was used.

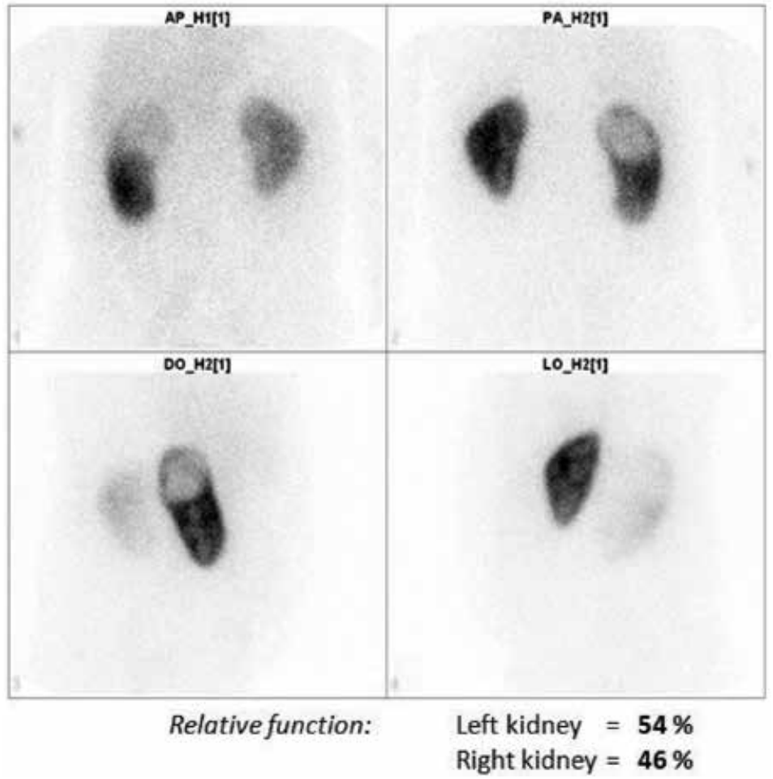

Figure 4. ^{99m}Tc-DMSA cortical renal imaging - afunctional upper pole of the right kidney with nearly absent tracer uptake

The final diagnosis was a double collecting system, double ureter, and duplex right kidney. The patient was asymptomatic, and regular US and laboratory check-ups were advised until the surgical procedure is performed.

Discussion

Duplicated renal collecting systems are most often diagnosed prenatally thanks to the improved fetal imaging, or in early childhood, with girls being two to five times more affected than boys (4). The most frequent complications of the duplex kidney that might develop at this age are

vesicoureteral reflux and/or consecutive hydronephrosis of the neonatal kidney, with the incidence of 2-9 per 1000 infants (11). Ultrasonography is included as a standard diagnostic procedure for prenatal screening during the18-20th week of gestation and it enables identification of possible intrauterine kidney anomalies (12).

Initially, the presence of prenatal or antenatal hydronephrosis was detected by Garett et al., in 1975 (13). Several factors have been identified as the possible underlying cause for intrauterine hydronephrosis development which can be divided as obstructive (ureteropelvic or vesicoureteral junction obstructions), VUR, duplex kidney, and 10-15% idiopathic (14).

However, if the condition of the duplicated renal collecting system or duplex kidney is either unrecognized or especially asymptomatic in early life, it can remain undiagnosed until adulthood. Usually, in adults it is discovered incidentally on abdominal imaging studies, or if symptoms, such as hematuria, flank pain or frequent UTIs arise.

Our patient was an adult male, who presented with a right flank pain a few years before the initial diagnosis was established. Previously, aUS examination was indicative of a simple renal cyst on the upper pole of the right kidney. It is not so uncommon for a dilated, hydronephrotic pole of a duplex kidney, to be misdiagnosed at the US examinations as a renal cyst, as previously reported in the literature (15). Raja et al. presented an unusual case of an adult female patient with recurrent UTIs, with a relatively delayed US diagnosis, which was later confirmed to be an abscess formation within a duplicated kidney (16). Arena et al. presented a VUR detection rate of only 17% of infants with prenatal intrauterine hydronephrosis which was later confirmed in the first year to be due to ureteropelvic or vesicoureteral junction obstructions. Low-grade VUR and consecutive hydronephrosis can easily be overlooked on prenatal diagnostic evaluation since renal pelvis dilatation might be missed at the US evaluation (17).

