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REVIEW

CARDIAC TUMORS

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Abstract: *Cardiac tumors represent a rare and challenging clinical situation. They can be primary (benign or malignant) or secondary (metastatic). Secondary tumors are more frequent than the primary tumors. Most of the primary cardiac tumors are benign and originate from the endocardium or myocardium, while the metastatic tumors develop from lung, breast, kidney carcinoma, melanoma and lymphoma. The diagnosis of cardiac tumors is often difficult because of their rarity, variety and nonspecific symptoms. The clinical manifestations depend on tumor's size, location, infiltration and consist of four categories: systemic manifestations, cardiac manifestations, embolic events, and metastatic manifestations. Echocardiography represents the main imaging technique used to detect cardiac masses. Computed tomography (CT) and magnetic resonance imaging (MRI) are used to achieve more information about tumor's composition, extension, vascularization, and possibility of surgical treatment. The histological evaluation is necessary for a positive diagnosis and staging of the cardiac tumor. The treatment of cardiac tumors depends on the type of tumor and symptomatology.*

Keywords: cardiac tumors, echocardiography, metastases.

INTRODUCTION

Cardiac tumors are extremely rare and represent a challenging clinical situation. They are classified in primary and secondary (metastatic). The prevalence of primary cardiac tumors is approx. 0.05% in autopsy series, while the secondary ones are 20-40 times more frequent than primary tumors [1]. 75% of primary tumors are benign (atrial myxoma being the most common) and 25% are malignant (mostly rhabdomyosarcoma) [1]. Usually, primary cardiac tumors originate from the myocardium or endocardium, while the metastatic cardiac tumors originate from lung, breast, kidney carcinoma, melanoma and lymphoma. 15% of patients suffering from a form of cancer develop heart metastases [2].

CLASSIFICATION

I. Primary cardiac tumors

I.1. Benign cardiac tumors

I.1.1 Myxoma

Myxoma represents the most common benign tumor, comprising 25% of all cardiac tumors and 50% of benign cardiac tumors [4]. It affects mostly women aged 30-65 years old. Myxomas have different locations: 75% in the

left atrium (originating from the fossa ovalis), 20% in the right atrium and 5% in the ventricles.

Myxomas may have a familial predisposition and be encountered in younger patients, consequently it is necessary to accomplish the screening of first-degree relatives. The most frequent syndrome is the Carney complex, an autosomal dominant inherited disease in which recurrent cardiac myxomas, extracardiac myxomas (skin, breast), pigmented skin lesions, schwannomas, and endocrine tumors (determining endocrine overactivity-pituitary adenoma, testicular tumors, thyroid adenoma, ovarian cysts) may coexist [5].

Myxomas originate from mesenchymal stem cells and can have a size up to 15cm. Most of them are pediculated and may obstruct the mitral valve, causing valvular dysfunction, while the rest are sessile and broad-based. They have a heterogeneous composition, with hemorrhage, fibrosis, calcification, and necrosis areas.

I.1.2 Papillary fibroelastoma

Papillary fibroelastoma represents the most common valvular tumor, accounting for 75-80% of cases. The papillomas appear frequently on the left heart and are small in diameter. They resemble 'sea anemonas' as they have a short pedicle arising from a central core [6]. They don't cause valvular dysfunction but have a high risk of cerebral and coronary arteries embolization, surgical resection being considered mandatory [7].

I.1.3 Rhabdomyoma

Rhabdomyoma represents the most frequent cardiac tumor in children, especially in those with tuberous sclerosis [1]. Rhabdomyomas are usually multiple, and they affect both ventricles, causing obstructive complications and arrhythmias. Sometimes, they regress spontaneously with age and treatment is usually conservative [8].

I.1.4 Fibroma

Fibroma represents the second most frequent cardiac tumor in children, even though it can also affect adults. Fibromas originate on the left side of the heart, mainly in the ventricular septum. They can constrain the conduction system, resulting in arrhythmias and sudden death. Sometimes, fibroma can be a part of a syndrome which associates generalized body overgrowth, skeletal abnormalities, and different benign and malignant tumors [1].

I.1.5 Lipomas and Lipomateous Hypertrophy of the Interatrial Septum

Lipomas represent the second most common primary tumor. They are located in the left ventricle, right atrium and interatrial septum. Many are asymptomatic, but some of them can determine conduction system disturbances, arrhythmias, and heart failure [9]. Lipomatous hypertrophy of the interatrial septum represents the accumulation of adipose tissue in the interatrial septum and affects the elderly and obese male patients [10].

I.1.6 Other primary benign tumors - angiomas, teratomas, mesotheliomas, paragangliomas are rare and affect children. Teratomas appear in the anterior mediastinum and determine constrictive pericarditis [2].

I.2. Malignant tumors

I.2.1 Sarcomas

Sarcoma represents the most frequent malignant cardiac tumor. It affects adults aged between 40-50 years old. 40% of them are angiosarcomas and originate in the right atrium and 60% are represented by rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, liposarcoma, which originate in the left atrium [11]. Angiosarcomas appears especially in men. Clinically, patients have signs of cardiac failure, pericardial effusion, and chest pain. They frequently extend to epicardium, endocardium and intracavitary, pleura or mediastinum. Pulmonary metastases are common, and the prognosis is unfavorable [12].

Rhabdomyosarcomas are more common in men. They are characterized by the occurrence of non-specific signs and symptoms and, in comparison with

angiosarcoma, rhabdomyosarcomas rarely invade across the parietal pericardium. The prognosis is poor [13].

I.2.2 Pericardial mesothelioma is extremely rare. It affects especially men of all ages. It can determine cardiac tamponade and spinal and brain metastasis [2].

I.2.3 Primary lymphoma occurs in patients with immunodeficiency or HIV/AIDS. They cause heart failure, cardiac tamponade, arrhythmias, and superior vena cava syndrome [2].

II. Secondary (metastatic) cardiac tumors

Metastatic cardiac tumors are 30-40% more frequent than primary cardiac tumors. They originate from melanomas, lymphomas, lung, breast, and renal cancer [14]. Metastases develop via blood dissemination, direct extension, or propagation via superior or inferior vena cava to the right atrium.

The most affected structure is the pericardium, resulting in pericardial effusion which sometimes consists of cancer cells, blood clots or fibrin. The occurrence of heart failure, arrhythmias, and cardiomegaly in a patient with malignant disease should raise the suspicion of cardiac metastases. However, cardiac metastases are clinically silent in 90% of cases [15].

Some studies showed that melanoma has a propensity for heart metastases, affecting all four chambers. Leukaemias and lymphomas regularly invade the heart, creating intramyocardial masses [16].

POSITIVE DIAGNOSIS

The diagnosis of cardiac tumors often represents a challenge because of their rarity, variety and nonspecific symptoms. Patient's history and clinical examination rarely lead to direct diagnosis. Paraclinical criterias (electrocardiography, laboratory, echocardiography, angiography, cardiac MRI, scintigraphy) are necessary, but histological evaluation via biopsy is essential for the final diagnosis [1].

CLINICAL DIAGNOSIS

Systemic manifestations and cardiac manifestations, embolic events and metastatic manifestations are part of the clinical diagnosis.

1.Systemic manifestations are represented by fever, fatigue, rush and Raynaud syndrome, resembling vasculitis or other connective tissue disease. These symptoms are determined by the secretion of interleukin 6 and endothelin from tumor cells [1].

2. Cardiac manifestations depend on the location of the tumor, its size and the extension on adjacent tissues. Cardiac manifestations are frequently caused by obstructive mechanism of heart chambers or valves (with valvular dysfunction), compression of coronary arteries, compression of conduction system and pericardial effusion.

On one hand, intramural tumors cause insignificant cardiac manifestations. If these tumors are small in diameter, they can be clinically silent, while if they are large in size, they can determine obstruction of the coronary flow or compression of cardiac chambers.

On the other hand, intracardiac tumors produce important signs and symptoms. Myxomas can determine the triad of heart failure, embolic events and systemic symptoms. Myxomas located in the left atrium cause mitral valve obstruction (via mitral prolapse) and, consecutively, specific signs and symptoms as syncope, dyspnea and a diastolic murmur that resembles the mitral stenosis murmur.

Tumors located in the right atrium produce clinical manifestations of right-sided heart failure.

Fibroelastoma is asymptomatic, but it can be a source of systemic emboli. Rhabdomyomas are asymptomatic. Fibromas can cause arrhythmias. Sarcomas cause obstruction of coronary flow and tamponade. Teratomas cause respiratory disease and cyanosis because of aorta and pulmonary artery compression [2].

3. Embolic events occur due to the capacity of embolization of tumor cells or thrombi formed on the tumor area. The risk of

embolization depends on type of tumor, location, and consistency. The highest risk is presented by the small tumors with friable surface [2].

4. Metastatic manifestations. The metastases are usually localized in the pericardium, determining pericardial effusion, constrictive pericarditis, tamponade, arrhythmias and sudden cardiac death [17]. Cardiac manifestations in a patient suffering from neoplasia are usually correlated to cardiotoxicity induced by chemotherapy or occurrence of cardiac metastases.

PARACLINICAL DIAGNOSIS

- **Imaging techniques** are used to determine the presence of the tumor and for differential diagnosis with thrombi and vegetations. They are represented by echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI).
  1. **Echocardiography** represents the most used technique for detecting cardiac function, chambers' dimensions and possible cardiac masses, as it can be easily performed at the patient's bedside [18]. Transthoracic echocardiography (TTE) can evaluate the location, size, shape, mobility and extent to other cardiac structures [19][20]. TEE can identify small tumors (<5mm) and tumors localized in the posterior cardiac segments [21]. Moreover, when the transthoracic image is difficult, TEE can be used to achieve clear information about the nature of the tumor and its consequences on cardiac function [22].

