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Original article

Renal vascular variations, split renal function and donor preferences: challenge and crossroads towards right kidney choice

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Abstract

Introduction. Renal vascular variations, split renal function (SRF) and potential donor's preferences interplay with the donation decisions in living donor kidney transplantation (LDKT). This study aimed to assess the challenges in decision for choosing an appropriate kidney for donation.

Methods. Retrospective study was performed through a review of the medical history charts and national electronic database of LDKT from 2013-2022, in one transplantation center. Those with significant missing data were excluded from the final analysis. Demographic characteristics, CT angiographic findings and Tc-99m DTPA renal scan for SRF and donor preferences were analysed. The bilateral presence and number of acessory renal arteries, their hilar or polar position in respect of the renal artery, early artery branching, variations of the vein number and left vein course were assessed. Significantly different SRF was defined as ≥10%.

Results. Out of 137 consecutive LDKT, 124 donors were included in the study. The mean age of donors was 59±11 years, 40(32%) were male and 14(11%) were unrelated. There were no variations in 88(64%) renal arteries on the right and 69(56%) on the left side. The most common variation from both sides was an accessory hilar artery (15%). An accessory inferior renal polar artery was observed in 7.6% and superior in 6.4% of kidneys. Three renal arteries or three veins on one side were observed in one donor. Variation of renal arteries on both sides was 13(5.2%). Early artery branching was found in 12.9% (8%-right and 18%-left side). Two renal veins were observed in 8(3.2%) kidneys. The Nutcracker phenomenon was found in 6 (4.8%). The donated kidneys in 60% was the left one and 10% were with vascular variation. In 33(27%) of donated kidneys we found at least one vascular variation. In 41(33%) of donors SRF was significantly different and in 8(18%) the better kidney was donated due to the donor preference.

Conclusion. Variations in renal vascular anatomy and different SRF are very often in kidney donors. Donors preferences additionally interfere with the transplanttation process. The quality of the decision process relies on good institutional policy and adequate pretransplant donor evaluation.

Keywords: vascular variations, anatomy, living donor kidney transplantation, split renal function, donor preferences

Introduction

Kidney transplantation remains the best quality of life providing and cost-effective renal replacement therapy for patients with irreversible chronic kidney failure [1]. It provides more freedom for the patients and comforttable life with less time spent in the medical centers. The preparation procedure for kidney transplantation is time consuming and a lot of medical examinations are performed before the final event happens in the urological room. The living donor kidney transplantation (LDKT) is especially important for organ procurement in countries with less developed diseased donation programs [2]. It is a big challenge for any transplant team to have a variety of examination results which helps choosing an appropriate organ for transplantation.

Living donor eligibility is an important factor for the transplant procedure. The requirements are defined by guidelines [3], with some expansions of the criteria in the field of the donor's age and comorbidities, especially in countries with predominant LDKT [4]. The relationship between the donor and the recipient is also defined by local site policies, and usually it is a family member or close relative, including spouses etc. In the literature it is known that the majority of living donors

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are related to the recipient [5]. In kidney transplantation the predominance of female-to-male donations (wife to a husband) are more likely to happen, since more than 78% of organ donors are women [6]. The relationship between female donors and recipients are most likely to happen between mother and child [6].

The variations in the renal vascular structures should be known prior to any type of renal surgery, primarily before any renal transplantat surgery. The prevalence of renal vascular variations is extremely divergent in different populations and it may be due to genetic difference across the population [7,8]. Computed tomography angiography (CTA) is the gold standard method to examine vascular structures like arterial and venous variations [9]. The most common kidney vascular variation is an accessory renal artery, from which most common is hilar artery, whereas polar arteries are less common. Early bifurcation of the renal artery has been also noticed as a common variation [10]. The presence of those variations are different in males and females. It has been concluded that renal artery anomalies of the kidney vascular pedicle are significantly correlated with the coexistence of venous system variations [11]. This is especially true for male patients, which in turn favors female kidneys for transplantation. Hence, the mothers were found as most frequent donors followed by wives [6]. In one retrospective study of 58 599 donors, 86,1% of the cases were chosen for the left kidney for transplantation. One of the main reasons for this choice, mainly of the surgeon, is that the left renal vein is longer which is advantageous for transplantation and the right one is prone to thrombosis as an shorter vessel [9].

Tc-99m diethylenetriaminepentaacetic acid (DTPA) renal scan is a widely used imaging technique that evaluates renal function of potential kidney donors. Split renal function (SRF) is a determination of the relative contribution of each of the two kidneys. It gives useful information in several conditions such as evaluating unilateral renal disorders, assessing individual kidney function before and after intervention, and before live donor nephrectomy [12-14]. The decision of choosing for the donation of the lower SRF kidney is ethical, but in some cases the opposite decision is made by the donor itself.

Renal vascular variations, SRF and potential donor's preferences interplay on the donation decisions in LDKT. This study aimed to assess the challenges in decisions for choosing an appropriate kidney for donation in a single transplantation center.

Material and methods

This retrospective study was performed through a review of the medical history charts and national electronic database of LDKT from 2013-2022, in one national transplantation center. Out of 137 consecutive LDKT, 124 donors were included in the study. Those with significant missing data were excluded from the final analysis. Demographic characteristics such as age, gender, relation to the recipient, CT angiographic findings, Tc-99m DTPA renal scan for split renal function (SRF) and donor preferences were analyzed. The renal vascular anatomy radiologist reports were all revised by one transplant surgeon. The bilateral presence and number of accessory renal arteries, their hilar or polar position in respect of the renal artery, early artery branching, variations of the veins number and left vein course were assessed according to the literature [15]. An early renal artery division was defined as a main renal artery branches within 1.5 cm of the ostium of the renal artery. Significantly different SRF was defined as ≥10% [16,17]. Statistical analysis was performed in SPSS version 21. Descriptive statistics such as frequencies and percentages were calculated. The data on the kidney vascular variations were compared with respect to patients' sex and laterality. Chi-square test was performed for categorical data, $P<0.05$ was considered as statistically significant.

Results

The mean age of 124 donors was 59±11 years, 40 (32%) were male and 14(11%) were unrelated. There were no variations in 88(64%) renal arteries on the right and 69(56%) on the left side (Figure 1), the difference was significant for overall variations considering the left kidney (Table 1). The most common variation on both sides was an accessory hilar artery in 15% of cases. An accessory inferior renal polar artery was observed in 7.6% (Figure 2a) and superior in 6.4% of patients, being significantly more frequent on the left side. Three renal arteries and three veins on one side were observed in only one patient. Variation of renal arteries (Figure 2b) on both sides was found in 13(5.2%) kidneys. Early artery branching was found in almost 13%,

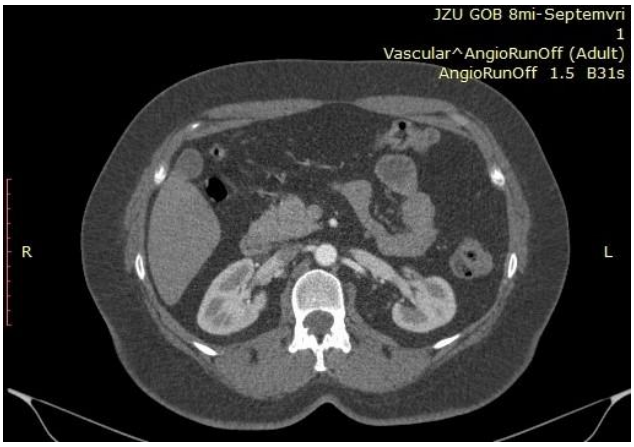

Fig. 1. Kidneys without renal vascular variations

Table 1. Renal vascular variations in donor right and left kidney

	Right N=124	Left N=124	All-248	Sig.
Any arterial variation	36(36%)	55(44%)	91(37%)	P=0.045
HAA	18(15%)	19(15.3%)	37(14.9%)	P=0.630
İnferior PAA	10(8%)	9(7.2%)	19(7.6%)	P=0.243
Superior PAA	6(4.8%)	10(8%)	16(6.4%)	P=0.033
Early branching	10(8.1%)	22(17.7%)	32(12.9%)	P=0.001
Three renal arteries	0	1(0.8%)	1(0.04%)	P=0.02
Two RV	4(3.2%)	4(3.2)	8(3.2%)	P=0.450
NP	0	6(4.8%)	6(2.4%)	P= 0.044

Abbreviations: HAA - hilar accessory artery, PAA - polar accessory artery, RV - renal vein, NP - Nutcracker phenomenon

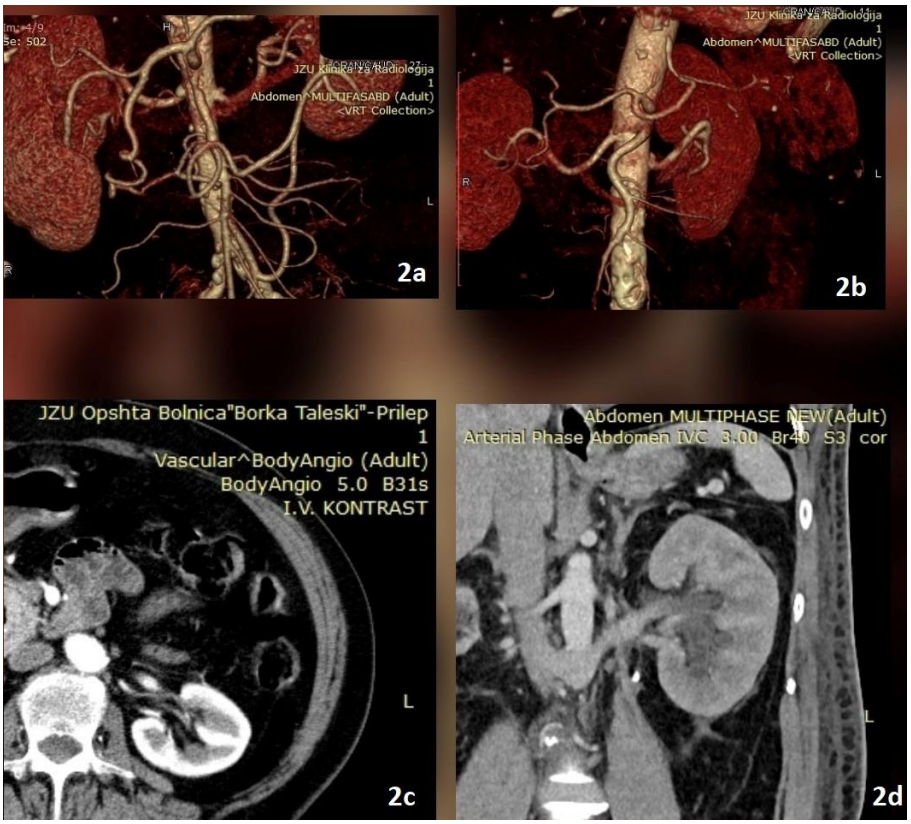

Fig. 2. Renal vascular variations: accessory polar artery, left prehilar branching - 2a; two arteries left and right - 2b; left prehilar branching - 2c; nutcracker - 2d

significantly more often on the left side (p=0.001), as shown in Figure 2c. Two renal veins were observed in 8(3%) and the Nutcracker phenomenon (Figure 2d) was found in 6(2.4%) kidneys.