Nuclear medicine cortical renal imaging is essential in the functional assessment, deciding the management and planning the surgical treatment for a malfunctioning or nonfunctioning duplex kidney moiety (18). However, the diagnostic and prognostic role of functional, dynamic renal scintigraphy is not so well defined in the evaluation of completely duplicated renal systems.

In our case, a nuclear medicine imaging method of first choice was the dynamic^{99m}Tc-DTPA scintigraphy followed by a diuretic renography. The study revealed a dilated upper pole of the right kidney with prolonged tracer retention in the collective system and no first phase scintigraphy elimination, which was concordant with the CT scan evaluation (presence of advanced hydronephrosis). The ureter was also visualized, which was previously described as hydroureter on the CT examination. On the subsequent furosemide (diuretic phase) study, the minimal diuretic response of 20% of the right upper pole kidney was observed. This can happen in dehydrated patients or in patients with azotemia or massive hydronephrosis, which were all excluded in our case. The only conclusion was that an obstruction was present, most likely on the ureterovesical segment, since visualization of the dilated upper ureter was noted. The CT indication about the presence of VUR was therefore also excluded.

Furthermore, as the literature suggests, even though VUR is the most common anomaly associated with duplex kidney, it occurs almost exclusively into the lower-pole moiety or in an incomplete duplication (19). A successful dynamic scintigraphic method using MAG3 was previously described for detection of urine reflux from one segment of the collecting system to the other, known as “yo-yo” reflux, which again, is not applicable in our case since yo-yo reflux is a phenomenon related with incomplete ureteral duplication(20).

Separate ROIs over the lower and the upper pole of the right kidney versus the ROI over the left kidney in the dynamic phase of^{99m}Tc-DTPA scintigraphy presented normal tracer accumulation and on-time elimination of the lower right kidney pole with decreased cortex accumulation, consecutive delayed and prolonged tracer retention of the upper right kidney pole. This finding was in favor of normal function of the lower right kidney moiety and hydronephrosis due to obstruction of the upper right kidney moiety. Additionally, separate ROIs over the lower and the upper pole of the right kidneyin the diuretic phase of^{99m}Tc-DTPA scintigraphy presented no contribution to the diuretic response of the lower right kidney pole due to its normal function and absent tracer retention in the dynamic phase and diminished diuretic response of the upper right kidney moiety of only 20% in favor of still functional renal parenchyma but with severe urethral obstruction and consecutive advanced grade hydronephrosis. Considering the above-mentioned findings, we concluded that the contribution of the^{99m}Tc-DTPA renal dynamic scintigraphy in the assessment of the separate kidney moiety function and also the overall function of the duplex kidney is immense, useful and easily applicable in clinical practice.

On DMSA cortical scintigraphy, we confirmed the non-functioning upper – pole moiety of the right kidney, thus helping the decision about further surgical treatment.

Conclusion

Up to date, the diagnostic and prognostic role of the functional dynamic renal scintigraphyin the evaluation of completely duplicated renal systems has not been well defined. Our case highlights the contribution and future possible applicative value of the^{99m}Tc-DTPA scintigraphy in the assessment either of the separate kidney moiety function or the overall function of the duplex kidney.

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CASE REPORT UDK: 616.89-008.42

VISUAL HALLUCINATIONS IN DEMENTIA, CHARLES-BONNET SYNDROME AND PITUITARY MACROADENOMA

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ABSTRACT

Visual hallucinations are related to phasic increases in activity within specialized visual cortex. The location of the increases defines the type of experience reported by patients (ex. colour/face/objects hallucinations) accompanied with increase of activity in the cortex specialized for colour/face/objects recognition). Several entities from neurological aspect are found to be followed with visual hallucinations. Visual Charles Bonnet syndrome is a syndrome one of them and is characterized with presence of formed and complex, persistent or repetitive, visual hallucinations, full or partial retention of insight, absence of hallucinations in other sensory modalities and cognitive decline. Additionally, dementia with Lewy bodies is associated with some combination of fluctuating cognition, recurrent visual hallucinations, REM sleep behavior disorders and parkinsonism starting with or after dementia diagnosis. We present a case of Charles Bonnet Syndrome with incipient dementia and random finding of pituitary macroadenoma.