     Malignant tumors are extremely vascularized, and they appear with higher accumulation on echocardiography when contrast is administered, leading to a clearer diagnosis. In comparison, benign tumors are less vascularized, the administration of contrast does not give a clear image of the origin of the tumor and, consequently, it can be difficult to differentiate them from thrombi [23].
  2. **CT** is less efficient compared to MRI, but it can provide useful information about the nature of the tumor by measuring X-ray attenuation and tumor extension to other cardiac structures. Multidetector CT can evaluate the grade of calcification of the mass tumor, define small lesions and is needed for staging of malignant tumors [24].
  3. **MRI** represents the most useful tool in detecting and diagnosing cardiac tumors. MRI can evaluate the extension to cardiac structures, its hemodynamic consequences and the possibility of a surgical intervention. It can also describe the content of the tumor by studying the signal in T1, T2-weighted images and help in differential diagnosis with thrombi by administering contrast [25]. Hence, MRI is capable of rapid acquisition of heart images with very high spatial and temporal acquisition and superior cardiac tissue description [26].
- **Histology.** The histopathological evaluation is necessary for a positive diagnosis and staging the cardiac tumors. This can be determined by using the cytological exam of pericardial or pleural fluid, percutaneous/transvenous cardiac biopsy conducted by echocardiography or via thoracoscopy/thoracotomy.

TREATMENT

1. **Benign tumors.** The treatment of benign primary tumors is surgical resection, followed by echocardiographic monitorization over 5-7 years. Surgical excision is curative, with 95% survival in 3 years [2].

   Myxomas have a high indication of surgical resection because of the risk of embolic events. However, rhabdomyomas do not require surgical excision, as they regress spontaneously.

   In case of large (>1cm) or mobile tumors, papillary fibroelastomas are surgically removed, while conservative treatment is preferred in small, immobile tumors, even though these

masses have a high risk of embolization [1].

Lipomas and lipomatous hypertrophy of interatrial septum are surgically removed in case of hemodynamic instability [27][28].

2. **Malignant tumors.** Treatment of malignant primary tumors is usually palliative (radiotherapy, chemotherapy, management of complications), as the prognosis is poor.
3. **Metastatic cardiac tumors.** The treatment of metastatic cardiac tumors depends on tumor's origin. It requires management of the primary tumor and control of the cardiovascular complications (chemotherapy, palliation, pericardiocentesis) [2][28].

CONCLUSIONS

In conclusion, a proper diagnosis of cardiac tumors is essential in order to initiate an appropriate treatment. Imaging techniques such as echocardiography, CT, MRI may increase the sensitivity and specificity for characterizing the lesions. However, a gold standard positive diagnosis requires histopathological examination for establishing the most appropriate treatment and prognosis.

Author Contributions:

L.B.G. conceived the original draft preparation. L.B.G. and C.D. were responsible for conception and design of the review. L.B.G. and C.D. were responsible for the data acquisition. L.B.G, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. L.B.G. and C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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REVIEW

WOMEN AND CARDIOVASCULAR DISEASES

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Abstract*: Cardiovascular diseases have been the leading causes of death worldwide. According to the World Health Organisation, an estimated 17.9 million people died from cardiovascular diseases in 2019, meaning 32% of all global deaths. In the last decades there had been ongoing efforts in raising awareness through campaigns about the impact of cardiovascular disease in women. These efforts, combined with a raise in the socio-demographic index, led to a global decline in age-standardised cardiovascular disease mortality in women in the past 30 years. There are many differences regarding the biological, social, research data, access to healthcare between men and women. This review summarises the latest evidence regarding the traditional risk factors for cardiovascular disease in women, the gender disparities that lead to different outcomes in the primary and secondary prevention in men and women and the under recognised risk factors of the modern society, such as depression, anxiety, chronic stress, abuse and intimate violency and environmental risk factors. Most of the risk factors can be identified early in the life of patients and are modifiable, therefore early screening and intensive risk factor modification, along with medications in certain patients, would make a difference in the outcome of the primary prevention.*

Keywords: cardiovascular risks, women, cardiovascular disease, menopause, gestational diabetes, pre-eclampsia.

INTRODUCTION

During the last decade it has been an accelerated process of social, cultural, scientific and technological development. The biological differences between men and women and the influence of cultures that conditionate the access to knowledge, scientific tools and qualitative healthcare are just a few factors that need to be unravelled for a better understanding of the sex-specific differences in outcomes and cardiovascular disease burden.

The Lancet women and cardiovascular disease Commission is the first effort of this kind that aims to reduce the global burden by 2030 through raising global awareness of gender-related disparities regarding cardiovascular disease, providing recommendations from an international team of experts in this field and a springboard for future research [1]. Cardiovascular disease mortality has indeed declined in the female population in the last 30 years but this effect was best noticed in high-income and well developed countries, while in the most other regions of the world the numbers remained unchanged and actually in the countries with a low-income and quality

of life, the mortality was greater in women compared to men [2].

Lately, some alarming trends were observed regarding cardiovascular disease morbidity and mortality, with a rise of mortality in women in the USA and Canada and a higher prevalence of myocardial infarction in younger French women [3-5]. The population who seems to be more affected lately is represented by women aged between 35-54 years old and the supposition is that it is a result of the obesity epidemic and rising prevalence of smoking and other traditional risk factors [4]. Although the decrease of cardiovascular disease mortality was mentioned, the morbidity remains high, especially due to stroke and ischaemic heart disease [6].

It is well known that hypertension, dyslipidemia, diabetes, obesity, sedentary lifestyle, poor diet and smoking are the main factors that predispose to ischaemic heart disease. The worldwide consensus strongly recommends that they should be first addressed in the primary prevention by introducing the necessary changes in the lifestyle of the patient, but at the same time there are factors of distinct natures that can pass unrecognised by the healthcare provider. Women seem to be more affected by depression, partner violence, socioeconomic deprivation, cultural rights restraints and in addition they are exposed to obstetrical and gynaecological conditions that contribute to the cardiovascular disease development [1].

Prevalence of cardiovascular disease, mortality and morbidity among women

The Global Burden Disease study represents an ongoing collaboration between countries that provides comparable and constant data from all the sources available regarding the population's health. Its main purpose is to estimate statistical features for 204 countries, as far as the data is available and accurate in every region of interest. To prevent and further diagnose and treat cardiovascular diseases, it is crucial that precise and comprehensive data are collected first locally and further at a regional level, so the healthcare systems can access global data in real time. The prevalence of cardiovascular disease has nearly doubled since 1990, when it was estimated at 271 million (95% UI of 257 to 285 million) to 523 million (95% UI 497 to 550 million) in 2019, from which 275.2 million worldwide cases were women [7]. *UI=uncertainty interval*

It was estimated that the global age-standardised prevalence of cardiovascular disease in women is 6403/100.000, with the highest rates documented in North Africa, Middle East, high-income North America, Eastern Europe and Central Asia. The lowest age-standardised prevalences were reported in Latin America, Western Europe and Australasia. Over the past 30 years most regions have had a decline in the prevalence of cardiovascular disease, a 4.3% overall decrease (95% UI of -6% to -4.6%), with highest results documented in high income Asia countries, Western Europe and high income North America, but at the same time there was an increase in prevalence in China, India, Indonesia, Oceania and western sub-Saharian Africa [1].

The cardiovascular disease mortality in women is estimated to have risen from 6.10 million (95% UI 5.62-6.41 million) in 1990 to 8.94 million (95% UI 7.92 to 9.71million) in 2019. Ischemic heart disease and stroke remain the most common causes of mortality. The regions with the highest mortality of this cause (316-486/100.000 deaths) are mainly the same that registered the highest prevalence: Eastern Europe, North Africa, the Middle East, Oceania, central Sub-Saharian Africa and central Asia [1].

There are sex differences in the disability adjusted life years (DALYs, a statistical measure that counts in the years spent with a disability and the years lost from the adjusted life expectancy caused by a certain disease, in this article the cardiovascular disease), with reports higher in men before 80 years of age and a reverse after this age. Also, men have more DALYs between 30 and 60 years of age, but women suffer more after the age of 80. These data should raise awareness for the

mortality causes at older ages and the secondary prevention interventions [7].

Ischaemic heart disease remains the leading cause of death worldwide and recent evidence suggests that there are differences between men and women regarding the pathophysiology, risk factors, outcomes etc. [1]. There are recent concerns regarding the risks that the young female population is at, since the prevalence of smoking, diabetes and obesity is high in young women and myocardial infarction rates are rising among them. Women have worse outcomes when it comes to STEMI and higher in-hospital mortality than men [1,4,5].

Women have greater prevalence of stroke, but age standardised DALYs and deaths numbers of this cause were higher in men, which points out that women have better survival after stroke, but a higher lifetime stroke risk [7]. In 2019, 58.2% of total stroke deaths occurred in women, and the incidence appears to be affected by age and race [8].

At a global level, when it comes to atrial fibrillation, under the age of 70, men are more affected compared to women, but at ages older than 75 women seem to be more affected, the data showing more years of disability caused by this condition among the female population. This information pushes towards the need of sex-specific and age-related treatment/management of atrial fibrillation and atrial flutter [7].