There was no gender difference in vascular variations between women and men [41(49%) vs 21(52%), p= 0.234], respectively. Most of the donations were between relatives 101 (87%) and the difference between unreal ted donations between women and men was insignificant [9(11%) vs 5(12%), p=0.100], respectively. In 41(33%) of donors SRF was significantly different and 8 (18%) of those donated the better kidney because of donor's preference. The preference of the donor to donate the kidney with significantly higher SRF was more present in women than in men [7(8%) vs 1(0.02%)], p= 0.034, respectively. From the donated kidneys in 74 (60%) it was the left one and 33% of those were with vascular variations. In 33 (27%) of donor kidneys we found at least one vascular variation (Table 2).

Table 3. Vascular variations, SRF and donor preferences according to gender

N=124	Women (N=84)	Men (N=40)	Sig
any vascular variations	41(49%)	21(52%)	0.234
Unrelated donations	9(11%)	5(12%)	0.100
Preference to donate higher SRF kidney	7(8%)	1(0.02%)	0.001

Table 2. Vascular variations in donated kidney by laterality

N=124	Left N=74 (60%)	Right N= 50 (40%)
Pre-hilar branching	13 (17.5%)	4 (3.2%)
≥2 arteries	12 (16%)	8 (6.5%)

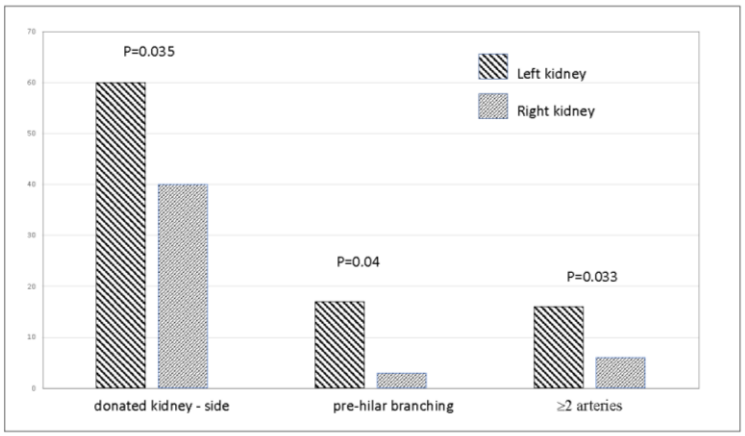

Fig. 3. Comparison of donated left or right donated kidney in respect of vascular variations

Both the perihilar branching and multiple arteries were present more often at the left side ($p<0.05$) (Figure 3).

Discussion

As result of the organ shortage, the number of LDKTs from marginal donors with age (>65 years) and comorbidities, is rising [2,18] the European Renal Registry data shows that over the last decade the mean age of donors has changed from 45 to 55 years [19]. Our analysis also found that the mean age of donors was above 55 where 43(35%) of donors were above 65 years. Female donors were predominant (68%) and that was in line with worldwide published results [20,21]. We found a lower percentage of unrelated donors (11%) compared to the previous report from ERA EDTA Registry (35%) [22]. The explanation of this discrepancy would probably be found in the traditional family bonds in our non-western families, where a broader and less rocky palette of choice (of relatives) is available for donation. Females were not only the more frequent donors but also the vast majority of those who donated the kidney with significantly higher SRF were women. We did not find such data in published studies, and it might be to a certain extend explained by the high altruistic stands of females in our milieu. Thus, female related donors donate their kidneys without concern for their own health being not aware they are committing a heroic deed. Wives donate as a form of empowerment and as a personal benefit: they donate in order to avoid taking on a carer role for their husband and as a way of protecting their children [23]. Our study did not confirm the gender discrepancy in unrelated donations which were more female as in Bal's study and in the registry data [22], so further studies are needed to explain the motives.
The relevance of the renal vascular variations might have an impact on the total surgery, cold and warm ischemia time and on graft function by many studies [24-26]. Our analysis also confirmed the presence of such anatomical variations with prevalence of any vascular variation on both sides at 37% which was similar to many published studies [27-29]. Also, the accessory hilar and polar renal arteries were found in 72 kidneys (29%) and early branching in 13% of kidneys as reported by others [28-30]. In respect of gender and side, women and left kidney were more affected by variations in our results. The previous published reports are divergent especially depending on the population specimen (cadaveric, radiological or transplant). Still all of them emphasize the need for pretransplant evaluation of the vessel's anatomy.
As far as we know this is the first study in our transplantation center about the donor characteristics, regarding demographics, renal vascular variations and donor preference. The limitation of our study was certainly the retrospective design, involving partly missing data which might interfere with the results. Considering that female gender is generally more prone to kidney donation and left kidney is preferable for transplantation, with this analysis we strongly underline the importance of vascular donor evaluation in our transplant population.

Consclusion

Variations in renal vascular anatomy and different SRF are very often in kidney donors. Donors preferences additionally interfere with the transplantation process. The quality of the decision process relies on a reasonable institutional policy and adequate pretransplant donor evaluation.

Conflict of interest statement. None declared.

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Short communication

Association of FGF23 with micro and macrovascular complications and bone mineral metabolism in patients with DMT2 in the early stage of CKD: a pilot study

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Abstract

Introduction. Diabetes mellitus type 2 (DMT2) is a multisystem disease with significant microvascular and macrovascular complications. Chronic kidney disease (CKD) is one of the leading causes of death, and DMT2 is the root cause of end-stage CKD. A scientific paradigm is whether the occurrence of chronic complications and disturbed bone-mineral metabolism (BMM) are significantly associated. In DMT2 with eGFR45-70ml/min, fibroblast growth factor (FGF23) as part of CMM is a targeted predictive biomarker for the occurrence of micro/macrovascular complications. Because scientific knowledge is still inconsistent, more research is needed to further define the role of FGF23 in DMT2 and CKD patients.

The aim of this research is to determine the association of FGF23 with ophtalmic microvascular complications, macrovascular complications as well as impaired BMM, in patients with DMT2 and eGFR45-70 ml/min/1.73m2.

Methods. As a pilot study, we present a group of 5 patients. Regarding the control of hypertension, dyslipidemia, and glycoregulation, the chosen group is homogeneous. BMD was evaluated using osteodensitometry to measure bone density and assessing the levels of vitamin D, parathyroid hormone (PTH), calcium, phosphorus, and FGF23. As a marker for subclinical atherosclerosis, carotid artery intima media thickness (IMT) was assessed using ultrasound (US) color Doppler, and the existence of peripheral arterial disease (PAD) was examined in seven blood vessels in the lower limbs. Albuminuria and eGFR following CKD-EPI, were assessed to evaluate renal consequences. Diabetic retinopathy (DR) was discovered during a fundus examination. Due to the small number of patients, the gathered data cannot be statistically analysed.

Results. All participants had at least one bone mineral or micro/macrovascular alteration. FGF23 has a value that is above average in three participants, or 60% of the sample. FGF23 was increased at all of the subjects with CVD and it was Inversely associated with value of eGFR. One participant had DR, another had osteoporosis, and one had albuminuria >30 mg/l, and all of them had increased FGF23. Two of the four individuals with PAB also had high FGF23.

Conclusion. The findings, even in a small sample of patients, suggest to a possible association between FGF23 and micro- and macrovascular complications as well as impaired CMM in DMT2 patients with early CKD. This indicates the need for additional research using larger samples.

Keywords: diabetes, microvascular complication, chronic kidney disease, bone mineral metabolism

Introduction

Fibroblast Growth Factor 23 (FGF23) is a circulating peptide hormone secreted by bone cells and its main physiological role in healthy subjects is to maintain stable serum phosphorus levels. It conducts three physiological functions: it increases phosphaturia, reduces the level of 1,25-dihydroxyvitamin D in the circulation, and suppresses the transcription of the PTH gene [1,2]. Research is currently underway to determine if the hormone FGF23 reacts to chronic changes in phosphorus levels as well as to the overall phosphate balance [3,4]. Patients with chronic kidney disease (CKD) are most suited to describe its function in pathophysiological mechanisms since there is evidence that it is elevated in the early stages of the disease before hyperparathyroidism and hyperphosphatemia appear [5,6]. Systemic disease known as CKD-associated mineral-bone

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disorder (CKD-MBD) consequences from CKD and includes soft tissue and/or vascular calcifications, disturbed bone remodeling and bone structure, and disturbances in the homeostasis of calcium and phosphorus, as well as their regulators parathyroid hormone (PTH), FGF23, Klotho, alkaline phosphatase, and vitamin D [7,8]. The relationship between FGF23 and bone-mineral metabolism (BMM) and the processes connected to it is unclear, as is whether it is a cause or result of the illness and what would occur if it could be neutralized [9].

As a regulator of phosphorus homeostasis, FGF23 is increasingly becoming a significant predictor of CVD risk in CKD patients [10-12] and even in those who have preserved renal function [9]. Because DMT2 is a systemic disease with other concomitant disorders frequently present, it is challenging to distinguish the role of FGF23 as a specific biomarker in the pathophysiological processes in DMT2 patients. Also, a significant number of studies continue to demonstrate a meaningful link between FGF23 and DMT2, independent of renal function [13,14]. Findings are that DMT2 patients have a 69% higher risk of fractures compared to non-diabetic individuals, and also that the skeleton is a powerful endocrine organ which participates in glycemic homeostasis [15,16].

There are still a small number of studies analyzing the correlations between bone mineral disorders and the occurrence of diabetic retinopathy. Current ones, however, demonstrate a link between decreased bone density and the development of diabetic retinopathy (DR) in individuals with diabetes mellitus (DM) [17,18]. All of the aforementioned entities may serve as prognostic indicators for the development of the CKD and DMT2 diseases.

The aim of this research is to demonstrate through a series of cases whether the level of FGF23 and the disturbed CMM or some of its components, metabolites, or regulators, can be used as predictors for the onset of micro and macrovascular complications in patients with DMT2 and CKD in the early stages.

Material and methods

A case series investigation of five DMT2-related patients with eGFRs of 45 to 70 ml/min/1.73 m2 is described. All cases were aged 18-80 years with DMT2 determined according to WHO criteria and eGFR calculated using the CKD-EPI creatinine equation formula (2021), on the MDcal calculator (https://www.mdcalc.com/).

The patients were recruited in the diabetes center at the General Public Hospital "Osmi Septemvri", Skopje. With previously given and signed informed consent, the study was conducted out in conformity with the Declaration of Helsinki.

Clinical evaluation: The following anthropometric variables were assessed: gender, age, height, and weight. NIH (National Heart, Lung, and Blood Institute) electronic calculator was used to calculate BMI. (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm).