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Case Report

We present a case of a 78 y.o woman with incipient clinical signs of dementia that were not recognized by her family. She was psychologically normal individual. The only thing she was complaining about was her progressive visual loss. She was admitted to the neurological department due to anamnesis of experienced complex visual hallucinations for the first time in her life. The hallucinations were episodic, binocular and lasted for hours, during the last three to four days.

Patient was conscious, with normal mental status. Her pharmacological history was negative for medications that could produce hallucinations (antipsychotics, barbiturates, sedatives, illicit drugs). She denied auditory or other sensory hallucinations, as well as headache, fever or trauma. Her past medical history was significant for hypertension and cardiomyopathy, hypothyroidism and bilateral cataract. On physical examinations she had normal vital signs, normal mental status, no neurological deficit, no Parkinsonism. Even though at first sight the condition resembled to dementia and we needed to differentiate the dementia type (Alzheimer's or dementia with Lewy bodies) follow up examinations were ordered neurophysiological and neuroimaging studies (Electroencephalography (EEG), Visual Evoked Potentials (VEP), brain CT and MRI), laboratory testing, as well as consultation with ophthalmologist.

Neuro imaging diagnostics studies (CT and MRI of the brain) revealed cortical reductive changes and additionally detected pituitary gland macro-adenoma, with compressive effect on the optic chiasm, and consequently obstructive hydrocephalus. (Shown on Image. 1 and Image. 2). Electroencephalography (EEG) showed attenuation of the physiological rhythms and Visual Evoked Potentials (VEP) showed affection of the visual pathways. Neuropsychological test- Mini Mental Score Examination (MMSE) 23/30.

Laboratory findings were within normal range. Ophthalmological checkup showed visual acuity was 20/60 OU, with presence of bilateral cataracts and pupil size of 3,5/3,9mm. Fundus was normal, and automated visual fields revealed loss of peripheral vision (Image. 3, Image. 4).

After the consultation with the neurosurgeon, which suggested antiedematous therapy and postponed surgical treatment, we treated the patient with tbl. Acetazolamide 250 mg 2×1/2, tbl. Furosemide 40 mg 1×1, and her chronic therapy, for about two weeks. One week after the initiation of the therapy, visual hallucinations improved gradually. She was put on donepezil (acethylcholinesterase inhibitor), and was stable thereafter. After two weeks she was released from our Clinic.

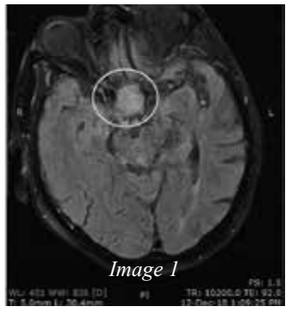

Image 1

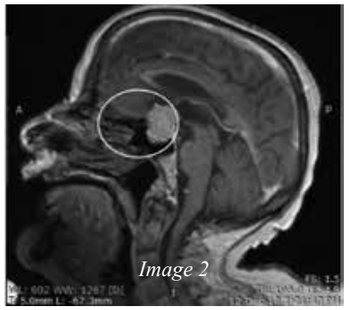

Image 2

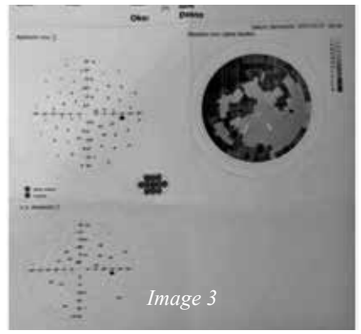

Image 3

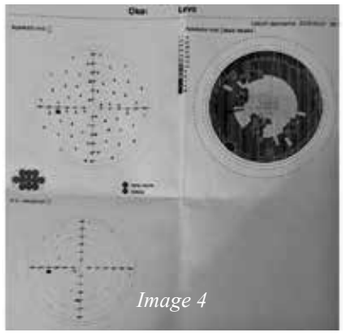

Image 4

Discussion and conclusion

Charles Bonnet syndrome, a form of release hallucinations, is a condition marked by vivid hallucinations that occur in people with any type of vision loss, from retina to occipital cortex changes, along the visual pathways (macular degeneration, diabetic retinopathy, lesions of visual cortex) (1,2). Patients acknowledge that these images are hallucinations. This may be mistaken for a delusional disorder or psychosis. But having the insight into the fact that these are hallucinations, helps rule this out. Pituitary gland tumor with compression of the optic chiasm is a rare cause of Charles – Bonnet syndrome (3,4).