Non-rheumatic degenerative mitral valve disease is most caused by mitral valve prolapse which, if left untreated, cand lead to chronic mitral regurgitation, rhythm abnormalities and even heart failure. Data shows that women had more years of life lived with a disability or lost caused by mitral valve disease than men in all age groups, but the levels have a significant diverge after 65 years of age, with a peak between 75 to 79 years [7]. There is some evidence that sustains the data. It was reported that women are less likely to have mitral valve replacement, less likely to receive mitral valve repair, have worse postoperative outcomes and higher in-hospital mortality in comparison with male counterparts. Theories that are warranted to provide a justification for these results praise that women present with worse conditions prior to diagnosis and treatment, such as heart failure and longer-standing mitral valve disease [1,9].

Rheumatic heart disease represents the most common cause of heart failure among the paediatric and young population, and the highest prevalence occurs in women of childbearing age. Higher rates are described in post-pubertal females, but without a clear explanation, and pregnancy represents a critical period for women affected by carditis or heart valve damage. The risk in developing the disease is 1.6-2 times greater for women than men. This condition has been largely eradicated in well developed countries, but the prevalence is still high in the low income regions as a result of biological, social and environmental risk factors. The regions with the highest prevalence and mortality in rheumatic heart disease are currently Africa, southeast Asia and western Pacific [1,7,10].

Peripheral arterial disease prevalence is increasing fast and especially in younger women (<45 years old), women representing about 52% of the patients affected by this condition. The highest prevalence is registered in low-income countries, where the well-established risk factors such as hypertension, diabetes, poor diet and smoking are more prevalent in the population. There is evidence that high body mass index (30 kg/m^2 and above) and low pulse pressure are risk predictors in these populations and also it has been documented a strong dose-response relationship for smoking as a risk factor for peripheral arterial disease in women. This condition indicates that the patient has a multivascular disease and the fact that women are more likely than men to have no symptoms or present with sex-specific symptoms is worrying data, leading to delayed diagnosis and management. Also, concerning morbidity, it seems that women are more likely to suffer complications from revascularisation procedures, wound infections, bleeding, periprocedural complications and higher in-hospital mortality [1,11].

Traditional risk factors

Hypertension is the number one risk factor for developing cardiovascular disease and the associated morbidity and mortality. Years of untreated hypertension lead to damage in organs such as heart, brain and kidneys. The heart response to high blood pressure is left ventricular hypertrophy. This natural response represents itself an independent risk because it involves alterations in the coronary hemodynamic, predisposition to lethal arrhythmias, cardiac failure and atherosclerosis and collagen deposition in the coronary arteries leading to ischemia, and ventricular fibrosis [12]. The harm produced by high blood pressures is mainly explained by the damage of the main organs and the left ventricle structural adaptation, but to a much deeper understanding the hypertensive heart disease is characterised by micro and macroscopical myocardial and arterial changes, adaptations that in the end lead to fibrosis of the structures involved [13]. Recent findings show that women are at higher risk of myocardial infarction, left ventricular hypertrophy, diastolic dysfunction, heart failure with preserved ejection fraction, arterial stiffness and chronic kidney disease and are less responsive with more side effects to antihypertensive treatment than men [1,14]. A recent study sustains that women have a different course in the development of hypertension than men, first with a more rapid beginning in their thirties and second, a faster increase in blood pressure over time, as the disease progresses [15]. The mechanisms leading to these differences have not been well understood and questions if different blood pressure targets should be used in women have been raised.

Dyslipidaemia is a well-established risk factor for developing cardiovascular disease, especially atherosclerosis and myocardial infarction. It was reported that in the female population, ratios of apoB to apoA1 and total cholesterol to HDL-cholesterol are more powerfully associated with myocardial infarction than in men [14]. Women could be more at risk while going through menopause. Studies found higher levels of total cholesterol and LDL-cholesterol one year after the debut of menopause which was associated with a later risk of developing carotid plaques [16]. Women are less likely to use a statin therapy and the reasons are not well established; statins have the same effectiveness in men and women and lately, the use of PCSK9 inhibitors have contributed to a reduction in ischaemic events in patients with coronary artery disease [1].

Diabetes is gaining a continuous rise in prevalence globally due to a multitude of factors which are connected one to another: poverty and poor diet, expanding urbanisation in populous countries with unhealthy lifestyle and sedentary young people. Diabetes contributes to development of ischaemic heart disease and recent studies show that the risk for new onset coronary heart disease and myocardial infarction is higher in women than their male counterparts. Women have better cardiovascular profiles until menopause than men, but this statement falls if there is an early poor glycaemic control. Women are also exposed during pregnancy to high fasting plasma glucose levels and this represents a risk factor for later development of type 2 diabetes and cardiovascular disease, therefore a careful screening and follow up is needed in these patients [1,17,18].

Obesity is increasing globally in prevalence, especially in the young population. Obesity itself, defined as a body mass index equal to 30 kg/m^2, is a risk factor that predisposes to hypertension and further cardiovascular disease and is more frequent in women [1]. Women can also be exposed during pregnancy and while going through menopause to this condition. Obesity is associated with obstetrical conditions such as hypertensive disorders during pregnancy and gestational diabetes while when going through menopause women seem to be more affected by central obesity, which is included in the metabolic syndrome [1,19,20].

Diet, sedentary lifestyle and smoking

An unhealthy diet lies at the heart of many risk factors for cardiovascular disease, it can lead to high values of LDL-cholesterol and total cholesterol, low values of HDL-cholesterol, high body mass index, high

apoB/apoA1 and inflammation. Lately it has been a trend towards a greater consumption of sweet beverages, fast food and high-energy density food, which corelates with a greater prevalence of obesity, especially in young people. Healthcare providers should raise awareness about future informative campaigns and tax policies on foods and beverages that are highly processed [1].

Women have a more sedentary lifestyle than men and tend to participate less in physical activities since childhood and over the years. Factors that could add to a greater prevalence in sedentarism are the social, religious and cultural norms that restrict women from participating to sports activities [1,21]. By initiating a regular physical activity, women contribute to lowering the incidence of cardiovascular disease, no matter the individual risk [22].

The youth seem to have a greater prevalence of smoking tobacco and usage of electronic smoking devices, this trend is increasing actually in women aged less than 25 years old. The prevalence of smoking in age standardised women in 2015 was 5.4%, with the highest values registered in western and central Europe and a very high percentage among adolescents. Smoking tobacco is clearly associated with myocardial infarction and the risk seems to be the same for men and women. Also, electronic devices affect the cardiovascular system by generating endothelial dysfunction, raising oxidative stress and platelet activation, all of these being manifestations of systemic inflammation [1,5,14,23].

Even though traditional risk factors remain the same for both genders, their potency seems to be different in men and women, therefore sex-specific approaches should be taken into account in all kinds of preventions.

Gender-specific risk factors

Menopause, hormone replacement therapy and the use of hormonal contraceptives

It is well known that cardiovascular disease appears later in the life of women compared with men, mostly because of the protective vascular effects of oestrogen, but the risk rises substantially after menopause. The loss of oestrogen has been claimed to lead to chronic endothelial dysfunction and inflammation by activating the renin-angiotensin-aldosterone system. Also, the years in the perimenopause were associated with higher risk of developing obesity and metabolic syndrome. Early menopause is believed to be a risk factor for developing cardiovascular disease before the age of 60. It seems that natural early and surgical early menopause both carry a risk for further development of cardiovascular complications [1,6]. A pan-European case cohort study compared the incidence of coronary heart disease events in premenopausal and postmenopausal women and the results showed that in the postmenopausal group every 1 year decrease in the age at menopause involved a higher 2% risk of developing coronary heart disease and the women with surgical menopause were at a higher risk than the ones with natural menopause [24]. Hormone replacement therapy is currently recommended against for primary or secondary prevention of cardiovascular disease by the current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines. Menopausal women put on oestrogen-progesteron therapy have a higher risk of cardiovascular disease and invasive breast cancer.

Hormonal contraceptives are associated with a 12 higher risk of myocardial infarction in women with history of hypertension and if there are multiple risk factors, the combined hormonal contraception should be discontinued because it would involve such a high cardiovascular risk that would exceed any benefit. There is no evidence that the past use of hormonal contraceptives has important effects on subsequent cardiovascular disease and the options for women with risk of infarction or stroke are: progesterone-only oral contraceptives, subdermal implants and intrauterine devices [1].

Obstetrical conditions

Healthcare providers and women should be aware of the risks involved when a woman develops pre-eclampsia, gestational diabetes or

pre-term delivery. These obstetrical conditions are known to be associated with high risk of developing cardiovascular disease later in life and patients should be assessed for other risk factors and prevention interventions should be started as early as possible. There are hypotheses that pregnancy is a stressful condition for the female body that unravels the existing traditional risk factors for cardiovascular disease events. Diabetes can have lasting effects even after pregnancy, patients with history of gestational diabetes having higher rates of reduced coronary flow, atherosclerosis and endothelial dysfunction. Therefore, even if the glucose intolerance and the pregnancy resolve, there should be an early screening for cardiovascular risk factors post-partum [1,6].

Polycystic ovary syndrome (PCOS) resembles polycystic ovaries, oligomenorrhoea and hyperandrogenism and affects 6-10% of reproductive age women. PCOS is associated with a higher risk of developing cardiovascular disease later in life; further research is needed to better understand the mechanisms involved. Current explanations claim that the syndrome is often associated (50-70%) with insulin resistance, which leads to chronic hypergliceamia and diabetes, obesity and metabolic syndrome [6,18].