A survey questionnaire was also used to gather information about the length of the DMT2 disease and the presence or consistent management of comorbidities as hypertension, dyslipidemia, osteoporosis, established cardiovascular disease, and diabetic retinopathy. Blood pressure was measured with a brachial mercury sphygmomanometer in a sitting position after resting for at least 10 minutes.

Complete blood count, C reactive protein, FPG, Hemoglobin A1C, cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL) were all measured after 12 hours of fasting, as well as urea, creatinine, uric acid, sodium, potassium, calcium, phosphorus, alkaline phosphatase, aspart aminotransferase (AST), alanine aminotransferase (ALT), presence of albumins in a single urine sample (quantitative analysis), Vitamin D, PTH were performed on central laboratory at General Public Hospital, "Osmi Septemvri", Skopje. At the Institute of Medical and Experimental Biochemistry, Faculty of Medicine - Skopje, single serum samples were used to calculate FGF23 (pg/ml) using the ELISA sandwich method. Elevated FGF23 was defined as a value >50 pg/ml [19].

Ultrasonographic color doppler device and analyses: Standard 2D ultrasonography with a linear Doppler probe 7.5 MHz, field of view 37 mm, on a General Electric Vivid 7 device was used. Seven arteries in the lower limbs underwent arterial doppler, as well as carotid arteries. As a benchmark, the guidelines from the European Society for Cardiology were used [20].

Osteodensitometer and analyses: Bone density was determined by analyzing the bone density of the lumbar spine and left femur. Osteodensitometry was performed on a DXA Medix90 device, France, according to the WHO standard [21] and the recommenddations of the International society for clinical densitometry (ISCD) from 2007 [22].

Ophthalmological examination: Biomicroscopy of the anterior and posterior eye segments with a slit-light biomicroscope - Alcon, SL 1000, USA. Native images and fundus (auto) fluorescence were made using a posterior eye segment camera - Canon CX-1, Japan. The categorization of the degree of diabetic retinopathy is according to the international classification for diabetic retinopathy [23].

Results

In Table 1, a descriptive analysis of the five cases that were discussed is provided.

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Table 1. Descriptive presentation of the five completely evaluated cases of our study

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	66	58	73	72	76
Gender	F	M	F	M	F
Height (cm)	155	190	161	177	162
Weight (kg)	78	140	65	98	79
Body mass index kg/m2	32.47	38.8	25.08	31.28	30.1
Systolic BP* (mm/Hg)	130	120	130	160	140
Dyastolic BP* (mm/Hg)	85	80	90	80	80
Duration of DMT2 (years)	5	5	7	15	20
Smoker	No	Yes	No	No	No
Antidiabetic therapy	M+I	M	M+SU	M+I	M+I
Hypertension	yes	yes	yes	yes	yes
Dyslipidemia	yes	yes	yes	yes	yes
Present osteoporosis	no	no	no	no	no
Established cardiovascular disease	no	yes	yes	yes	no
Diabetic retinopathy	no	no	no	no	no
Biochemical characteristics of the subjects					
*Hgb	12.9	14.8	11.0	12.5	13.5
*CRP mg/l	2.68	6.75	2.86	2.86	2.86
*FPG	6.51	5.81	7.60	8.91	5.09
*HgA1C (%)	6.5	6.4	6.2	6.9	6.4
Total cholesterol	3.29	3.97	3.92	5.3	3.84
Tryglicerides	1.13	1.20	1.47	2.63	1.09
*HDL mmol/l	1.45	0.96	1.35	0.96	1.07
*LDL mmol/l	1.62	2.96	1.92	3.1	2.65
BUN mmol/l	6.4	5.2	4.7	8.8	4.7
Creatinine umol/l	86.1	109.0	100.6	142.8	75.6
eGFR (ml/min/1.73m2)	65	63	51	45	70
Uric acid (umol/l)	315	414	227	509.43	211
Sodium (mmol/l)	138	140	143	139	141
Potassium (mmol/l)	4.3	4.7	4.2	5.0	4.7
Calcium (mmol/l)	2.38	2.37	2.44	2.38	2.07
Phosphorus (mmol/l)	1.17	1.11	1.11	1.02	1.2
*ALP (U/L)	54	79	69	42	82
*AST (U/L)	29	14	28	22	14
*ALT (U/L)	27	15	22	27	14
Albumin (g/l)	50	46.5	46.1	48	43
Total proteins (g/l)	74	81.5	79.5	76	78
Vitamin D (nmol/l)	20.05	61.82	93.95	41.8	31.84
PTH (pg/ml)	98.2	94.9	19.4	113	73.4
Albuminuria mg/l	11	50.5	12.3	23.9	11
FGF23(pg/ml) (mean value 50pg/ml)	36	56	78	101	42
Results from osteodensitometry					
T score left hip	-1.2	-1.2	-1.7	2.0	-1.5
T score lumbar spine	-1.1	-0.3	-3.1	3.1	-1.1
Results of Doppler US of the blood vessels					
IMT bifemoralis	0.7	0.7	/	/	0.6
a. femoralis sup.	0	0	Stent	Stent	Stent
a. tibialis ant.	0	0	/	/	/
a.tibialis post.	0	0	/	/	/
a. peronealis	0	0	/	/	/
IMT *ACD	0.6 + pluck	0.7	Stent	0.75	0.6
IMT *ACS	0.7 + pluck	0.7	Stent	0.75	0.6
Oftalmology findings					
Posterior segment	normal	normal	RDNP	normal	normal

*BP-blood preasure, *M-Metformin, *I-insulin, *SU-sulfonil urea, *ALP-alkaline phosphatase, *AST-aspartate

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aminotransferase, *HgA1C-HaemoglobinA1C, *ALT-Alanin aminotransferase, *LDL-Low density lipoprothein, *HDL-High Density lipo, *FPG-Fasting Plasma glucose, *CRP-C reactive protein, *Hgb-Haemoglobin, *ACDarteria carotis l.dex., *ACS - arteria carotis l.sin.*RDNP– retinopathia diabetic nonproliferativa

FGF23 has a value that is above above mean value in three participants, or 60% of the sample. All participants had at least one micro/macrovascular complication or BMM disorder, indicating that chronic DMT2 complications start developing early regardless of severity of CKD.

FGF23 increases inversely correlated with eGFR. One participant has albuminuria > 30mg/l, one has DR and both have elevated FGF23 above mean value.

Four of the disturbed KMM had increased PTH, two of whom also have raised FGF23, and one has osteoporosis and elevated FGF23. Three of the four have low vitamin D. Two of them had FGF23 above mean value.

Macrovascular consequences include three cases of established cardio-vascular diseases and all of them have increased FGF23 above the mean value. Four cases of peripheral artery disease (PAD), two of which also have elevated FGF23.

Discussion

The most common reason for death, diminished work capability, and disability is chronic consequences from DMT2. CKD is also one of the main reasons of death in numerous nations around the world. It is normal to predict a combination of the two entities in 40% of people with CKD or DMT2. This necessitates discovering the basis for the possible amalgamation of reasons for DMT2 complications. As a result, during the past ten years, researchers have focused more on the role of CMM in their occurrence, and FGF23 is frequently cited as one of the components, particularly in patients with CKD [14].

We conducted a pilot study to determine FGF23 in DMT2 patients with early-stage CKD and an eGFR of 45-70 ml/min/1.73m2, and we sought to understand its relationship to micro- and macrovascular problems as well as impaired BMM.

Recent studies have shown that elevated levels of FGF23 in the general population are associated with a variety of conditions, including excessive body weight and obesity (BMI>25 kg/m2), abdominal obesity, [24] metabolic syndrome, [25] elevated levels of adiponectin, [26] a higher risk of cardiovascular events [11,12,27], lifestyle factors etc. FGF23 is elevated in smokers compared to the non-smoking population [28,29], in those with low physical activity [30], when consuming foods rich in phosphates used for food preservation [31]. The cumulative effect of all this is multiplied in the DMT2 and CKD population.

In our investigation, FGF23 was elevated in a subject who had DMT2 for 5 years, with an eGFR of 63 ml/min/1.73m2, but a long-term heavy smoker and a BMI of 38.8 kg/m2. The patient just recently developed diabetes and is in the early stage of CKD, with no other concomitant diseases that are out of control, but due to long-term exposure to the effect of cigarettes and overweight condition there is a possibility that individual levels of FGF23 will rise.

FGF23 is confirmed to be inversely correlated with the severity of renal impairment in CKD by numerous research [5,6]. The possibility that BMM involves a substantial role in the pathophysiological pathways behind the development of complications in these individuals was first highlighted from CKD-MBD [8,32]. Many publications suggest that altered BMM and FGF23 are linked to DMT2 complications [33,34].

Additionally, patients with DMT2 who did not have early nephropathy had higher levels of FGF23. This contradicts the theory that FGF23 rises only when kidney function declines and shows that FGF23 can be elevated even before early nephropathy manifests. Due to such inconsistent findings, the causal relationship between FGF23, DMT2 and kidney dysfunction remains unclear [35].

The participants in our study were treated for hypertension, dyslipidemia, and have adequate glycoregulation. FGF23 was highest in the patient with the lowest eGFR, 45 ml/min/1.73 m2, and when eGFR decreases, mean value of FGF23 increases, supporting the idea that the two are not positively corelated. The patient with the highest albuminuria (50.5 mg/L) also had elevated FGF23, which is associated positively to the progression of DN.

The bone mineral indicators in the blood, including FGF23, were evaluated in a study aimed at the predisposition to fractures in individuals with DMT2 and early stage CKD [36]. In comparison to subjects without a fracture and in good health condition, individuals with a history of fracture had decreased levels of osteocalcin, Klotho, and vitamin D. As opposed to other patients, those with fractures have greater values for FGF23, phosphorous, and PTH. This suggests that the FGF23 marker could be used to predict fractures in these patients. Another study looked at how vitamin D replacement affected bone health and bone-mineral indicators like FGF23 [37]. Elevated FGF23 and Vitamin D insufficiency were present in all patients with CKD and DMT2. After substitution with Vitamin D, a moderate impact on bone markers was observed, including FGF23, which poses a dilemma for the mutual association of the components of BMM, especially Vitamin D over the others.

Inconsistency in the results is an issue that also occurs in our pilot study. Three patients had high FGF23 values. Three of them were found to be vitamin D deficient, although only one had high FGF23. Four patients had increased PTH, and two of those also had raised FGF23. These outcomes are inconsistent, as well. A participant of ours had osteoporosis with a T score of -3.2 and an elevated FGF23 level. The patient with the highest FGF23 value, on the other hand, had normal bone density. Additionally, in this section, the findings indicating the connection with FGF23 are conflicting.

The association of FGF23 with peripheral arterial disease (PAD) has been demonstrated both in vitro [38] and in vivo in patients with established cardiovascular disease [39], CKD [40], predialysis patients, and DMT2 patients. [41]. The mechanism of action of FGF23 on these processes and whether its neutralization would result in any benefit is unclear.