As we can see in our case and the results from ophthalmological tests, this patient has a severe vision loss, especially loss of peripheral vision. That means that pituitary macro adenoma is not the only cause of vision loss (otherwise the patient should have bilateral hemianopsia heteronym), but probably cortical atrophy, especially posterior (occipital) cortical atrophy has a key role in this kind of visual loss.

Dementia with Lewy bodies (DLB) is considered the most common type of degenerative dementia after Alzheimer's disease. The classic triad of DLB is consisted of parkinsonism, fluctuating cognitive impairment and visual hallucinations. There are other clinical features in addition to this triad, for example dysautonomia, sleep disorders, neuroleptic sensitivity, etc. In DLB, fluorodeoxyglucose **(FDG)-**positron emission tomography **(PET)** scan imaging reveals bilateral occipital hypometabolism greater than temporoparietal hypometabolism. Some studies reveal that visual hallucinations consistent with Charles – Bonnet syndrome, may occur in the early stages of DLB (5,10). In our patient we cannot predict the rate of further cognitive decline or what kind of dementia will develop. However, several treatment modalities are proposed in different findings of this syndrome.

As a conclusion, in our case, the criteria for Charles – Bonnet syndrome are fullfield, whether the main cause is a pituitary gland tumor, or, the tumor is a random finding and the main cause are other factors, including degenerative disease of the brain. If the patient undergoes an operative treatment, than it would be easier to differentiate the etiology of the Charles-Bonnet syndrome. With conservative treatment the patient remained stable up to present.

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REVIEW UDK: 616.2-008.64

ACUTE RESPIRATORY DISTRESS SYNDROME: IS THE CONCEPT OF PROTECTIVE VENTILATION AND DRIVING PRESUURE THE REAL FUTURE?

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ABSTRACT

Since the original description of acute respiratory distress syndrome was made 50 years ago, much has been learned regarding the pathology and pathophysiology of the clinical syndrome. However, no pharmacologic treatments aimed at the underlying pathology have been shown to be effective, and management remains supportive with lung-protective mechanical ventilation. Controlled mechanical ventilation of patients with acute respiratory distress syndrome (ARDS) may contribute to morbidity and mortality by causing ventilator-induced lung injury (VILI). As well mechanical ventilation is critical for survival for many ARDS patients, numerous efforts over the past 50 years have been directed towards minimizing lung injury during mechanical ventilation.

Lung-protective ventilation strategy suggests the use of low tidal volume, depending on ideal body weight, limited plateau pressure, and adequate levels of PEEP. We can't always prevent overstress and overstrain by reducing tidal volume according to ideal body weight. On the contrary, titrating mechanical ventilation on airway driving pressure, should better reflect lung injury.

Key words: acute respiratory distress syndrome, driving pressure, protective ventilation, ventilator-induced injury,

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Introduction

The acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome whose incidence and mortality has remained high over the past 50 years. For the first time it was described in 1967 by Ashbaugh et al. in the Lancet (1), but prior it was published it had been rejected by the American journals who interpreted it as another case of left ventricular failure (LVF) (2). In 1994, ARDS was given a new definition by the American European Consensus Conference (AECC), but this system had limitations (3), so in 2011, a team of European and American doctors attempted to redefine ARDS in what became known as the Berlin Definition (4). Globally, ARDS accounts for 10% of intensive care unit (ICU) admissions, representing more than 3 million cases annually (5), and overall until now, the hospital mortality rate of severe ARDS has exceeding 40% in major observational studies (6, 7). In intensive care units (ICUs) in European countries the incidence of ARDS is 7.1–12.5% (8). ARDS is the most serious complication of acute lung injury (ALI) (9), characterized by acute heterogeneous inflammation of the lung leading to deterioration in effective gas exchange, worsening lung compliance, increasing pulmonary shunt and non-cardiac pulmonary edema (10, 11). The treatment, historically, has focused on two strategies: pharmacologic and ventilation manipulation, and to date the majority of treatments are extensively theoretical (9).

The current evidence-based management goal in patients with ARDS is lung protective ventilation which includes several components, the most important are lowering tidal volume (VT), limiting plateau pressure (Pplat) and higher end-expiratory pressure (PEEP) in order to mitigate ventilator induced lung injury (VILI) (12, 13). New strong evidence suggests driving pressure as a strong predictor of mortality in patients with ARDS (14, 15).

In this article we further will discuss the concept of protective mechanical ventilation and the concept of driving pressure in patients with ARDS.