Autoimmune conditions are more prevalent among women (78% of patients with autoimmune diseases are women) and this pattern represents a risk for developing cardiovascular diseases. Autoimmune conditions are characterized by chronic inflammation which affects the endothelium, leading to dysfunction and an ongoing atherosclerotic process, to which the steroid therapy with its implications is added. A preventive measure for these patients would be the early introduction of statins in their chronic therapy [1].

Under-recognised risk factors

Psychosocial risk factors, abuse and violence and environmental influences

Depression is an independent risk factor for coronary artery disease in women and alongside with anxiety increases the risk for developing cardiovascular disease. It seems that women are more at risk than men, because they have suffered more psychosocial disadvantages like higher rates of unemployment, stress, poor social support. Depression and anxiety often receive little attention in the clinical practice, but they have an important role in a good treatment outcome for cardiovascular disease. Another important factor which is worth mentioning is abuse. It has been reported that 15-71% of women are abused physically or psychologically in their lifetime, and this represents a risk factor for later development of cardiovascular disease, because it involves chronic stress and depression, which are biologically translated as chronic high rates of cortisol and chronic inflammation. Abuse influences mental health and behaviours, with tendency to smoking, binge drinking or eating and not seeking healthcare services [1].

Air pollution is another risk factor that has gained solid evidence regarding its implications in the development of cardiovascular conditions. The European Society of Cardiology sustains that air pollution leads to higher oxidative stress and inflammation, atherosclerotic plaque progression, endothelial dysfunction, platelet hyper-reactivity and arrhythmogenesis. Women can also be exposed to high amount of particulate matter and carbon monoxide while cooking on indoor stoves [1,25].

There are many factors of other natures rather than biological characteristics of the human female body that need to be further researched in order to get close to the understanding of differences between the risks of a woman and a man. Women seem to have less access to healthcare, especially in low income and medium income countries, have been less included in studies throughout the years and are underestimated in terms of cardiovascular risk factors [1].

Raising awareness

Differences in the regional and national burden and mortality of cardiovascular disease also reflect the differences in the prevalence of the risk factors and the access

to healthcare, to primary and secondary prevention. This aspect is a very important matter to have in mind while checking the data from low and middle income regions [7]. The statistical data regarding stagnation and actually higher prevalence of cardiovascular disease among women points out to the highly populated and industrialised regions of the world [3]. This is a call to action to expand the access to healthcare, prevention strategies focused on sex-specific risk factors, the diagnosis tools and better individualised prevention and treatment for women.

Author Contributions:

M.D. conceived the original draft preparation. M.D. and C.D. were responsible for conception and design of the review. M.D. and C.D. were responsible for the data acquisition. M.D. was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. M.D. and C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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REVIEW

Initial approach to the patient with abdominal pain

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Abstract
Abdominal pain is one of the most common symptoms for which patients present to the hospital. The causes of abdominal pain are diverse, so the diagnosis management often involves a multidisciplinary team. The initial evaluation of patients with abdominal pain must focus on excluding conditions that may endanger the patient's life in short time. The prognosis of patients complaining of abdominal pain proved to be different depending on age. Despite the progress registered in the field of imaging and molecular investigations in recent years, in a significant percentage of patients who present with abdominal pain, the cause is not identified.

Keywords: *abdominal pain, etiology, diagnosis, prognosis.*

Introduction

Worldwide, an increase in the demand for emergency medical services has been observed [1]. Among the reasons suggested for this phenomenon are ageing of the population, the increase in health awareness and socio-demographic factors [2,3].

Abdominal pain is one of the most frequent symptoms that determine the patients to present to the emergency department [4]. This symptom is encountered in approximately 5-10% of emergency departments visits [5,6]. In the United States, in 2006, of the 119 million presentations in emergency departments, 8 million presentations (7%) were for abdominal pain [6]. In Western Sweden, for the year 2020, 48,311 ambulance missions were reported and in 1,747 cases the reason for the request was represented by abdominal pain [3]. Despite the progress made in the diagnosis management of abdominal pain, in approximately 25% of patients receiving medical care in emergency departments and in 35-41% of hospitalized patients no specific cause for abdominal pain is identified [7,8]. In approximately 80% of patients discharged with the diagnosis of undifferentiated abdominal pain, this symptom resolves within 2 weeks of presentation [8].

Abdominal pain is associated with a different prognosis depending on age. Thus, older patients presenting to emergency departments with abdominal pain have a 6-8 times higher mortality rate compared to younger patients presenting for the same symptom [9,10]. 20% of adults who presented

to emergency departments are aged > 65 years and in 3-4% of cases they complain of abdominal pain as the dominant symptom [9,10]. Up to two thirds of these patients required hospitalization and one third required surgical interventions [5,11].

Differential diagnosis

Conditions that can lead to abdominal pain are divided into three categories: immediate life-threatening conditions, common conditions and other conditions (Table 1) [12-15].

Table 1. Classification of conditions that cand lead to abdominal pain, depending on severity

Immediate life-threatening conditions			
1. Abdominal aortic aneurysm 2. Mesenteric ischemia 3. Acute bowel obstruction 4. Intestinal volvulus 5. Perforation of gastrointestinal tract 6. Ectopic pregnancy 7. Myocardial infarction 8. Splenic rupture			
Common conditions			
Gastrointestinal - Appendicitis - Biliary disease - Pancreatitis - Diverticular disease - Peptic ulcer disease - Incarcerated hernia - Gastroenteritis - Foodborne disease - Complications of bariatric surgery - Inflammatory bowel disease - Hepatitis - Spontaneous bacterial peritonitis - Irritable bowel syndrome	**Genitourinary** - Urinary tract infection - Pyelonephritis - Nephrolithiasis - Adnexal torsion - Ruptured ovarian cyst - Preeclampsia - Pelvic inflammatory disease - Tubo-ovarian abscess - Fitz-Hugh Curtis syndrome - Endometriosis	**Common extra abdominal diseases** - Diabetic ketoacidosis - Alcoholic ketoacidosis - Pneumonia - Pulmonary embolus - Herpes zoster	**Trauma-related**
Other conditions			
1. Toxin/drug- related (corrosives, anticholinergics and narcotics, amphetamines, etc) 2. Neoplasms 3. Sickle cell disease 4. Toxic megacolon 5. Mesenteric lymphadenitis 6. Porphyria 7. Infectious mononucleosis 8. Systemic lupus erythematosus, Immunoglobulin A vasculitis, polyarteritis nodosa, eosinophilic enteritis, hypercalcemia 9. Pheochromocytoma 10. Ovarian hyperstimulation syndrome			

Considering the diverse etiology of abdominal pain, the patient evaluation in the emergency department is a challenge. Doctors must consider multiple possible diagnoses but focus on the conditions that can threaten the patient's life and require rapid management. The cornerstone of an accurate diagnosis consists in the combination of a careful history and physical examination [14]. Thus, the physician must obtain a series of information from the patient, such as the complete description of the pain, associated symptoms, the social, medical and surgical history [14]. In elderly patients we can expect more severe conditions, with atypical symptoms [16]. According to the data from specialized literature, after 50 years of age, the risk of mesenteric ischemia, abdominal aortic aneurysm, myocardial infarction with atypical presentation and colon cancer increases [17]. In women of childbearing age who present with abdominal pain, pregnancy and its complications (ectopic pregnancy, preeclampsia, HELLP syndrome, hemolysis, etc) should be excluded. Also, the pregnant women may present common conditions such as appendicitis or cholecystitis.

Other data that can guide towards a specific etiology are medical and surgical history, as well as outpatient medication. For example, peripheral vascular disease, atrial fibrillation, coronary heart disease, arterial hypertension are common risk factors for mesenteric ischemia [18,19]. The presence of atrial fibrillation in women particularly increases the risk of thromboembolic events [20]. In patients with history of abdominal surgery, it is recommended to rule out intestinal obstruction in case of presentation to the emergency room with abdominal pain. Yang *et al.* reported several independent risk factors for early postoperative intestinal obstruction, respectively chronic obstructive pulmonary disease (COPD), hypothyroidism, duration of antibiotics therapy, and duration of postoperative feeding [21]. The use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of peptic ulcer, while the use of corticosteroids may mask some symptoms [22,23]. The use of NSAIDs is associated with an increase in the risk of peptic ulcer by approximately 9% in patients who associate other risk factors, such as older patients (>65 years), heart disease, coprescription of anticoagulants, antiplatelets or corticosteroids, Helicobacter pylori infection, history of peptic ulcer [22-24].

Obtaining data on alcohol consumption or smoking can be of great importance in diagnosis management. Thus, in the case of patients who claim chronic alcohol consumption, we can expect to identify pancreatitis, alcoholic hepatitis or spontaneous bacterial peritonitis as causes of abdominal pain. A study that followed 157,026 individuals reported that alcohol consumption >40 g/day increases the risk for both acute and chronic pancreatitis [25]. In the United States, excessive alcohol consumption is the third preventable cause of death [26]. Alcoholic hepatitis is a condition with a very poor prognosis and a 28-day mortality rate of 30-50% [27]. In addition, approximately 50% of patients with alcoholic hepatitis already have a positive diagnosis of liver cirrhosis at the time of presentation to emergency department with manifestations of acute hepatitis [28]. Patients addicted to opioids may experience abdominal pain and nausea when withdrawing from opioids [29]. Smoking has been shown to increase the risk of malignant diseases such as bladder or pancreatic cancer [31,31].