FGF23 is an important regulator of mineral metabolism and directly contributes to the process of mineral deposition in tissues and blood vessels as a result of phosphatemia and calcemia dysregulation [39]. It has been demonstrated in both basic and clinical research [10,13] that phosphatemia regulation is a significant predictor of CVD risk in individuals with CKD in all stages, including those with maintained renal function [12,42].

There have been conflicting results on the relationship between FGF23 levels and blood phosphorus in people with CVD but without CKD, despite the fact that the majority of studies that failed to discover a change in FGF23 levels were small and the phosphate load insufficient [43-45]. The ARIC study, however, showed that FGF23 is substantially linked to CVD regardless of all other known CVD factors or renal failure [27]. A Chinese study found that the presence of PAD of the lower extremities in DMT2 is independently and positively correlated with FGF23 [46]. The mechanism still needs to be further understood.

Two individuals in our investigation had established lower extremity PAD and increased FGF23. One patient had increased FGF23 but no lower extremity PAD, and the other had normal Doppler results. Our results point to a connection between FGF23 and the development of PAD.

Contradictory results have been found regarding the relationship between FGF23 and IMT. FGF23 has been shown by some writers to be a predictor of subclinical atherosclerosis in CKD patients, [47] but others have questioned this association on its own [48,19].

All of the patients in our study had normal IMT, ranging from 0.6-0.75.

A small number of publications have looked at relationships between BMM and DR in DMT2 patients with CKD, and those investigations have produced conflicting findings.

According to a sizable investigation, hyperphosphatemia and FGF23 independently predict the occurrence and severity of retinopathy in CKD patients. Independent of comorbidities, the severity of CKD, and the value of FGF23, hyperphosphatemia is positively correlated with the degree of DR, whereas FGF23 is not independently correlated with the degree of DR [18]. Another study verified the link between DR and increased prevalence of osteoporosis and lower bone density in women with DM as determined by DEXA. This study's shortcomings include the absence of male participants and the lack to distinguish DMT1 from DMT2 [17].

A significant intergroup difference in terms of bone metabolites and vitamin D levels was seen in a study of DMT2 participants with non-proliferative diabetic retinopathy (DRNP), proliferative diabetic retinopathy (DRP), and nondiabetic retinopathy (NDR). DRP having the lowest and NDR having the highest levels [49]. Another study revealed a connection between bone markers and diabetic microangiopathy, showing that changes in bone-mineral markers occur in patients with early-stage CKD before changes in bone density [50]. These studies' limitations include the fact that they used small samples and did not fairly represent the range of ages and lifestyles.

One participant to our survey has DRNP. The retinopathy patient has osteoporosis, high FGF23, and established PAD. This result suggests the possibility that DR and impaired BMM are related.

Conclusion

According to our results and previous research, our pilot study suggests a link of FGF23 with micro- and macrovascular complications in DMT2 patients in the early stage of CKD and supports the hypothesis that the disturbed BMM seems to have some role in the development of the same while FGF23 has a significant place in all that. For this paradigm to be defined, more research is required.

Conflict of interest statement. None declared.

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Case report

A Case of Waldenstrom Macroglobulinemia Presenting with Acute Kidney İnjury

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Abstract

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic hematological malignancy that may present with infiltration of the bone marrow, spleen and lymph nodes and IgM monoclonal gammopathy. WM rarely shows extranodal involvement and the diagnosis is made by lymph node or bone marrow biopsy. The rates of hepatomegaly, splenomegaly, and lymphadenopathy in patients with WM, respectively; 20%, 15% and 15%. Symptoms usually present with dizziness, blurred vision, epistaxis, or exacerbation of congestive heart failure when the IgM level is above 3 g/L. High IgM level and hyperviscosity symptoms require treatment. In this case report, we discuss the diagnosis of WM and the regression of renal damage after treatment in a 72-year-old female patient admitted with dizziness and nausea, who was hospitalized with acute kidney injury (AKI).

Key words: Acute kidney injury, Waldenström macroglobulinemia

Introduction

WM is a malignancy characterized by an increase in lymphoplasmacytic cells, which is seen in 2-3% of hematological malignancies. In this malignancy in which bone marrow, spleen and lymph node infiltration, hepatomegaly, splenomegaly and lymphadenopathy can be seen, patients often present with symptoms of hyperviscosity. Hyperviscosity symptoms occur when IgM levels are above 3 g/L. Rarely, peripheral neuropathies, vasculitis secondary to immune complex deposition can be observed [1]. Lung, central nervous system, gastrointestinal system, eye or renal system involvement can also be seen. Renal involvement is less common than plasma cell dyscrasia such as multiple myeloma. Proteinuria, microscopic hematuria, and rarely Bence-Jones proteinuria can be seen in patients with renal involvement [2]. Acute kidney injury occurs as a result of damage caused by aggregates formed by IgM, IgG, complement, cryoglobulins and light chains. In most cases, it is thought that atypical lymphoid cells cause renal damage by forming pseudo thrombus of IgM aggregates [3].

Case

A 72-year-old female patient with known diagnoses of hypertension and diabetes mellitus was admitted to the emergency department with complaints of decreased urine output, nausea, vomiting, abdominal pain, dizziness and weakness. Initially, she was admitted to the internal medicine clinic, considering AKI. She had no history of chronic kidney disease, and she had no history of recent contrast exposure and nonsteroidal anti-inflammatory use. The patient had complaints of dizziness, headache and tinnitus that had been going on for months. Medication revision was performed in the patient who was using candesartan and thiazide diuretics for hypertension and acarbose for diabetes. She had a history of diarrhea lasting longer than 1 month accompanying abdominal pain. On admission, the patient's blood pressure was 117/58 mm Hg, body temperature was 36.5, and O2 saturation was 94. ECG was consistent with left bundle branch block and atrial fibrillation, echocardiographic evaluation revealed 30% ejection fraction, pulmonary hypertension (left pulmonary artery pressure 50 mmHg), biatrial dilatation, left ventricular wall motion defect, and 1st degree mitral insufficiency. In the physical examination findings, she was conscious, oriented, cooperative, and diffuse minimal tenderness on palpation in the abdomen. On physical examination, there was no defense or rebound. Gas and stool discharge were present. Extremity examination revealed bilateral 1+ pretibial edema. The oropharyngeal mucosa was dry, with widespread dryness on the skin.

The patient, who was given hydration therapy during the emergency department follow-up, had a urine output of approximately 400 cc/day in the foley catheter.

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Laboratory findings were as follows: Blood gas pH 7.38 mmHg, pCO2 37.9 mmHg pO2 55.3 mmHg lactate 2.2 mmol/L, bicarbonate 22.8 mmol/L, hemoglobin 11.4 g/dL, MCV 99.1 fL, Leukocyte 6900 /uL, Neutrophil 3900/ul, Lymphocyte 2300/uL, 435000 /uL, urea 94 mg/dL, creatinine 3.5 mg/dL, potassium 4.17 mmol/L, calcium 7.9 mg/dL, aspartate transaminase 36 U/L, Alanine aminotransferase 13 U/L, Bilirubin (total) 0.27 mg/dL, bilirubin(direct) 0.24 mg/ dL, C-reactive protein 61.4 mg/l, albumin: 2.1, globulin: 4.1, erythrocyte sedimentation rate: 103 mm/h, troponin: 1021, urine analysis: density 1021, erythrocyte +1 , protein +3, ketone and glucose were negative. No significant pathology was detected in brain CT, diffusion MR, abdomen and thorax CT. Immunoglobulins, kappa/lambda were studied for further testing because of normocytic anemia and suspected AKI in the examinations. Kappa light chain 132 mg/L, lambda light chain 77.1 mg/L kappa/ lambda:1.71 globulin 4.1 g/dL, albumin 2.4 g/dL, Total protein 6.5 g/dL, IgM 27.1 g/L, IgG 3.75 g/L , Ig A was 1.41 g/L, Ig E was 26 IU/mL, C3 was 0.91 g/L, C4 was 0.23 g/L. Peripheral blood smear showed rouleaux formation in macrocytic erythrocytes, and a few lymphoplasmocytic-like cells were observed. Because of IgM over 3 g/dL and symptoms of hyperviscosity, bone marrow aspiration biopsy was performed for diagnostic purposes. In bone marrow aspiration, only a few lymphoplasmocytic-like cells were observed, and no increase in plasma cells was observed. After bone marrow biopsy, plasmapheresis treatment was started to prevent the development of renal damage secondary to hyperviscosity. After five days of plasmapheresis treatment, the control IgM value was 3.52 g/L. Plasmapheresis was performed with 8 cycles of fresh frozen plasma in total, correlating with the clinical evaluation. In the bone marrow biopsy, there was marrow tissue showing approximately 60% cellularity, and hematopoietic cells belonging to all three series were found in these areas. There was no maturation arrest in the myeloid series. Megakaryocytes increased in focal areas, with CD34 in 1% cells except vascular structures; CD117 (except for increased number of mast cells) was positive in 2% of cells. Small mature lymphocytes, most of which were CD20 positive, were scattered in the interstitium and formed paratrabecular aggregates. In addition, these cells with IgM; some of them stained positively for CD19 and Bcl2. It is negative with CD23, CD56, CD25, cyclinD1, Bcl6, CD10, CD5, IgG, IgD and IgA. There are also CD38 and CD138 positive plasma cells in between. Plasma cells were stained closely with kappa and lambda. The reticular fiber grade is consistent with grade 2 in focal areas. No amyloid deposition was detected due to Congo red negative staining. It was thought to be compatible with "Lymphoplasmacytic Lymphoma" containing CD20 positive lymphocyte aggregates as a diagnosis (Figure 1a, Figure 1b). After the R-Bendamustine treatment protocol was started by the hematology unit, the patient was discharged an outpatient follow-up 10 days later to monitor the treatment response. Significant regression was observed in renal function tests after plasmapheresis and chemotherapy.