Acute respiratory distress syndrome

Acute respiratory distress syndrome is life-threating form of an acute respiratory failure caused by an inflammatory edema secondary to increased lung capillary permeability. This causes alveolar flooding and subsequently deep hypoxemia, with intrapulmonary shunt as its most important underlying mechanism, which also explains the alteration of CO_2 clearance (16). A draft of Berlin definition suggested 3 categories of ARDS based on degree of hypoxemia: mild (200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg), and severe (PaO_2/FIO_2 ≤ 100 mm Hg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤40 mL/cm H_2O), positive end-expiratory pressure (≥10 cm H_2O), and corrected expired volume per minute (≥10 L/min) (17). In the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (Lung SAFE) study, 60.2% of all patients with ARDS were clinician recognized, and the clinician's diagnosis of ARDS ranged from 51.3% for mild ARDS to 78.5% for severe ARDS (18). Controlled mechanical ventilation

(CMV) with muscle paralysis with neuromuscular blocking drugs (NMBD) is required only during the restoration of circulation and pH, only during treatment of the acute cardio-ventilatory distress, to suppress additional metabolic acidosis (19). Once the improvement is noticed with ventilatory and metabolic requirements being fulfilled, CMV should be switched immediately to spontaneous ventilation.

In this regard, a complete understanding of gas exchange mechanism in ARDS is imperative for individualized symptomatic support of patients with ARDS (20).

Concept of protective mechanical ventilation

Crucial demand in the effective clinical management of ARDS is to minimize injury of lungs which are highly sensitive to damage by mechanical ventilation inducing ventilation-induced lung injury (VILI), while maintaining satisfying gas exchange. Currently, there is confusion how to achieve protective ventilation, with many strategies have been proposed (10).

"Traditional" approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight. Whereas atelectasis and edema reduce aerated lung volumes in patients with the acute respiratory distress syndrome, inspiratory airway pressures are frequently high, what indicate excessive distention, or "stretch" of the aerated lung. The current strong recommendation proposed by ARDSnet study (ARDSnet protocol), for providing protective ventilation in ARDS patients includes using of low tidal volume (between 4-8 ml/kg predicted body weight), limit plateau pressure below 28-30 cm H2O and higher end-expiratory pressure (21). This ventilator intervention has been shown to significantly improve survival so far (21). From physicians point of view this strategy should minimize the mechanical end-inspiratory lung stress (the applied force), strain (the magnitude of lung deformation) and the opening and closing trauma (22). The benefit from low tidal volume ventilation was maintained, although reduced, when considering mortality reduced at day 28 and at the end of hospital stay, but the effect on the development of organ failure is uncertain. Conversely, lower tidal volumes are effective on a short-term endpoint, protecting aerated lung parenchyma, leading to lung recovery (23, 24). In ARDS the lung available for ventilation is significantly and not uniformly reduced among patients, so a similar tidal volume based on ideal body weight, can promote different lung stress (25). It has been reported that VILI develops proportionally to the external energy applied by the ventilator to the lung, mainly due to the dynamic strain and stress caused by tidal volume (26). However, reducing the tidal volume on the basis of ideal body weight, according to the current recommendations, does not always prevent VILI. The apparent reduction in lung compliance is reminiscent of the respiratory distress syndrome seen in preterm neonates (27). Titrating the mechanical ventilation on the airway driving pressure (ΔP), measured as the airway pressure changes from PEEP to end-inspiratory plateau pressure, equivalent to the ratio between the tidal volume and compliance of respiratory system, should better reflect the lung injury because in each patient the applied tidal volume is related to the available lung gas volume (26).

According to the research of Guérin et al. in patients with severe ARDS application of prone-positioning for at least first16 h significantly decreased 28 day and 90 day mortality (28). Prone positioning has been used for many years in treatment of ARDS, the initial reason was for improving oxygenation, and later was shown that prone positioning can be less injurious to the lung, preventing VILI (29).

Concept of driving pressure

In 2015, Amato el al. presented retrospective study with the conclusion that the driving pressure (Δ) is better linked to survival in ARDS patients than tidal volume or plateau pressure as independent variables (12). The potential importance of driving pressure was recognized in patients with ARDS in 1998 (30). In patients without spontaneous breathing efforts, the driving pressure of the respiratory system is defined as the difference between plateau pressure and positive end-expiratory pressure, or as the ratio of tidal volume to respiratory system compliance. Amato el al. indicated that reductions in VT or increases in PEEP were only beneficial if associated with decrease in airway driving pressure, and no other ventilation variable had such a mediating effect (12). Researchers identified appreciable correlations between VT and survival or between VT and barotrauma only when we scaled VT to individual respiratory system compliance (CRS) values (ΔP= VT/CRS).