Paraclinical assessment

To increase the diagnostic accuracy, the clinical evaluation must be continued with individualized paraclinical tests depending on the risk factors and patient's symptoms. A study that included 124 patients concluded that the paraclinical evaluation in the emergency department changed the initial diagnosis, based only on clinical judgment, in 37% of cases [15]. Paraclinical investigations fall into two major categories: biological investigations and imaging investigations. In a healthy adult caution is recommended in requesting paraclinical tests. Thus, paraclinical investigations should be requested specifically to validate a clinical suspicion. In elderly patients or those with significant comorbidities,

the diagnosis management must be extensive, to avoid diagnostic errors, even life-threatening.

In patients known with type 2 diabetes mellitus, immediate evaluation of the serum glucose level is recommended to rule out diabetic ketoacidosis [32]. If hyperglycemia is identified, it is recommended to continue the investigations by evaluating acid-base balance and the serum values of electrolytes, to establish the severity of the disease [32,33].

The complete blood count is routinely required, but it rarely changes the diagnostic and therapeutic management of patients. For example, the number of leukocytes can be increased in 80% of patients with acute appendicitis, but also in 70% of patients with other causes of pain in the lower abdomen [34]. Also, immunosuppressed or elderly patients with acute abdomen may have a normal number of leukocytes, while a healthy pregnant woman may present leukocytosis [35,36].

In patients presenting with upper abdominal pain, the assessment of liver and pancreatic enzymes is recommended [37,38]. Increased serum values of lipase are more sensitive and specific than increased serum values of amylase for establishing the diagnosis of acute pancreatitis [39]. However, the positive predictive values of hyperlipasemia for acute pancreatitis does not exceed 38.1% [40]. Other diseases in which increased values of serum lipase can be found are malignancy, shock or cardiac arrest [40]. Alanine aminotransferase (ALT) is a more specific biomarker for liver damage, but elevated serum values of aspartate aminotransferase (AST) may be more specific for the diagnosis of alcoholic liver disease or some forms of autoimmune hepatitis [38].

Another paraclinical test useful to establish the etiology of abdominal pain is urine analysis. Thus, the presence of leukocytes, nitrites, proteins or erythrocytes in the urine can suggest the diagnosis of urinary tract infections (UTI) [41]. Approximately 10% of women between the ages of 16 and 35 years develop an episode of UTI annually and approximately 40-60% of women have at least one episode of UTI during their lifetime [42,43]. Urine analysis can be also misleading. For example, in 20-48% of patients with appendicitis we can identify the presence of erythrocytes and leukocytes in urine and up to 55% of patients with abdominal aortic aneurysm can present hematuria [44,45].

The imaging investigations that can be used for the initial assessment of patients with abdominal pain are abdominal X-ray, abdominal ultrasound and computed tomography (CT) scan. Abdominal X-ray should be limited to patients suspected of having a radiopaque foreign body, bowel obstruction or bowel perforation [46]. In the other cases, this investigation has a very low diagnostic sensitivity [46]. Abdominal ultrasound is a feasible imaging method, with significant diagnostic accuracy and low costs [47]. For example, a meta-analysis that evaluated 18 studies reported an overall sensitivity of 77.2% and a specificity of 60% for establishing the diagnosis of acute appendicitis [47]. Also, this investigation can contribute to the rapid diagnosis of some diseases that can put the patient's life in danger in short time. Among these are abdominal aortic aneurysm leak or rupture, traumatic hemoperitoneum or ruptured ectopic pregnancy [48]. However, the diagnostic accuracy of this investigation depends very much on the experience of the evaluator [49]. The imaging method of choice for evaluating the patient with undifferentiated abdominal pain is CT scan [50]. In approximately two-thirds of the patients who present to the emergency room with abdominal pain, CT identifies a cause of this symptom [50]. Later, depending on the risk factors, symptoms and the results of initial paraclinical investigations, the diagnostic management will adapt specifically.

Conclusions

Abdominal pain is one of the most common symptoms that patients present to the emergency room. The severity of the conditions behind the abdominal pain varies from very low to conditions that can put patient's life at risk in short time. The correct initial evaluation from a clinical and paraclinical point of view is essential for the subsequent evolution of the disease.

Author Contributions:

V.A.I and G.G. conceived the original draft preparation. V.A.I., G.G., and F.G1. were responsible for conception and design of the review. V.A.I., G.G. and F.G2. were responsible for the data acquisition. F.G2, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. V.A.I., G.G., F.G1., and F.G2. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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CASE REPORT

Renal Abscess – A Case Report

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Abstract

Introduction. *Renal abscesses can be the result of haematogenous spread or as a rare complication of upper UTI particularly in the setting of renal stones or diabetes. Classically it may present as loin pain, fever, rigors, and tenderness in the costovertebral angle, but may simply manifest as a pyrexia of unknown origin and a raised acute phase response.*

Case report. *We report the case of a 73-year-old female patient with type 2 diabetes mellitus, who presented for abdominal pain, chills, confusion and deterioration of general condition with progressive aggravation of the symptoms, the clinical examination revealed a respiratory rate of 14 breaths per minute, blood oxygen saturation of 98%, heart rate 82 beats per minute, blood pressure 137/75 mmHg and no fever. She had peripheral cyanosis and peripheral pulses were weak in the lower limbs; diuresis was present on the urinary catheter the laboratory and imaging investigations showed inflammatory syndrome (CRP=255 mg/l) and the CT showed both kidneys with normal position, a bilateral reduction in renal size, bilateral dilated pyelocaliceal system grade I developed a left renal abscess as a complication of acute pyelonephritis. The primary pathogen identified was Escherichia Coli. Computed tomography revealed a well-defined mass on the left kidney with low attenuation in contact with the renal fascia. Broad spectrum antibiotics and haemodialysis were used as part of conservative management regimen. The patient achieved clinical improvement after 3 weeks and was discharged.*

Conclusions. *The particularities of the case are represented by the fulminant evolution of the infection in a patient with poorly controlled diabetes, the acute kidney injury caused by urosepsis and the progression of pyelonephritis towards the development of a renal abscess. Diabetes mellitus is a disease with a significant prevalence, the incidence of which increases with age and which develops multiple complications. In addition to vascular lesions, diabetic neuropathy or nephropathy, patients have a high risk of developing an infection, the most common being those of the upper urinary tract, which evolve aggressively. The renal abscess is a rare complication of pyelonephritis, but it is to be considered in patients with persistent inflammatory state in despite of the right management.*

Keywords: renal abscess, diabetes mellitus, pyelonephritis, acute kidney injury

Introduction

Renal and perinephric abscesses are uncommon; however they can become potentially lethal complications of urinary tract infection. Intra-renal abscess or a "renal carbuncle" is encapsulated necrotic material within the renal parenchyma and account for 0.2% of all intraabdominal abscesses [1]. The predisposing factors for renal abscesses include diabetes mellitus, ureteral obstruction, vesical-ureteral reflux and renal calculi. A retrospective analysis performed during 2002-2009 in Western Romania showed a percentage of 1.5% of patients with upper urinary tract infections who developed renal abscess and the most frequently isolated pathogen was Escherichia Coli-25% and rarely other germs (e.g. Citrobacter and Candida albicans) [2]. In the past, renal abscesses were associated with significant morbidity and mortality, which was in part due to their obscure symptoms and lack of detection using low quality imaging systems [3,4]. Recently, computed tomography and magnetic resonance imaging have become more available, and the quality of renal ultrasound examination has increased. The advances in imaging techniques have led to earlier diagnosis of renal and perinephric abscesses. Furthermore, novel antibiotics and percutaneous drainage have reduced surgery-related morbidity and mortality [5,6]. The diagnostic and treatment developments are believed to have improved outcomes for the disease process [7].

Case report

A 73- year-old female patient with type 2 diabetes mellitus insulin-dependent, ischemic heart disease and superficial femoral artery stenosis, who had been experiencing abdominal pain, chills, confusion, and deterioration of general condition with progressive aggravation of the symptoms was admitted to the Department of Internal Medicine, Clinical Emergency Hospital of Bucharest, Romania. The initial physical examination revealed a respiratory rate of 14 breaths per minute, blood oxygen saturation of 98%, heart rate 82 beats per minute, blood pressure 137/75 mmHg and no fever. She had peripheral cyanosis and peripheral pulses were weak in the lower limbs; diuresis was present on the urinary catheter. The patient also reported transit disorder, diarrhea in the last two days. The remaining physical examination was unremarkable. The results of routine laboratory tests are presented in Table 1.

Table 1. The results of routine laboratory tests performed at admission.

Parameters	Results	Normal reference values
White cell count	19.09x10^3/µL	4-9 x10^3/µL
Haemoglobin	9.28 g/dL	11.7-16.0 g/dL
Glucose	180 mg/dL	65.00-105.0 mg/dL
Serum Creatinine	4.37 mg/dL	0.60-1.20 mg/dL
Urea	157.9 mg/dL	15-37 mg/dL
Fibrinogen	258 mg/dL	200-393 mg/dL
C-reactive protein	255.63 mg/L	0.000-5.00 mg/L

The electrocardiogram showed normal sinus rhythm with no signs of ischemia. The chest X-ray and the abdominal anterior-posterior X-ray showed accentuation of bilateral perihilar interstitial opacities and horizontalization of the heart, without signs of pneumoperitoneum. Due to the reported diarrhea, Clostridioides difficile toxins A/B were tested and have been found negative. The subsequent computed tomography (CT) result showed both kidneys with normal position, a bilateral reduction in renal size, bilateral dilated pyelocaliceal system grade I (Fig. 1).