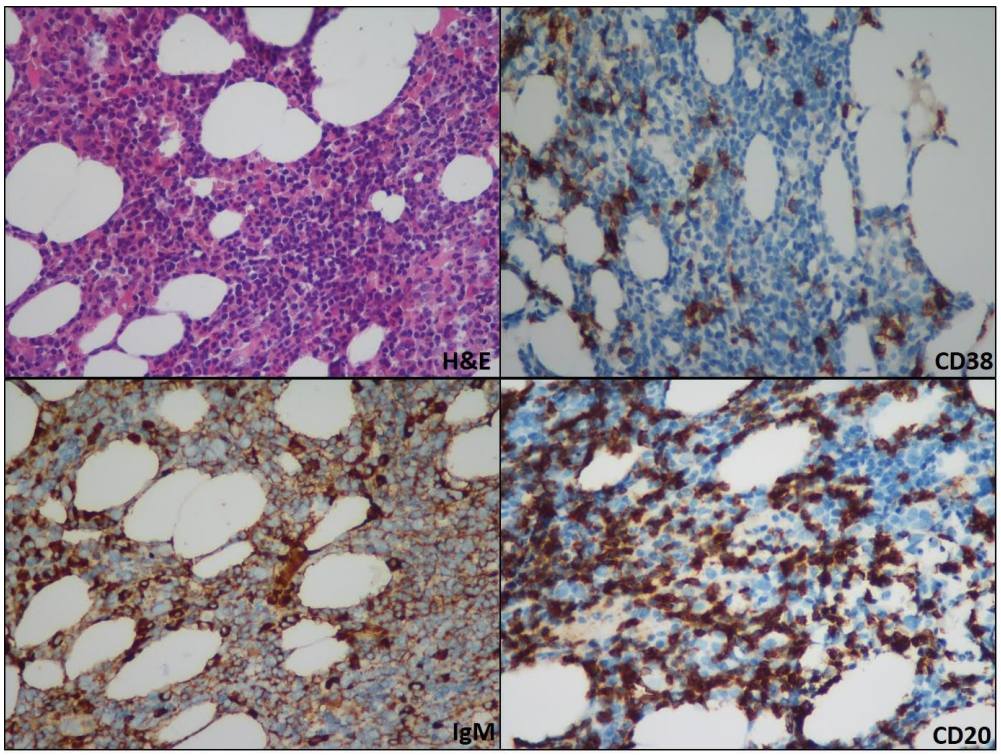

Fig. 1a. Hypercellular bone marrow biopsy for age, Hematoksilen & Eozin, 40x

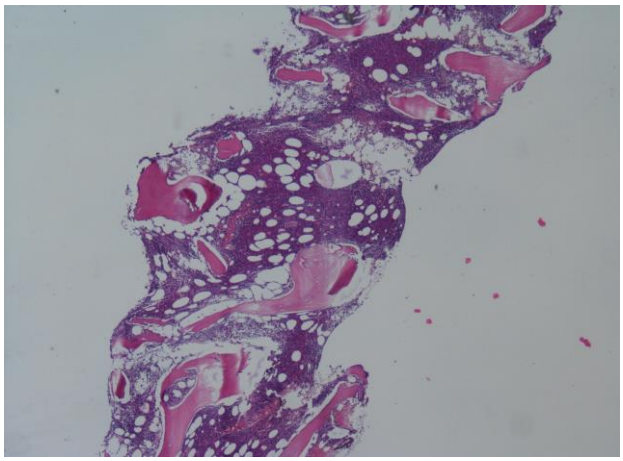

Fig. 1b. Lymphoid cells forming aggregates, Hematoxylin & Eosin, CD38 positive plasma cells, IgM and CD20 positive lymphoid cells, 400x

Discussion

WM is a rare B-cell lymphoproliferative disease that can present with different clinical presentations, multiple organ and system involvement, and mortality due to complications secondary to direct tumor infiltration and IgM accumulation if early diagnosis and treatment is not initiated. WM should be considered as a differential diagnosis in patients describing symptoms of hyperviscosity. Definitive diagnosis is made by demonstrating IgM concentration as well as infiltration in bone marrow biopsy. Decrease in IgM level and tissue response are determinants in the treatment response [4]. There is no cure in its treatment.

Allogeneic bone marrow transplantation may be considered in young patients, most of whom are resistant to standard chemotherapy and who have advanced organ involvement who are resistant to standard chemotherapy. Although serum monoclonal IgM elevation is a laboratory finding with a high positive predictive value for WM, it is not possible to define a specific concentration in the differential diagnosis of similar pathologies [5]. The most common diagnosis among individuals with monoclonal IgM increase but asymptomatic of course with a monoclonal IgM <3 g/dl and without severe anemia (Hb>12 g/dl) is MGUS [6].

The distinction between MGUS and a patient with asymptomatic WM can only be made by demonstrating bone marrow infiltration. Since lymphadenopathy and hepatosplenomegaly accompany in approximately one third of the cases in WM, it should be kept in mind that the diagnosis of WM and examination of serum immunoglobulins should be considered in patients with lymphadenopathy and hepatosplenomegaly of unknown etiology as a result of imaging methods. Central nervous system involvement; It can give a wide range of clinical manifestations, ranging from increased hyperviscosity due to malignancy and loss of concentration due to microcirculation disorder to coma [7]. From this point of view, no pathology was detected in the brain CT diffusion MRI requested from our patient who was described with a headache. An increased number of lymphoplasmacytic-like cells were also observed in the peripheral blood smear, which was performed to exclude microangiopathic hemolytic anemia due to thrombocytopenia and impaired renal function tests, which developed during the normocytic anemia follow-ups at the patient's hospitalization. It is thought that it would be useful to initiate early plasmapheresis in order to prevent tissue damage caused by hyperviscosity and to evaluate with peripheral smear before bone marrow biopsy in cases with suspected diagnosis. Since renal damage can be prevented in certain patient groups as a result of reducing hyperviscosity with plasmapheresis and chemotherapeutic agents, it would be beneficial to study serum Ig levels, kappa/lamp levels, erythrocyte sedimentation rate and C3-C4 levels in patients presenting with AKI. In the case described, renal biopsy was not performed due to the onset of urine output after plasmapheresis and the regression of AKI, and no need for hemodialysis developed during the follow-up. In the detailed history taken after hospitalization, the patient had neuropathic characteristics such as pain, numbness, and tingling in the bilateral lower extremities, which had recently progressed. Before the diagnosis of WM was made, diabetic neuropathy secondary to long-standing type-2 diabetes was considered in the patient's history. It should be kept in mind that neuropathy may develop and treatment should be started in order to control it. The most common neuropathy seen; distal, symmetrical chronic demyelinating peripheral neuropathy [8,9].

Although it is rare in WM, IgM accumulation may develop in the lamina propria and submucosa of the intestine independent of amyloidosis, which may develop secondary to the disease, and patients may present with gastrointestinal symptoms such as gastrointestinal bleeding-diarrhea-malabsorption [10]. In the patient who developed diarrhea during his clinical follow-up, and whose stool direct examination and parasite examinations were negative, and who described recurrent diarrheal attacks lasting longer than 1 month before hospitalization, it was also informed that the diarrhea regressed after 8 cycles of plasmapheresis, according to the history taken. The development of primary amyloidosis as a result of fibrillar deposition of the monoclonal light chain has also occasionally been reported. At the same time, the incidence of cardiac and pulmonary involvement was found to be higher in patients with IgM-related amyloidosis compared to other Ig types [11]. Rarely, secondary amyloidosis may also develop in the context of WM. When ventricular hypertrophy on Echocardiography and low voltage on ECG are correlated with clinical findings, it should be suggestive of possible cardiac amyloidosis secondary to WM. It should be kept in

mind that patients with suspected WM should be evaluated by echocardiography and the bone marrow material taken should also be stained for the presence of amyloidosis. In the echocardiography of our case, myocardial involvement/additional pathology in favor of amyloidosis was not observed, in fact, Congo Red staining in terms of amyloidosis was negative in the bone marrow biopsy. In addition, the initial pro-BNP level should be measured in every patient with suspected cardiac amyloidosis [12]. The point we would like to mention in this case is that WM-related acute kidney injury rarely develops and regression is possible with treatment [13]. In previously reported case series, PAS-positive subendothelial deposits were found in the glomerular capillaries in biopsy samples of WM-associated renal lesions. In the case described, biopsy was not considered necessary as a result of the regression of renal damage, as soon as the diagnosis was made quickly after the evaluation of serum IgM level and peripheral smear, and plasmapheresis treatment was started without wasting time with our preliminary diagnosis. Since the patient had a background of neuropathy during the treatment phase, bortezomib was not preferred in chemotherapy and R-bendamustine treatment was started. In patients describing symptoms of hyperviscosity, in patients with hepatosplenomegaly/lymphadenopathy detected as a result of imaging methods for various reasons. WM should be considered as a differential diagnosis and bone marrow biopsy should be performed in patients with suspected primary/secondary amyloidosis at the stage of AKI etiology investigation. In patients describing symptoms of hyperviscosity, in patients with hepatosplenomegaly/lymphadenopathy detected as a result of imaging methods for various reasons, WM should be considered as a differential diagnosis and bone marrow biopsy should be performed in patients with suspected primary/secondary amyloidosis at the stage of AKI etiology investigation. In patients describing symptoms of hyperviscosity, in patients with hepatosplenomegaly/lymphadenopathy detected as a result of imaging methods for various reasons, WM should be considered as a differential diagnosis and bone marrow biopsy should be performed in patients with suspected primary/secondary amyloidosis at the stage of AKI etiology investigation. In our case, although renal biopsy was not performed, improvement in renal function following alleviation of hyperviscosity was consistent with a possible ATN.We can report the fact that kidney biopsy was not performed in our case as a limitation of the study.

Conflict of interest statement. None declared.

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Case report

Challenging Case of Multisystem Inflammatory Syndrome in a 19-Year Old Female: A Case Report

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Abstract

Introduction. In comparison to older adults, SARS-CoV-2, leads to a mild illness in children and young adults typically manifested with fever, cough and gastrointestinal symptoms. However, the multisystem inflammatory syndrome in children and young adults (MISC) emerged during the coronavirus disease in 2019 pandemic.

Case report. We report a challenging case of a 19-year old female patient with signs and symptoms of multisystem inflammatory syndrome and SARS-CoV-2 infection, most probably as a post infectious disease with onset between 2 to 4 weeks after the infection. Its clinical symptoms may have overlaped with classical Kawasaki disease (systemic vasculitis) or Kawasaki-like syndrome (atypical) with fever, gastrointestinal symptoms, rash, conjunctival injection, hypotension, sore throat, mucosal changes with a relative lack of severe respiratory disease, myocarditis, hypoalbuminemia and elevated inflammatory markers. And indeed, the clinical presentation of COVID-19 in young adults resembles Kawasaki disease with gastrointestinal manifestations to severe inflammation with myocarditis.

Conclusion. Timely diagnosis and proper treatment of the multisystem inflammatory syndrome and SARS-CoV-2 infection are real challenge requiring multidisciplinary approach and tertiary resources.

Keywords: coronavirus disease, young adults, pneumonia, pleural effusion, rash, Kawasaki like disease

Introduction

In comparison to older adults, SARS-CoV-2 in children and young adults leads to a mild illness typically manifested with fever, cough and gastrointestinal symptoms. Nevertheless, the multisystem inflammatory syndrome in children and young adults (MISC) emerged during the coronavirus disease in 2019 pandemic [1]. It seems to be a post infectious disease with onset between 2 to 4 weeks after infection. Its clinical symptoms overlap with classical Kawasaki disease (systemic vasculitis) or Kawasaki-like syndrome (atypical) with fever, gastrointestinal symptoms, rash, conjunctival injection, hypotension, sore throat, mucosal changes with a relative lack of severe respiratory disease, myocarditis, hypoalbuminemia and elevated inflammatory markers [2].

We report a challenging case of a young female patient with signs and symptoms of MISC and SARS-CoV-2 infection.