The physiological basis of these assumptions in patients with ARDS is that CRS is directly related to functional lung size (the volume of aerated lung available for tidal volume). Observations suggest that the aerated lung in a patient with ARDS is not “stiff” but is small, with normal compliance per unit of lung volume in preserved areas. Driving pressure is defined as the amount of cyclic parenchymal deformation imposed on ventilated, preserved lungs. The hypothesis of benefits of driving pressure rests on that the functional lung size during disease is better quantified by CRS than predicted body weight. The driving pressure is the variable that is the most strongly associated with mortality in patients with ARDS in further studies (12, 31). Suggested targeting driving pressure is below 13-15 H2O (30). Further evaluating of best targeting driving pressure is needed (31).

Airway driving pressure is a mode of representing the tidal volume adjusted for the respiratory system compliance, thus one reason that lower driving pressure may be associated with lower mortality rate may be due to a resultant reduction in cyclic lung stretch/inflation (32). This hypothesis is supported by the strong correlation between cyclic stretch, VILI, driving pressure, and survival in patients with ARDS - with driving pressure having a stronger association than the unadjusted tidal volume (12).

In the presence of spontaneous breathing, the negative change in pleural pressure triggered by spontaneous breathing becomes additive to the distending pressure; hence, driving pressure may be underestimated without considering these efforts (13). In these circumstances, the plateau pressure should be measured using a brief inspiratory hold to calculate actual driving pressure. The effects of driving pressure on clinical outcomes in the context of spontaneous breathing remain uncertain.

About 25% of ARDS survivors up to 5 years after discharge from intensive care unit (ICU) present persistent disabilities some degree of decrease in the forced vital capacity (FVC), decrease in diffusion capacity, and also muscle weakness and impaired mental health and cognition (33). The risk factors for reduction of long-term function are still unknown, but it could be related to long-term lung fibrosis. Results of recent studies (33, 34) highlighting the possible role of driving pressure in long-term outcomes, because even in context of protective tidal volume and plateau pressure, mechanical ventilation can still promote lung injury and fibrosis.

The majority of the respiratory system driving pressure was accounted for by the lungs, but a significant portion (roughly 33% on average) is the result of the chest wall. The retrospective analysis on 56 patients conducted by BaedorfKassis *et al.* in 2016 reported transpulmonary driving pressure (the difference between end-inspiratory transpulmonary pressure and end-expiratory transpulmonary pressure) for monitoring and prognostication of ARDS, which eliminates the variable effects of the chest wall on the respiratory system (35). Introducing transpulmonary pressure into the bedside management has then been proposed for two main purposes: 1. Know the influence of the chest wall on airway pressure; 2. Determine the pressure needed to keep the lung open (36). The measurement of transpulmonary pressure may be limited by several assumptions and potential sources of error, because it requires the estimation of pleural pressure from esophageal manometer (through dedicated catheters provided with esophageal balloons) (37). Additionally, because chest wall compliance and pleural pressure vary widely between patients measuring transpulmonary driving pressure instead airway driving pressure may be the more appropriate measure.

Conclusion

The studies to date are generated on hypotheses and currently there is lacking data to support the routine clinical use of driving pressure. Ongoing clinical trials of driving pressure in patients with ARDS concentrate mainly on physiological processes rather than clinical outcome but will provide important access for the design of future clinical trials. Future randomized controlled trials are needed to confirm clinical benefits of driving pressure in reducing mortality in ARDS patients.

All authors declined any conflict of interest.