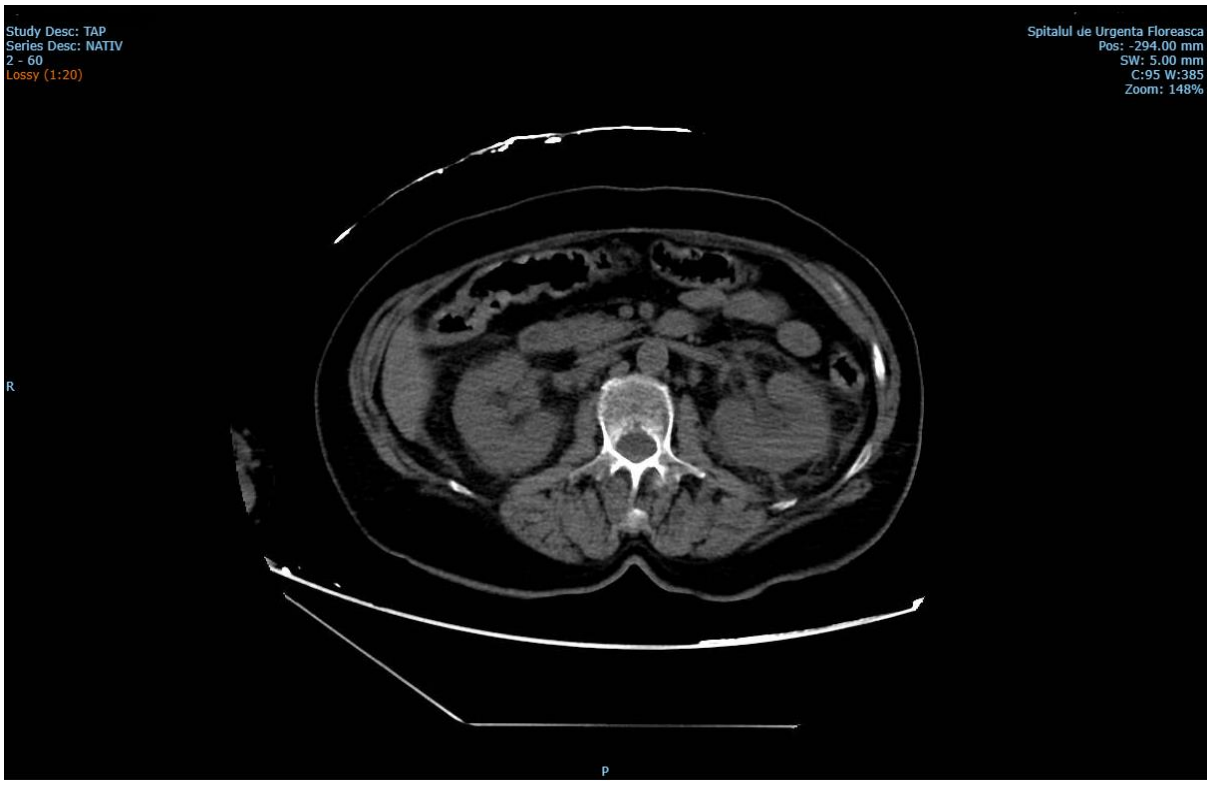

Fig. 1. Nonenhanced computed tomography (CT) images showing a bilateral reduction in renal size.

Moreover, the urine culture yielded *Escherichia coli* multisensitive. Acute pyelonephritis was diagnosed, and intravenous antibiotics with piperacillin-tazobactam 4.5g q6h were prescribed for 7 days. Considering the nitrogen retention syndrome, with a serum creatinine of 5.5 mg/dL (eGFR=8ml/min/1.73m^2) a nephrology consultation was requested, with the following recommendations: strict monitoring of diuresis, diuretic treatment with furosemide 240mg/day via continuous iv infusion, maintaining blood pressure (BP) greater than 110 mmHg, avoidance of nephrotoxic drugs and reevaluation when necessary. In the following days there had been progressive impairment of renal function, with an increase of serum-creatine levels and a declining eGFR= 4ml/min/1.73m^2, thus haemodialysis was initiated via a central catheter. A follow up abdominal CT scan was performed on the 14th day of hospitalization, which revealed a well-defined mass of 35/30/47 cm on the left kidney, with low attenuation, in contact with the renal fascia, infiltrating it and focal perirenal fatty blurring (Fig. 2).

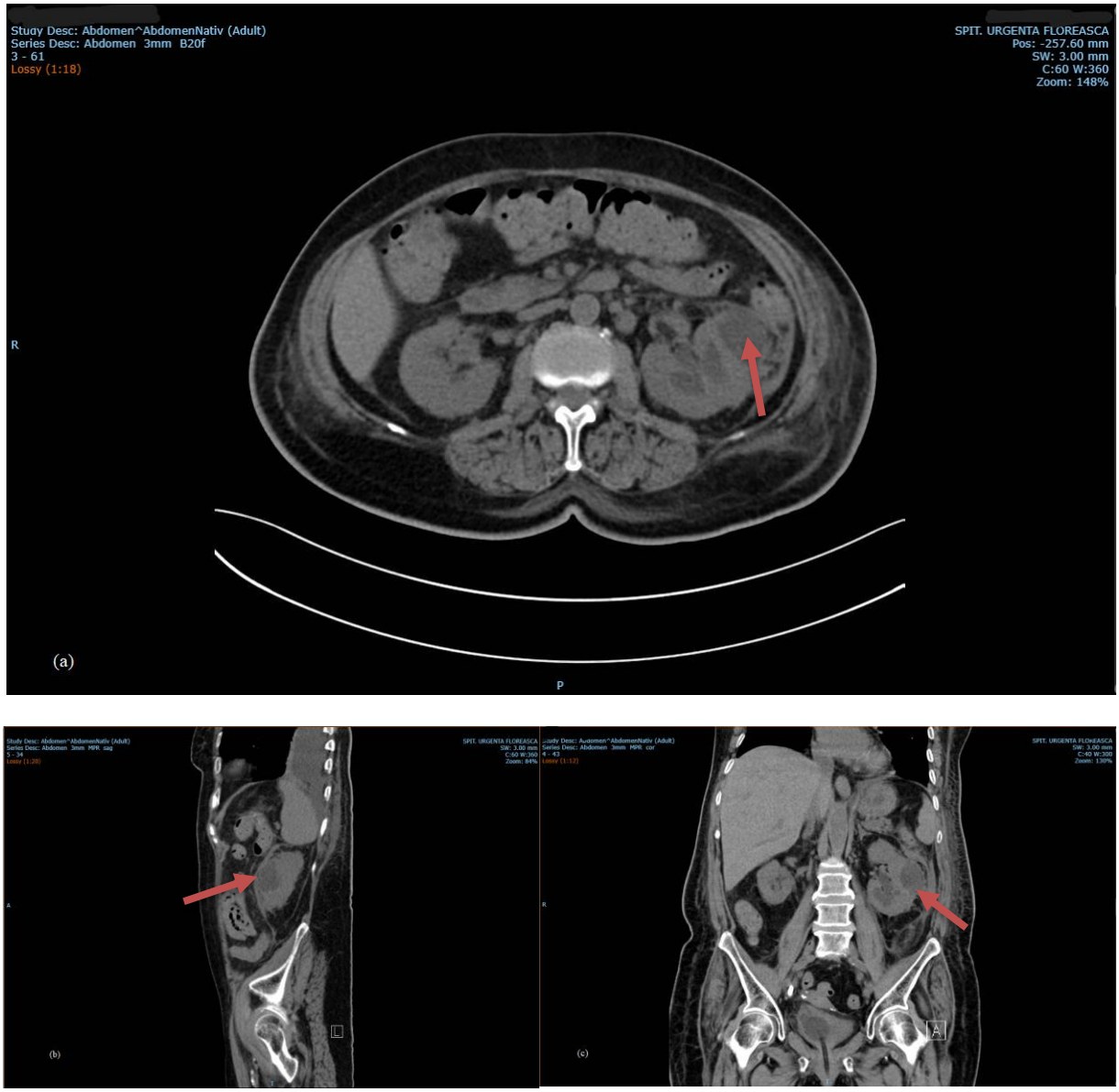

Fig. 2 (a,b,c). Nonenhanced computed tomography (CT) images showing a well-defined mass of 35/30/47 cm on the left kidney, with low attenuation.

The patient presented persisting symptoms of abdominal pain and dysuria; the physical examination revealed diffuse pain on deep abdominal palpations, with no signs of peritoneal irritation and no changes in cardio-pulmonary auscultation. A second urine culture was positive for *Candida albicans*, thus an antimycotic (Fluconazol 200 mg loading dose, followed by 100 mg per day for 7 days) was added to the therapeutic regimen. Considering the escalation of the inflammatory syndrome, an infectious disease consultation was required, with the following recommendations: intravenous antibiotherapy with moxifloxacin 400 mg per day and vancomycin 1g per day after the dialysis session, associated to the previous therapeutic regimen. The patient achieved clinical improvement after three weeks and was discharged.