Case report

A 19-year old female patient, SARS-CoV-2 PCR positive, was admitted to the University Clinic of Nephrology - Skopje (Covid 19- dedicated ward for adults). Initial symptoms included sore throat and fever treated with antibiotics with no improvement. After two weeks with positive SARS-CoV-2 test she was admitted to our hospital due to blood in the stool, body rash, severe anemia, elevated liver enzymes, elevated D-dimer, hypotension, tachycardia and heaptomegaly. Before admission due to her symptoms and the difficulty of a diferential diagnosis, the patient was examined by a hematology and a gastro-entero-hepatology specialists.

Laboratory findings timeline during hospitalization is shown in Table 1. At admission the patient presented with marked anemia with hemoglobin level below 50g/l, elevated inflammatory markers as leukocytes, thrombocytes, ferritin and C reactive protein. Electrolytes were all lower than referent levels. Increased transaminase activity, hyperbilirubinemia and hypoalbuminemia indicated a possible liver affection. Virology

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Table 1. Biochemical findings during hospitalization

Parameter	December 18	December 22	December 28
Hb (g/l)	42	86	111
RBC (10^{12}/l)	1.4	2.2	3.8
WBC (10^9/l)	25.5	18.3	12.9
PLT (10^9/l)	724	547	465
Ferritin (ug/l)	840		450
AST (U/l)	39		27
ALT (U/l)	134	76	73
LDH (U/l)	696	400	320
Total protein (g/l)	36	55	57
Albumin (g/l)	19	28	32
Total bilirubin (umol/l)	53		18
Direct bilirubin (umol/l)	43		10
Sodium (mmol/l)	130		142
Calcium (mmol/l)	1.6	2.0	2.2
Potassium (mmol/l)	3.5		4.4
Iron (umol/l)	2.1	2.5	9
Glucoses (mmol/l)	6.3	4.5	5.6
Creatinine (umol/l)	57		56
C-reactive protein (mg/l)	107	55	4.8

Abbreviations: Hb-hemoglobin, RBC-red blood cells, WBC-white blood cells, AST-aspartate aminotransferase, ALT-alanine aminotransferase, LDH-lactate dehydrogenase, alkaline phosphatase

Table 2. Hemostasis during hospitalization

Date	PLT (10^9/l)	Htc	Prothrombin time (s) (9.8–14.2)	Activated partial (s) (27.9–29.1)	Thrombin time (s) (16.1–19.01)	d-dimers (0–500)
Dec,18	589	012	12	32	14	7923
Dec, 22	378	034	11.1	29	16.8	15679
Dec, 28	287	050	10.5	31.5	18.9	8076

Abbreviations: PLT – platelets, Htc – hematocrit

findings on acute Hepatitis B and C were negative. Hemostasis findings showed marked elevation of D dimers during the whole hospitalization as shown in Table 2.

Interdisciplinary approach defined the treatment including antibiotics, low molecular weight heparin, several blood and plasma transfusions, cryoprecipitate, somatostatin analogue, proton pump inhibitors and low dose corticosteroids. Considering high inflammatory markers and fever, antibiotics were administrated with consecutive worsening of the rash and in consultation with pulmologist, the therapy was stopped. The patient underwent serological tests to detect antibodies, complement activity, proteinuria and results were in referent levels (IgE 64IU/ml, IgA 1.2 g/L, IgG 5.9g/L, IgM 0.84 g/L, C3 1.5g/L, C4 0.29g/L, rheumatoid factor 10 IU/ml, proteinuria 0.6g/L…0.09g/D). Microbiological and laboratory markers for sepsis were also negative (Procalcitonin 0.2 ng/ml, sterile hemoculture).

The fever and inflammation subsided after treatment with corticosteroids. Due to repeated rectorrhagia, gastroscopy and colonoscopy were performed. The gastroscopy findings were multiple ulcers in esophagus and stomach. The colonoscopy showed multiple ulcers in colon indicative of Crohn's disease or enteropathy due to the coagulopathies. The patient underwent serological tests (antineutrophil cytoplasmic antibodies, antinuclear antibody, anti-double stranded DNA, anticardiolipin antibodies, antiphospholipid antibody) for systemic diseases due to suspicion for vasculitis, but the tests returned as negative. Computer tomography was performed with findings of viral pneumonia, bilateral pleural effusion and pericarditis. The patient was on minimal oxygen support, therapy continued, the condition gradually improved, and there was an improvement in the laboratory analyses (Table 1). The patient was discharged after 10 days in stabile health condition, afebrile, with corrected anemia, normal liver enzymes, inflammatory markers, no signs of active bleeding with recommendation to continue the therapy with corticosteroids, low molecular weight heparin and proton pump inhibitors.

Discussion

Since an arising cluster of pneumonia cases was first reported in Wuhan (China) in December, 2019, the COVID 19 pandemic caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread worldwide. Children and adolescents presented a small proportion of COVID 19 cases. Starting from April 2020, there had been an abnormal increase in cases of Kawasaki-like disease and myocarditis in children. The cases were more frequent in places heavily affected by the SARS-CoV-2 epidemic (Italy, UK and US) [3]. Risk factors for developing severe disease among children infected with SARS-CoV-2

included age, viral load, and chronic comorbidities. The epidemic curve of the Pediatric Inflammatory Multisystem Syndrome (PIMS) cases followed that of COVID-19 with a lag time of 4-5 weeks, supporting the hypothesis of PIMS being a post-infectious manifestation [4].

Kawasaki disease is a systemic vasculitis in children and one of the leading causes of childhood acquired heart disease. There are similarities between these symptoms and Kawasaki disease, but also there are differences. The patients are older than in classical Kawasaki. In classical Kawasaki disease vomiting, diarrhea and abdominal pain are present in less than 18%, but gastrointestinal signs seem to be more present in COVID-19 linked Kawasaki like disease [2]. The virus has been detected in respiratory secretions, feces and blood. Also, these two could be different diseases with several presentations (ranging from Kawasaki disease, atypical Kawasaki disease, toxic shock syndrome and myocarditis) and different mechanisms (post-infectious reaction or cytokine storm as observed in adults with COVID-19).

One should differentiate between the "classical Kawasaki disease" triggered by COVID-19, atypical Kawasaki disease and a systemic inflammatory presentation similar to cytokine storm observed in adults. We can't rule out the implication of other factors, either infectious or environmental. Nevertheless, the incidence seemed to be low. WHO has developed a case definition and case report form for multisystem inflammatory disorder in children and adolescents [5].

Patients presenting with Kawasaki Disease and MISC can have similar symptoms, physical findings, and laboratory results, but they have different diagnostic criteria [6]. Children with MISC are usually older, have more symptoms consistent with clinical shock, have involvement of gastrointestinal and cardiovascular symptoms, and have lymphopenia with elevated inflammatory markers. Our patient's findings were in line with those of MISC rather than the Kawasaki disease. Because many cases met the diagnostic criteria of classic or incomplete Kawasaki disease, most reported MISC cases were treated using the standard protocol for Kawasaki disease, which is intravenous immunoglobulin with or without aspirin. A large proportion of MISC cases have a similar presentation to Kawasaki disease shock syndrome, mainly shock, so supportive and inotropic or vasoactive treatment should also be applied. Our patient also did not present with shock or the need of inotropes. Steroids have also been used to treat MISC. Many children with MISC also present with hypotension. If signs of shock are present, patients should be resuscitated with volume expansion using buffered or balanced crystalloids and should stay under close monitoring. Broad spectrum antibiotics are also appropriate because the clinical presentation (high C reactive protein, increased neutrophils) makes it difficult to exclude bacterial infection, but antibiotic treatment should be stopped once the infection has been excluded and the patient is clinically improved [3]. Inflammatory markers are useful for stratifying risk and monitoring response to therapy [7]. In our case, considering high admission inflammatory markers antibiotics were started, but immediately when infection was rolled out, only corticosteroids were administrated.

A hallmark of COVID 19 in adult and pediatric patients has been the coagulopathy [1,3]. Some patients have developed major vessel thrombosis. Although mechanisms underlying the coagulopathy in COVID 19 are still unknown, anticoagulant therapy (mainly heparin or a low molecular weight heparin) is currently recommended for patients with severe COVID 19. Many children with MISC have elevated D dimers which, in some institutions, is used as a guide for anticoagulant treatment, especially for those with a high concentration of D dimers. Our patient presented with coagulopathy, hemorrhagic syndrome and marked anemia requiring appropriate therapy. Hence, our patient belongs to the group of younger adults and according to the symptoms and laboratory parameters was supposed to have MISC. The patient had a good response to the therapy and she was completely cured.

Conclusion

The clinical presentation of COVID-19 in young adults resembles Kawasaki disease with gastrointestinal manifestations to severe inflammation with myocarditis. Physicians should be aware of the possibility of post COVID 19 inflammatory syndrome and MISC with all the potential for complications. Timely diagnosis and proper treatment of multisystem inflammatory syndrome and SARS-CoV-2 infection are real challenge requiring multidisciplinary approach and tertiary resources.

Conflict of interest statement. None declared.

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Case report

Acute Life-Threatening Complications During Hemodialysis in the Era of the Modern Devices

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Abstract

Serious complications during hemodialysis (HD) are rarely observed in part owing to more sophisticated devices and experienced staff. However, such complications carry the risk of catastrophic consequences including death. This report highlights major emergencies in three cases that may occurred during HD treatments while alarm mechanisms did not work.

Keywords: adverse event, needle dislodgement, renal dialysis

Introduction

Although hemodialysis (HD) is a complex procedure, it has become a safe treatment modality with modern devices. However, life-threatening complications may still occur due to HD components or human error. Problems such as intradialytic hypotension, muscle cramps, nausea, itching, anemia, bone disease, fluid overload, post-dialysis fatigue, sleep problems, depression are associated with loss of kidney function and prescribing hemodialysis. They are frequently encountered and resulting poor health-related quality of life [1,2]. On the other hand, procedure-related serious adverse events such as air embolism, vascular access hemorrhage, and venous needle dislodgement called as dialysis emergencies are very rare but they can result in mortality [3-5].

With this case series, we aimed to attract the attention of clinicians and machine manufacturers that alarm systems might not work in rare circumstances.

Case 1: An 82-year-old man has been undergoing maintenance HD for the last 2 years. He had experienced ischemic stroke with hemiplegia two months ago. In the last hour of a HD session, he became unresponsive, tachypneic with shallow respiration. Blood pressure was 70/40 mm Hg (110/60 mm Hg at the beginning of the session); a bolus of %0.9 sodium chloride was infused. Airway was inserted and non-invasive ventilatory support was provided. During intervention, it was noticed that the vein needle was decannulated from the fistula in the hemiplegic arm. Pump was stopped. It was thought that bleeding could not be detected early because the fistula arm was under the blanket during the HD session. The patient was transferred to the intensive care unit. Vasopressor support was provided. Three units of erythrocyte suspension were given. The patient, who recovered, was discharged after two days with gradual discontinuation of support. During this life-threatening blood loss, any alarm mechanism did not work about venous needle dislodgement (NIKKISO, DBB05, Tokyo, Japan). It was thought that the decrease in venous pressure was not sufficient to trigger the alarm algorithm.