Authors contribution:

AV- literature collection, idea and writing parts of the article

MS-literature collection, idea and concept writing

IB, VM -correcting and writing some parts of the article

MJS- reviewing and rewriting part of the article

SD- collection of the data, conceptual changes

SS-reviewing and rewriting part of the article

DS- idea, conceptual writing and proofreading

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CASE REPORT UDK: 618.19-073.95:616-002.524

UNUSUAL MASSIVE MACROCALCIFICATIONS FOUND ON MAMMOGRAPHY

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ABSTRACT

Patients with Systemic Lupus Erythematosus (SLE) are challenging for diagnostic and therapeutic measures due to their condition. Lupus panniculitis is a chronic (autoimmune) inflammatory reaction of the deep breast tissue, accompanied by lymphocytic lobular panniculitis with plasma cells and hyaline necrosis. Here we highlight the radiological changes in mammography and ultrasound in this rare presentation of the disease, in 57-year-old woman found on regular breast examination

Key words: Lupus erythematosus systemic (SLE), mammography, panniculitis, ultrasound.
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Case presentation

We present 57-year-old women referred to our hospital for breast examination. At the time of examination patient was afebrile and had pain in the breasts. Physical examination revealed symmetry of the breasts and palpitation was positivefor retro areolar coarse granulations. The skin was intact, no efflorescence or color change was noticed.

Anamnesticly, the patient had diagnosed Systemic Lupus Erythematosus (SLE) several years ago and experienced occasional exacerbation and remissions followed by feline changes in the lymph glands. At the time of the examination patient was in remission of the systemic disease.

Additionally, patient had documents for previous occurrence of lump in the left breast and biopsy was done on one occasion. Also, patient had additionally diagnosed diverticulitis and polyp of the colon and surgically removed colloid ovarian cyst.

Due to the anamnesis, physical examination, past illnesses history a mammography and Ultrasound (US) examinations of the breasts was proposed.

Mammography findings (shown on Figure 1 and 2) showed massive macrocalcifications on both breasts with architectural distortions.

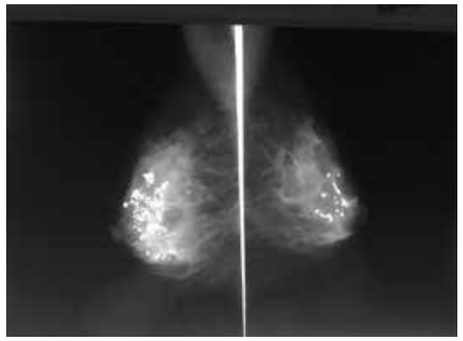

Figure 1. and 2. Mammography of the patient with SLE Massive macrocalcifications are shown with Enlargement of the axillary lymphoglandulas

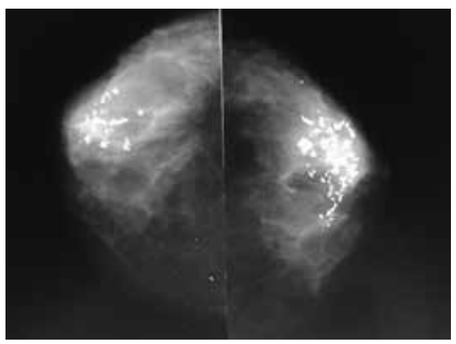

Figure 2 and 3. US presentation-Enlargement of the axillary lymphoglandulas with massive vascularization on Doppler.

The ultrasound examination showed diffusely present coarse calcification with acusive bilateral attenuation (on the left breast at 1 o'clock and on the right breast at 2 o'clock). In the same zones, a glandular pattern with indicated massive vascularization was followed. Axillary lymphoglandulas were increased with the change of the architectonics, an unclear demarcation of the cortex/medulla and pathological vascularization together with the mammographs finding lead us to diagnosis of lupus panniculitis.

Discussion

Lupus panniculitis or Lupus erythematosus profunda is a chronic reaction that occurs in inflammation of the deep layer of adipose tissue, accompanied by lymphocytic infiltration of the hyaline mass necrosis, as well as lymphocytic vasculitis. It is a rare presentation of SLE on the breasts tissue (1).

Most often, the skin may not have been altered or may show different skin erosions. However, changes in mammography and ultrasound as well as differential diagnostic, may be in favor of breast cancer (2,3,4). These changes may be exacerbated by different trauma; therefore, biopsy of the changes can aggravate radiological and clinical expression of the disease (4,5).

Histopathological criteria in the diagnosis of lupus mastitis are debated in the literature. Major histopathologic criteria are fatty hyaline necrosis, lymphocytic infiltration with the appearance of lymphocyte nodules that surround necrosis, periseptal or perilobular panniculitis (4).