Discussion

Renal and perinephric abscesses are uncommon; however they can become potentially lethal complications of urinary tract infection. Renal abscesses can be the result of haematogenous spread or a rare complication of upper UTI particularly in the

setting of renal stones or diabetes. As presented in our case, renal corticomedullary abscesses most commonly occur in individuals with diabetes mellitus with or without urinary tract obstruction [8]. Classically, it may present as loin pain, fever, rigors, and tenderness in the costovertebral angle, but may simply manifest as a pyrexia of unknown origin and a raised acute phase response. A renal abscess may not be associated with a positive urine culture or may arise following inadequate treatment of pyelonephritis and should always be considered in a patient with pyelonephritis not responding rapidly to treatment [9]. Most renal abscesses are caused by enteric Gram-negative bacilli, often associated with urinary tract abnormalities. *E. coli* is responsible for 75% of these infections. Approximately 15-20% of cases are caused by *Klebsiella*, *Proteus*, *Enterobacter*, and *Serratia* species. The few remaining cases of renal corticomedullary abscess are caused by gram-positive bacteria, including *Streptococcus faecalis* and, less commonly, *S. aureus* [10].

As with other renal infections, CT scan is the imaging of choice, but ultrasonography (US) is helpful if aspiration or sequential imaging is required. Renal abscess is characterized by hypoechoic or anechoic complex masses at ultrasound, with increased transmission of US and borders that become defined as the abscess encapsulates. Internal echoes, moving with patient position, may also be seen within the cavity, forming solid–fluid interfaces or echogenic areas with acoustic shadows suggestive of air, there may also be present loculations and septations [11]. US is less sensitive than CT scan in the detection of abscesses and on many occasions, it fails to detect abscesses seen on CT. CT is the most accurate imaging investigation for the diagnosis and follow up regarding the evolution of the abscess. Abscesses initially appear as peripheral cortical lesions and are small wedge or rounded areas of hypoattenuation on CT or a well-defined low-density mass with a postcontrast enhancement of an abscess wall [11,12]. The mature abscess is sharply marginated, with peripheral enhancement in up to half of cases and the thick and irregular wall or pseudocapsule is better demonstrated after enhancement and often during the excretory phase, when there is contrast material in the pelvicalyceal system [11]. On magnetic resonance imaging (MRI), abscesses appear as low, inhomogeneous signal intensity on T1-weighted imaging with increased inhomogeneous signal on T2-weighted imaging depending on amount of protein, fluid and cellular debris present [13]. MRI is seldom a first-line investigation.

Most renal abscesses respond to appropriate parental antibiotics, without the need for percutaneous drainage, but the bigger the abscess, the less likely conservative management will be effective without percutaneous or sometimes surgical drainage [9]. Early diagnosis and antibiotic therapy are essential for a good clinical outcome. An immediate intravenous therapy, with coverage for Enterobacteriaceae (if suspected association with pyelonephritis) and staphylococcal bacteraemia for 3–6 weeks is recommended. Subsequently, the initial antibiotic regimen should be tailored to culture and susceptibility results [12]. Small sized renal abscesses (<3cm), as well as medium sized renal abscesses (3-5 cm), are successfully treated with intravenous antibiotic therapy alone, especially if therapeutic drainage is deemed to be a considerable risk.

Conclusions

In conclusion, this case report is an example of medium sized renal abscess, which presented as a complication of acute pyelonephritis in a patient with associated risk factors (diabetes mellitus type 2 insulin requiring). Numerous reports observed that medium renal abscesses were effectively treated with a course of intravenous antibiotics. The key features of management of renal abscess are prompt identification of risk factors, diagnosis with the use of computed tomography and adequate treatment.

Author Contributions:

H.M, C.D., A.S, I.S., and G.C. conceived the original draft preparation. H.M, C.D., A.S, I.S., and G.C. were responsible for conception and design of the review. A.S., I.S., and G.C. were responsible for the data acquisition. G.C, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. H.M, C.D., A.S, I.S., and G.C contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements: "*The authors declare no conflict of interest regarding this article".*

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CASE REPORT

Persistent Hypokalemia: Case Report and Literature Review

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Abstract

Introduction. *Hypokalemia is a common clinical disorder. The most common causes of hypokalemia are decreased intake, intracellular shift and increased loss of potassium. In clinical practice, most frequently patients present with hypokalemia due to increased loss of potassium, especially renal loss.*

Case presentation*. A 62-year-old woman, known with hypothyroidism under treatment with Euthyrox, diagnosed with COVID-19 four months before, presented for nausea and vomiting, headache, generalised muscular hypotony and palpitations, with the onset three weeks before. On physical examination, the blood pressure was 140/90 mmHg, regular pulse frequency of 96/min, the patient had pale skin and mucosa and abolition of osteotendinous reflexes at the inferior members. The laboratory tests revealed severe hypokalemia and moderate normocytic normochromic anemia, mixed alkalosis. The patient had no history of treatment with diuretics or penicilines, or any other condition that could have explained the severe hypokalemia. The patient was admitted in the Internal Medicine Clinic and treatment with high doses of intravenous potassium chloride, potassium - sparing diuretic (Spironolactone) and supplements of potassium and magnesium was initiated, with partial correction of the serum potasssium level. The patient was extensively investigated, to establish the etiology of kypokalemia. Finally, the only identified cause was a nephropathy with losses of potassium.*

Conclusions. *Hypokalemia can be determined by multiple factors, such as digestive or renal losses, during a long term hospitalization. Proper treatment of substitution may lead to normal values of serum potassium and a better life quality.*

Keywords: *persistent severe hypokalemia, mixed alkalosis, COVID-19.*

Introduction

Potassium is the main intracellular cation, only 2% of the total potassium in the body is extracellular [1]. The serum potassium levels are maintained by the uptake of K^+ into cells (governed by the activity of Na^+/K^+-ATPase), renal excretion (increased by aldosterone) and extrarenal losses (e.g. gastrointestinal, skin) [2]. Hypokalemia is defined as a serum potassium level of less than 3.5 mEq/L and

represents a common electrolyte disturbance mainly in hospitalized patients, having various causes [3]. It results from the intracellular shift or increased potassium excretion (renal or non-renal) and rarely from reduced potassium intake [3]. The most common causes of chronic hypokalemia are hyperaldosteronism and diuretic treatment (especially thiazides) [2]. However, in hospitalized patients, acute hypokalemia is mainly caused by the use of intravenous fluids without potassium, diuretic treatment (loop/ thiazide) and redistribution into cells (especially in diabetic ketoacidosis) [2].

Hypokalemia is usually asymptomatic but severe hypokalemia (<2.5 mEq/L) causes muscle weakness, which can lead to paralysis and respiratory failure [1]. Hypokalemia is associated with an increased frequency of atrial and ventricular ectopic beats [4].

The underlying cause oh hypokalemia must be established, for a correct management. In most cases, withdrawal of the hypokalemic medication (oral diuretics or purgatives) accompanied by the oral administration of potassium supplements are enough for the correction of the serum potassium.

Case presentation

A 62-year-old woman, known with hypothyroidism under treatment with Euthyrox, diagnosed with COVID-19 four months before, presented in February 2022 for nausea and vomiting, headache, generalised muscular hypotony, and palpitations, with the onset three weeks before.

The patient had a severe form of COVID-19 in October 2021, for which she was intubated and ventilated, complicated by massive pulmonary embolism treated by thrombolysis in November 2021. Also, the patient had a resuscitated cardiac-pulmonary arrest in November 2021, several infections treated with numerous classes of antibiotics for long periods of time (Clostridium difficile infection treated with glycopeptides –Vancomycin and imidazole derivatives - Metronidazole, urinary infection with Proteus mirabilis and Klebsiella pneumoniae in tracheal secretion, treated with third generation cephalosporins combined with beta-lactamase inhibitor - Ceftazidime/Avibactam, another urinary infection with Providentia Stuartii treated with aminoglycosides – Gentamicin and tetracyclines - Tigecycline), reinfection with SARS-CoV-2 in February 2022. She also had laparoscopic cholecystectomy for an acute cholecystitis in February 2022.

On physical examination, the blood pressure was 140/90 mmHg, regular pulse frequency of 96/min, pale skin and mucosa, abolition of osteotendinous reflexes at the inferior members. The laboratory tests revaled severe hypokalemia (K 2.03 mmol/L) and moderate normochromic normocytic anemia. At the time of admission, the patient presented mixed alkalosis, both metabolic and respiratory (pH 7.6, pCO_2 29 mmHg, HCO_3 28.5 mmol/L). Throughout the hospitalization, the alkalosis persisted as a partially compensated primary respiratory alkalosis (pH 7.46, pCO_2 25.1 mmHg, HCO_3 17.8 mmol/L). The chest computed tomography (CT) revealed interstitial septal thickening in all the pulmonary lobes, interstitial fibrosis, and also difuse peripheral cylindrical bronchiectasis, especially in the middle lobe and lingular segments.

In our hospital, the patient was admitted dirrectly in the Intensive Care Unit, for 3 weeks and received antibiotic treatment with tetracyclines (Tigeciclina), carbapenems (Meropenem), aminoglycosides (Amikacin), monobactams (Aztreonam), polymyxins (Colistin), antifungal treatment with Fluconazole, because of positive results for Pseudomonas aeruginosa, Klebsiella pneumoniae and Candida albicans from tracheal secretion, and also for Staphylococcus haemolyticus from plague culture (presacral bedsore).