Case 2: An 70-year-old man with a history of type 2 diabetes has recently experienced intradialytic hypotension, which he never developed since the initiation of HD 3 years ago. Ultrafiltration (UF) was stopped. Blood sugar was measured as 130 mg/dL. The electrocardiogram was shown sinus tachycardia. Bolus isotonic infusion (250 cc) was given. Symptomatic recovery did not improve. It was noticed that the outer wall of the single-use dialyzer (NIPRO ELISIO-21H, Synthetic hollow fiber polynephron, Hefei, China) was cracked and there was fluid leakage. The color of the dialyzer was light red-pink. HD was discontinued and symptoms resolved. Subsequently, dialysis was restarted with new equipments. UF around 2400 cc was performed and blood pressure was 110/60 mm Hg at the end of dialysis. Although UF was made as much as the target planned at the beginning of the dialysis session, the patients exit weight from HD was found to be 1.3 kg less. Meanwhile, alarm mechanisms did not work in the HD device (NIKKISO, DBB05, Tokyo, Japan) at any time during the session.

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Case 3: An 84-year-old man with chronic obstructive pulmonary disease and stage 3B chronic kidney disease underwent a surgery for obstructive nephropathy due to bladder cancer. Following transurethral resection, he was transferred to the intensive care unit due to delayed awakening. On the second day of the follow-up, a decision was made to prescribe HD for non-anion gap metabolic acidosis and hyperkalemia. Following HD, the metabolic acidosis of the patient did not improve and even worsened. The patient did not need vasopressor therapy and was stable. Despite the prescription of a second session of dialysis, acidosis did not correct. Intravenous sodium bicarbonate was started. The HD device used in the intensive care unit was newly procured and although installed by the authorized service, the need for a technical review arose. It was determined that the device did not absorb enough concentrated dialysis solution. The device did not give any warning about whether sufficient amount of bicarbonate in the applied dialysate (NIKKISO, DBB06, Tokyo, Japan) existed or not.

Discussion

We emphasized the life-threatening complications of HD in 3 cases. Essentially, the devices with very sensitive alarm mechanisms against almost every unfavorable situation did not give any warning in these life-threatening events. Of course, these situations are not unique to the brand of HD devices we use. Similar complications were reported using devices with other brands. Fortunately, serious complications are quite uncommon. For example, in the report of Karnik *et al*., cardiac arrest was determined as only seven times per 100.000 HD sessions [6]. Allergic reaction was reported to be as one episode in 12.000 HD sessions by Daugirdas *et al*. [7]. In a study in Pennsylvania [8], venous needle dislodgement was seen as one episode in 70.000 HD sessions among in center HD patients, while this rate was one episode per 11,000 sessions in home HD in Canadian series [3].

Venous needle dislodgement is a rare but serious complication of HD. Hemorrhagic shock may develop within minutes. Until the pump is stopped, 350-400 ml of blood per minute can be lost. In arteriovenous fistulas, the intravascular pressure is usually low, and if the alarm limit is set to a very low level, the alarm mechanism may not be triggered when the needle becomes dislodged. Clinicians, dialysis staff and biomedical engineers around the world strive to reduce venous needle dislodgement. Van Waeleghem *et al*. published 12 practical recommendations by identifying patients at risk for venous decannulation in order to correctly fix the dialysis needle [9]. Devices used in the detection of enuresis have been used in some units for the detection of blood loss (Redsense) [10]. When the patch placed over the venous needle, the device correctly alarmed in cases with blood leakage [11]. Although blood sensors brings additional cost for dialysis, it can be used in patients at risk for needle dislocation such as dementia, difficult access such as deep angle of cannulation, difficult location of access, restless patients, who are not fully conscious, who are allergic to the standard tape used to secure the needles. Tapes can be used to fix the vein needles, and it can be ensured that the fistula extremities of the patients are constantly visible by nurses or dialysis staff.

In our second case, the problem was intradialytic hypotension (IDH), which occurs in approximately 10-12% of treatment sessions [12]. The most important factor in the development of IDH is fluid removal faster than refilling. UF rates that exceed 13 mL/kg/h are associated with an increased risk of IDH and mortality [13]. This is more pronounced in patients with have autonomous neuropathy, cardiac failure and/or macro-microvascular disease [14]. IDH can also be seen in patients whose dry weight was not updated, who take antihypertensive drugs before dialysis and who consume food during dialysis. In our case, the UF target was adjusted according to body weight at the beginning of dialysis. The cause of hypotension was cracked dialyzer and the membrane rupture allowing blood loss to cross over the membrane into the dialysate. In case of hypotension occurring at the beginning of HD, the connections and dialyzer must be reviewed.

Persistent metabolic acidosis resistant to HD treatment may be seen in metformin intoxication [15]. Also, hemodynamically unstable patients (sepsis, circulatory failure, intestinal ischemia etc.), may experience lactic acidosis during or after conventional HD, and the metabolic status may deteriorate further. Dialysis-related acidosis may be observed in patients with underlying severe pulmonary disease [16]. In our case, a non-anion gap acidosis was captured, and it worsened following HD. It was deemed to be related to the newly installed dialysis device. Hardware settings of the device were rearranged, and effective dialysis could be performed. While venous blood gas testing is not routinely done after HD, the complication occurred in ICU where frequent blood gas analysis is performed. On the other hand, machine-related factors may be overlooked in intensive care settings, where there may be many other factors that may alter pH. Blood gas evaluation should be done after the first dialysis in newly installed HD devices. A detector for blood gas measurement may be placed in the HD device, and an alarm mechanism can be activated in case of getting enough dialysate. Collaboration with biomedical engineers may be of benefit. This patient may be a better example of dialysis inefficiency, rather than it's complication.

Adequate staffing which is defined as being able to see every patient during treatment, provide routine care and respond to changes in patient situation and emergencies [18], is a crucial factor that helps to mitigate complications of hemodialysis. No study has been conducted that reports a possible relationship between the specific staff to patient ratio and hemodialysis outcomes. Local government rules apply to how many patients should be cared for per nurse.[17] Care barriers such as shortage of nurse, financial problems of nurses, family problems, inexperienced nurses, nurse's fatigue and mental pressure, and heavy work shifts, lack of equipment technician, shortage of devices and equipment should be recognized and fixed in order to reduce hemodialysis complications [19,20]. In conclusion, serious complications may still be observed despite sophisticated machines. In order to develop dialysis devices, feedback should be obtained on a continuous basis, from dialysis practitioners about recent mechanical or hardware problems.

Conflict of interest statement. None declared.

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Case report

Enterorrhagia Presented in Patient with Granulomatosis and Poliangitis - A Case Report

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Abstract

Introduction. ANCA - associated vasculitis (AAV) as a term includes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). GPA is characterised by formation of granulomas and inflammation of small and medium-sized vessels leading to organ dysfunction, with a predilection for respiratory tract and kidneys. Gastrointestinal (GI) involvement happens rarely in GPA but when affected, has a poor prognosis.
Case report. We report a case of 50-year-old male with GPA who presents with pulmonary and renal syndrome, along with enterorrhagia due to GI vasculitis. The patient was treated with: hemodialysis, pulse methylprednisolone, cyclophosphamide, and plasmapheresis. Our systematic review of the literature found only a few case reports where gastrointestinal symptoms were one of the first signs of GPA, however, this entity might be more frequent if physicians would think of this possibility more often.
Conclusion. In cases of high clinical suspicion of GI involvement in GPA, an early aggressive immunosuppressive therapy and eventual surgical intervention remains the cornerstone of the management.

Keywords: ANCA vasculitis, gastrointestinal manifestation, granulomatosis with polyangiitis

Introduction

ANCA- associated vasculitis (AAV) as a term includes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. GPA is characterised by formation of granulomas and inflammation of small and medium arteries, arterioles, venules, and capillaries [2]. GPA is a small and medium vessel vasculitis with a predilection for respiratory tract and kidneys. It causes fibrinoid necrosis of small and medium-sized vessels leading to organ dysfunction. Gastrointestinal (GI) involvement happens rarely in GPA but when affected, has a poor prognostic factor [3]. Both small and large bowel can be affected leading to life-threatening complications.

Case report

We report a 53-year old man presented to otorhinolaryngology outpatient clinic with complaints of vertigo and decreased hearing, after being treated with antibiotics, corticosteroids and vitaminotherapy. CT scan showed right mastoid with reduced pneumatization, left mastoid with completely shaded mastoid cells, and cavum tympani filled with fluid bilateral. Fiberlaryngoscopy findings showed tumor formation, visualized in the area of the soft and hard palate. Biopsy was done and patohystology finding showed granuloma, with presence of a discontinuous multi-layered squamous epithelium, next to which an ulceration covered by a fibrinopurulent membrane was observed. The bottom of the ulceration is covered with young granulation tissue. Beneath the epithelium and ulceration, there was an edematous stroma with numerous capillaries with fibrin deposition, infiltrated with a mixed inflammatory infiltrate of lymphocytes, plasma cells, macrophages, and polymorphonuclear granulocytes and giant cell type. Immunohistochemistry p53 was negative excluding malignant neoplasm. Three days later, the patient was admitted at our clinic due to anuria, elevated inflammatory markers (procalcitonin and CRP), elevated levels of serum creatinine 1539 umol/, urea 37 mmo/l, hyperkalemia 6.5 mmol/l, hemoptysis and low haemoglobin 70 g/dl level. Central venous catheter was placed and hemodialysis treatment was initiated with simultaneously administered parenteral dual antibiotic and antifungal therapy. At the same time, we started with substitution with multiple red blood cell transfusions and blood derivatives.