Minor histopathological criteria are associated with discoid lupus erythematosus of the dermo-epidermal zone, vasculitis, mucinous deposits, and hyalinization of the subepidermal papillary zone. In these situations, if 4 major and 4 minor signs are fulfilled or if there are linear deposits of IgM and C3 of the dermo-epidermal junction and immunofluorescence, then the diagnosis is confirmed (4,5,6).

We present a case with typical SLE features, where as macrocalcifications present on mammography with enlargement of the axillary lymphoglandulas confirmed on mammography and ultrasound as well as features of massive vascularization confirmed by ultrasound Doppler.

Literature shows that in SLE mastitis according to the calculations of mammography thin, linear or diffuse coarse macrocalcifications can be found. These features are also fund in patients with diabetes mellitus so differentiation should be considered. In SLE they usually occur as a result of varying degrees of fat necrosis (2,3,5).

The Magnetic Resonance Imaging (MRI) can help with the diagnosis sometimes additionally. SLE mastitis is followed by the existence of focal and irregular masses of mammography, whereby a type 3 curve with a ring-like reddish after the contrast application obtained (7).

Conclusion

Lupus panniculitis is characterized by fluctuations of exacerbation and remission accompanied with clinical signs of pain in the breast, redness of the skin, but without laboratory typical findings

for mastitis. It is a rare condition but it should be considered in patients with SLE. Differential diagnosis should exlude conditions like calcium deposits seen in diabetes mellitus patients or even more carcinoma.

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The Journal is published twice a year (April and November), but additional supplements might be published when needed. MJA publishes original (professional and scientific) articles, review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate.

Manuscripts that are published should have not been published previously. Manuscripts that have been previously published only in form of abstracts are eligible for publishing in the journal but should be followed by additional letter send to the Editor, where the abstract details are noted (abstract number, which book of proceeding or doi, date and place).

The authors are responsible for respecting the ethical guidelines for medical researches, as well as for all that is explained, attitudes, analyses and shown results.

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The guidelines for authors adhere to the uniform Requirements for Manuscripts submitted to Biomedical Journals:www.nlm.nih.gov.

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The manuscript has to be written in **English**, followed by an abstract in Macedonia (after the references section).

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Abbreviations and correct medical terms should be used according to the International Committee of Editors of Medical Journals (http://www.icmje.org). Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

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Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

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The title of the manuscript written in CAPITAL LETTERS.

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Abstract in English. Abstract should include up to 250 words and should contain goals of the paper, important elements from the methodology, concisely displayed results and conclusion. Each abstract at the end must have **Key words**: in alphabetical order.

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Introduction section should include a literature overview in relevance to the elaborated problem. In this sections 3-5 key references are citied and this section should not be longer than 2 pages.

Material and method sections includes detailed description of the performances in the research as well as the statistical analyses used. This section should include: time during what the research was conducted, type of the study, place of where the research was undertaken, randomization or stratification used (clear description of the examined groups), exclusion and inclusion criteria, method, analysis types, apparatus and instruments used and referent values of the examined features (in SI-International System units).

Results are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

Title and the number of the charts and tables are placed above them while the explanations, abbreviations and comments are placed below. Images title and number is placed below and the image should include proper explanation.

Discussion section emphasize the key finding of the actual research and compares these result to other relevant literature data.

Conclusion section should not include more than 150 words and shoul be drown from the relevant elaborated results.

Acknowledgment and Author contributions sections are displayed after the conclusion and before the reference section.

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This sections include only the citied references. **The references** are listed in order of appearance in the paper and the citation is standard numbers enclosed in small brackets in the same line with the text ( ).

For each reference if more than three authors appear provide the names of the first three authors and followed by **et a**l.

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5. Electronic reference

Dag Stat. Mackinnon A. Available from :http//www.mhri.cdu.au/biostats.Accessed May 5th 2006.

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Macedonian abstract should include title (in capital letters) and all the needed features as the English abstract only written in Macedonian with Times New Roman, font size 12 with Macedonian support in Microsoft Word.

Prepared manuscript should be submitted electronically to **macedoniananesthesiology@gmail.com.**

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We autors_____

_____(FULL NAME AND SURNAMES OF THE AUTORS AND SIGNATURES) are responsible for the etic, profesional and scientific content of the study.

I _____(THE FIRST AUTHOR FULL NAME) declare Conflict of interest or declare non Conflict of interest.

_____(FIRST AND SURNAME OF THE CORESPONDING AUTHOR, …….. (ADRESS), ……,….. (TELEPHONE NUMBER) ……., E-MAIL