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Pseudomonas aeruginosa was isolated from the urine, the blood culture remained sterile. PCR test for Sars CoV2 infection, serological findings for infectious agents such as: anti Treponema pallidum IgG and IgM, Lowenstein culture, Fluorescent microscopy of sputum and Genexpert MTB/RF sputum remained negative. Immunohematological analyses: IAT, DAT, Enzyme test, Cold autoagglutinins, Cold isoagglutinins, Coombs autoagglutinins and Isoagglutinins with Coombs remained negative as well. The antinuclear factor (ANA) was negative and cytoplasmic anti-neutrophilic cytoplasmic antibody (c-ANCA) was 3+ positive. Routine urine examination showed trace of proteins, 8-10 erythrocytes, and plenty of leucocytes. Ultrasonography revealed that both kidneys were normal in size and slightly increased echogenicity. Due to the appearance of hemoptysis and a drop in oxygen saturation, a pulmonologist was consulted, and CT scan of the lungs was performed in addition to nodules and alveolar hemorrhage (Figure 1 and Figure 2). The patient was treated with high-dose of pulse corticosteroids followed by an intravenous cyclophosphamide (1g) pulse and plasmapheresis. Thereafter the hemoptysis resolved

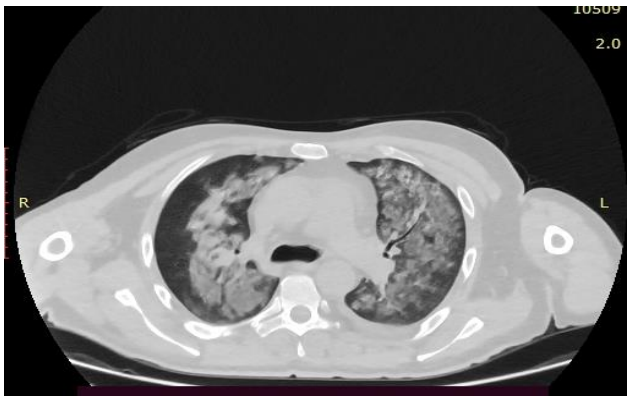

Fig. 1. Bilateral ground glass opacification more pronounced on the left, with perihilar predominance component and relative sparing of the pulmonary parenchyma subpleural, thickened walls of small blood vessels, air bronchogram present as well as small pleural effusion on the left. A finding indicative of alveolar hemorrhage

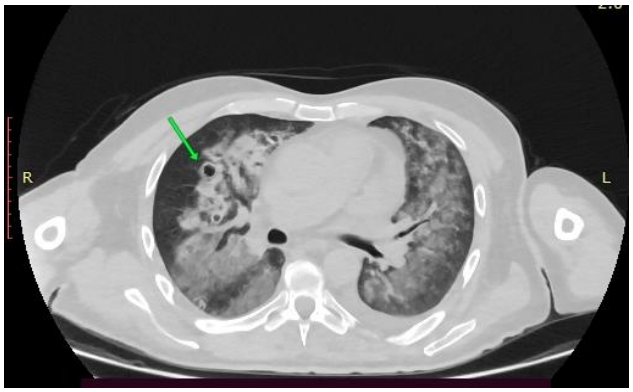

Fig. 2. The arrow points to a cavitating lesion with thickened wall and irregular margins

and the oxygen saturation was improved. Due to the occurrence of melena and blood in stool, gastroscopy was performed and upper digestive bleeding was ruled out. Digital rectal examination was performed and showed that it is not melena but enterorrhagia.

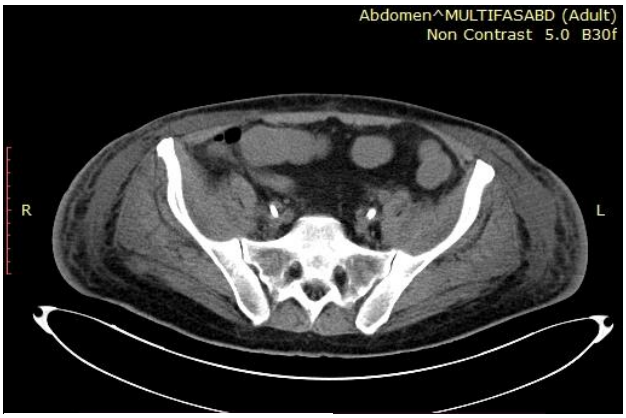

Fig. 3. Suspicious for hemorrhage

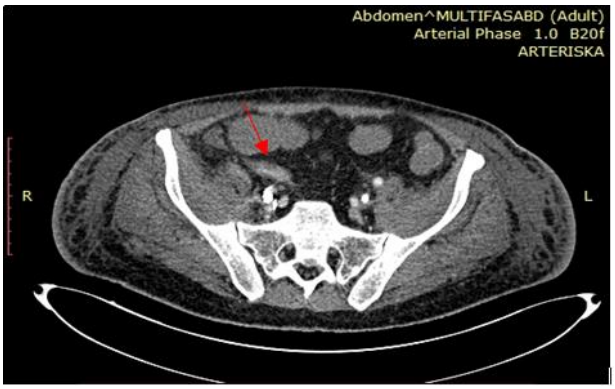

Fig. 4. Showed a discrete hyperdense linear zone in part of the wall of the distal ileum with increased density compared to the native series

In consultation with a transfusionologist and gastroenterologist, intensive therapy was started to correct blood count and hemostasis (including tranexsamic acid, sandostatin, low-molecular heparin, FFP, cryoprecipitate and platelet mass). The patient continued to have a drop-in hemoglobin despite frequent blood transfusions. Hemodialysis were guided by heparin-impregnated membranes without supplemental heparin. Due to the enterorrhagia and severe anemia, CT angiography of the abdomen was performed to localize the site of bleed, arterial phase of scans (Figure 4) showed a discrete hyperdense linear zone in part of the wall of the distal ileum with increased density compared to the native series (Figure 3), being suspicious for hemorrhage. Enterorrhagia was accepted as part of the vasculitis, continuing with conservative treatment, replacement therapy and because of haemodynamic instability a continuous veno-venous hemodiafiltration (CVVHDF) was initiated. Two weeks after the first, the second dose of cyclophosphamide was administered. The digestive surgeon suggested eventually

operative treatment after hemodynamic stabilization. Unfortunatelly, the patient continued to have downhill course and required frequent blood transfusions and continued to have enterorrhagia. However, the patient developed hypotension, affection of consciousness and sustained a refractory cardiac arrest.

Discussion

American College of Rheumatology (1990) defines GPA by the presence of at least two of the four criteria: (1) nasal or oral inflammation, (2) abnormal chest radiograph with either the presence of nodules, fixed infiltrates, or cavities, (3) urine sediment with hematuria or red cell cast, and (4) granulomatous inflammation on biopsy within an artery or in the perivascular or extravascular area of an artery or arteriole. The presence of two or more of these four criteria is with sensitivity of 88.52 and specificity of 92%. A classification tree of five criteria is also constructed, they are the same as previous four criteria including hemoptysis with sensitivity of 87.1 and specificity of 93.6% [4]. Around 90 percent of patients with multisystemic active GPA have ANCA positivity. Thus, an absence of ANCA not necessarily rules out the diagnosis [5].

GPA is characterised by necrotising vasculitis and granulomatous inflammation. The disease has a predilection to the upper and lower respiratory tract and the kidneys, but most patients also show systemic disease. Gastrointestinal tract involvement is less common, effecting 10% to 24% of patients with GPA, and is usually detected on autopsy. Vasculitis can cause local or diffuse pathologic changes in the gastrointestinal tract [6].

Pagnoux *et al*. conducted a study looking at 62 patients with GI involvement in small- and medium-sized vessel vasculitis. It was noted that abdominal pain was the most common symptom (97%) followed by nausea and vomiting (34%), diarrhea (27%), and hematochezia and melena (16%) [7]. The variety of lesions includes submucosal oedema, haemorrhage, ulcer, paralytic ileus, mesenteric ischaemia and infarction, bowel obstruction, appendicitis, cholecystitis, acute pancreatitis and life-threatening perforation [7-11]. GPA very commonly affects multiple GI sites, most commonly affecting the small bowel. GI involvement occurs within the first two years of diagnosis [12].

In the current report, we highlight an uncommon presentation of GPA presenting with GI bleeding. Despite the aggressive management with steroids, cyclophosphamide, plasmapheresis, the prognosis was poor. In literature, it is suggested that the use of corticosteroid therapy may be responsible for the development of intestinal manifestations. Nevertheless, and irrespective of GI involvement, immunesuppressive therapy should be used [13]. When present, GI complications adversely affect prognosis and are an indicator of the disease severity [14].

Conclusion

GI involvement in GPA is uncommon but not unknown and can have a poor outcome. High clinical suspicion with early aggressive immunosuppressive therapy and eventual surgical intervention remains the cornerstone of the management.

Conflict of interest statement. None declared.

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Letter to the Editor

Immunoadsorption Use in Patients with Antibody Mediated Rejection

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Dear Editor,

In recent years, antibody-mediated rejection (AMR) has been increasingly recognized as contributing to most kidney graft failures. Intensification of immunosuppression and antibody removal by therapeutic plasma exchange or immunoadsorption (IA) has been a mainstay of treatment in most centers. The efficacy of IA in treating AMR was suggested in a relatively small series of patients [1-3], but knowledge of its efficiency in removing specific antibodies is lacking.

We present a case of a 69-year-old kidney transplant male patient who is refractory to immunoadsorption (IA) removal of donor-specific antibodies (DSA), human leukocyte antigen (HLA) class II, specificities DQ2 and DQA1*05.

He was diagnosed with autosomal dominant polycystic kidney and liver disease in 2013. From August 2013, kidney function was replaced with intermittent hemodialysis until the transplantation from a deceased donor was performed in May 2016. He received standard triple oral immunosuppressive therapy (IS)-tacrolimus, mycophenolate mofetil, and prednisone. His posttransplant course was uneventful until December 2021, when he required hospitalization due to extensive bilateral COVID-19 pneumonia requiring oxygen supplementation, with modification of immunosuppression. His clinical status improved, but laboratory tests showed kidney allograft deterioration with increased serum creatinine (sCr) from initial values of 130 to 220 μmol/L. Luminex-based panel-reactive antibodies detection showed donor-specific antibodies, HLA class II, DQ2 specificity with MFI: 19800-20500, and DQA1*05 specificity with MFI: 16900-20000). The pathohistological analysis of the kidney allograft biopsy specimen revealed chronic active, C4d positive, AMR, associated with acute cellular rejection, Banff classification grade Ia.

Due to cytomegalovirus (CMV) reactivation, he was treated with ganciclovir and CMV-specific polyclonal immunoglobulin. Rejection was treated with 6-methylprednisolone pulses. Fifteen IA procedures were performed, with 1.5 to two plasma volumes treated during each session. The control Luminex-based PRA detection (done after the first five consecutive IA procedures) showed a unchanged titer of DSA. Control PCR of CMV DNA was negative. After the planned 15 IA procedures were completed, the Luminex-based PRA detection was repeated, which again verified the high value of DSA, HLA class II (DQ2 with MFI: 18300-19900 and DQA1*05 with MFI: 16100-19900), which indicated refractoriness to DSA removal by IA. At the subsequent outpatient control examinations, sCr was 200 and 170 μmol/L. Proteinuria remained unchanged. His treatment was continued with an increased dose of a steroid.

Immunoadsorption in the indication of acute or chronic AMR has efficiently been initiated after other treatments, such as depleting anti-lymphocyte antibodies, high-dose steroids, or even TPE, have failed [1,2]. However, the refractoriness of antibodies to removal by IA is unknown. The method failed to decrease antibody titer in some patients [3] and with different ligands [4]. The immune adsorber Globaffin® uses Peptid-GAM® ligands for the binding of antibodies. Some antibodies may have physical or chemical characteristics, making them refractory for removal.

With this case report, we would like to emphasize that IA may be inefficient in removing some DSA and, therefore, be unsuccessful in recovering graft function. Further studies with larger groups of participants are needed to determine the antibodies that may be refractory to removal by IA.

Conflict of interest statement. None declared.

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