The first step of investigation has aimed to establish the differential diagnosis (DD)

of hypokalemia and metabolic alkalosis. The DD of hypokalemia includes three main categories. First, decreased potassium intake is not relevant because no clinical signs of malnutrition and no other laboratory nutritional deficiencies were observed, and hypokalemia was persistent despite continuous potassium replacement. Hypokalemia also persisted despite the treatment of nausea and vomiting.

Secondly, potassium redistribution into cells can also cause hypokalemia, mainly due to hormones, drugs, and anabolic states (e.g. insulin, β-agonists, granulocyte-colonystimulating factor [G-CSF] analogues, vitamin B12 supplements); however, all of these causes were excluded by history and laboratory tests. Two other specific diseases, familial hypokalemic periodic paralysis and thyrotoxic periodic paralysis, are also not relevant because in the former hypokalemia should be corrected by supplements and in the latter, thyroid function tests should reveal hyperthyroidism.

The third category, which is relevant to this case, includes potassium renal loss. Because of her persistent hypokalemia, supplementary investigations were performed, meaning collecting total urine for 24 hours with determination of potassium (K 37.9 mmol/L), sodium (Na 148 mmol/L), creatinine (Cr 4.8 mg/dL) and proteins (0.27 g/L). Following the diagnostic algorithm, the results were suggestive for a renal cause of potassium deficiency. Because renal causes for potassium loss are numerous, the first step was to exclude the possibility of drug renal impairment, that causes increased distal delivery of non reabsorbed anions and this was possible because none of the medications the patient has received has such an effect (an example of such drugs being the penicillins, which the patient did not receive). Also, we excluded at an early stage the use of diuretics as a possible cause of renal excess excretion of potassium – diuretics increase the distal renal flow and distal delivery of sodium and they determine an increase in the renal loss of potassium. Because the value of the proteins lost through urine in 24h is only 0.27 g/L, the nephrotic syndrome was excluded.

The next step was an endocrinological evaluation, so the blood levels of the adrenocorticotropic hormone and aldosterone were measured, also the plasma renin concentration. All three values were normal, so hyperaldosteronism, Bartter or Gitleman syndrome were excluded. Besides, these syndromes usually have the onset in adolescence or early adulthood. The plasma cortisol level was also determined, with normal result, so a Cushing syndrome was excluded. There was no imaging suspicion for an adrenocortical adenoma or other secretant tumours.

During hospitalisation, the normal values of potassium were maintained only with high doses of intravenous potassium chloride, potassium-sparing diuretic (Spironolactone) and supplements of potassium and magnesium. Initially, the patient received a 100mg/24h dose of Spironolactone, further increased to 225 mg/24h. After approximately 2 months of intensive treatment, the serum potassium values stabillised around 4 mmol/L.

Discussion

Causes of hypokalemia

The main three mechanisms that can lead to hypokalemia are: decreased intake, intracellular shift and increased loss of potassium. Decreased intake can result either from dietary deficiency or by administration of intravenous fluids without potassium.

Intracellular shift is defined by the uptake of the potassium in the cell (mainly stimulated by insulin and beta-adrenergic stimulation) and can result from an anabolic status, hormonal changes, acid-base disorders or other conditions that stimulate the uptake of the potassium in the cell. The anabolic status appears in the following conditions: total parenteral nutrition or

enteral hyperalimentation that cause hypokalemia due to glycogenesis which is stimulating insulin release, correction of megaloblastic anaemia (e.g. B12 vitamin or folic acid deficiency) which results in red blood cell production and treatment with granulocyte-macrophage colony-stimulating factor which results in white blood cell production. Insulin administration, the stimulation of the sympathetic nervous system (through beta-adrenergic stimulation, beta-2 agonist administration such as salbutamol, acute myocardial infarction or thyrotoxicosis-hypokalemic thyrotoxic periodic paralysis) and the downstream stimulation of Na^+/K^+-ATPase by theophylline or caffeine are some of the causes of hypokalemia through hormonal mechanisms. Regarding the acid-base status, that promotes the uptake of the potassium in the cell, there is alkalosis (metabolic more often than respiratory) that stimulates the exchange of the potassium and H^+ between the intracellular and extracellular space to restore the pH balance [1]. Other causes that stimulate the uptake of the potassium in the cell are pseudohypokalemia (in patients with chronic myeloid leukemia with more than 10^5/uL leucocytes, if the blood sample remains at room temperature before being processed - the false hypokalemia appears due to absorption of the potassium into the abnormal leucocytes), hypothermia, familial hypokalemic periodic paralysis (rare autosomal dominant channelopathy characterized by muscle weakness or paralysis when there is a fall in potassium levels in the blood - usually occurs in childhood or adolescence) and barium toxicity (systemic inhibition of “leak” K+ channels) [1,7].

Increased loss of potassium can occur in both renal and non-renal conditions. The non-renal causes consist in gastrointestinal loss (in which the urinary K^+ is less than 20 mmol/day) and integumentary loss (sweat). Gastrointestinal losses of potassium usually are due to prolonged diarrhea (potassium is secreted by the colon and diarrheal fluid contains 10-30 mmol/L of potassium; profuse diarrhea can therefore induce marked hypokalemia) or vomiting (vomiting contains only around 5-10 mmol/L of potassium but prolonged vomiting causes hypokalemia by inducing sodium depletion, stimulating aldosterone, which increases renal potassium excretion), chronic laxative abuse, ileus, intestinal obstruction or infections [2]. Other causes involving gastrointestinal losses are villous adenoma of the colon (can rarely cause massive potassium secretion), ileostomy or ureterosigmoidostomy, fistulae and clay ingestion (binds potassium and greatly decreases absorption).

Excessive excretion of potassium in the urine (kaliuresis) may result from increased distal flow and distal Na^+ delivery (in which the urinary K^+ is greater than 20 mmol/day) or from increased secretion of potassium. Diuretics (thiazides more often than loops diuretics), osmotic diuresis and salt-wasting nephropathies increase the distal flow and the distal Na^+ delivery and therefore can result in hypokalemia. The main hormone involved in the urinary secretion of the potassium is a mineralocorticoid hormone (aldosterone), therefore a mineralocorticoid excess may lead to hypokalemia in the following conditions:

- primary hyperaldosteronism;
- primary or unilateral adrenal hyperplasia;
- idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia and adrenal carcinoma;
- familial hyperaldosteronism;
- secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia);
- Cushing's syndrome;
- Bartter's syndrome (characterized by metabolic alkalosis, hypokalemia, hypercalciuria, occasionally hypomagnesemia, normal blood pressure and an elevated plasma renin and aldosterone);

- Gitelman's syndrome (characterized by metabolic alkalosis, hypokalemia, hypocalciuria, hypomagnesemia, normal blood pressure and elevated plasma renin and aldosterone);
- nephrotic syndrome;
- heart failure;
- liver failure;
- Conn's syndrome;
- ACTH- producing tumors;
- administration of exogenous mineralocorticoid: corticosteroids, liqorice (potentiates renal actions of cortisol).

An apparent mineralocorticoid excess can appear in:

- a genetic deficiency of 11 B-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess);
- an inhibition of 11 ß-dehydrogenase-2 (glycyrrhetinic/ glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs);
- Liddle's syndrome (characterized by alkalosis, hypokalemia, high blood pressure and low renin and aldosterone production).

A high secretion of urinary potassium can also result from a distal delivery of non-reabsorbed anions, a phenomenon that can appear in:

- vomiting;
- nasogastric suction;
- renal tubular acidosis types 1 and 2;
- Fanconi syndrome;
- diabetic ketoacidosis;
- glue sniffing (toluene abuse);
- administration of penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin).

Finally, hypomagnesemia is very important. More than 50% of clinically significant hypokalemia cases associate concomitant magnesium deficiency and is clinically most frequently observed in individuals receiving loop or thiazide diuretic therapy [3]. Hypomagnesemia can itself lead to increased urinary potassium losses via an uncertain mechanism.

Clinical features of hypokalemia

Hypokalemia is usually asymptomatic but severe hypokalemia (<2.5 mEq/L) causes muscle weakness, which can lead to paralysis and respiratory failure [1]. Hypokalemia is associated with an increased frequency of atrial and ventricular ectopic beats [4]. Hypokalemia increases the risk of digoxin toxicity by increasing binding of digoxin to cardiac cells, potentiating its action and decreasing its clearance [2]. Other signs and symptoms include metabolic acidosis, rhabdomyolysis, leg cramps, fasciculations, tetany, ascending paralysis, ileus, polyuria with polydipsia (hypokalemia can reduce the renal capacity of concentration), renal failure, ECG changes (U wave, T wave flattening, ST-segment changes), heart failure [1,2,5,6].

Diagnostic algorithm in hypokalemia

The diagnosis of hypokalemia is made by measuring a low potassium level in the blood (<3.5 mEq/L). The underlying cause of hypokalemia is usually obvious from history, physical examination, and/or basic laboratory tests. If there is no obvious cause in the history (especially medication) further investigations are required (Fig. 1.) [4].

Management

Hypokalemia is treated by identifying and treating the underlying cause. In most cases withdrawal of the hypokalemic medication (oral diuretics or purgatives) accompanied by the oral administration of potassium supplements are enough for the correction of the serum potassium. Hypokalemia is resistant at any correction if there is hypomagnesemia, which should be measured and corrected. Intravenous potassium replacement is needed only in conditions such as cardiac arrhythmias, muscle weakness or severe diabetic ketoacidosis. For the intravenous

replacement, the potassium should be mixed in 0.9% saline, not in glucose solution, as this would make hypokalemia worse due to the increase of the insulin [2,4,6].

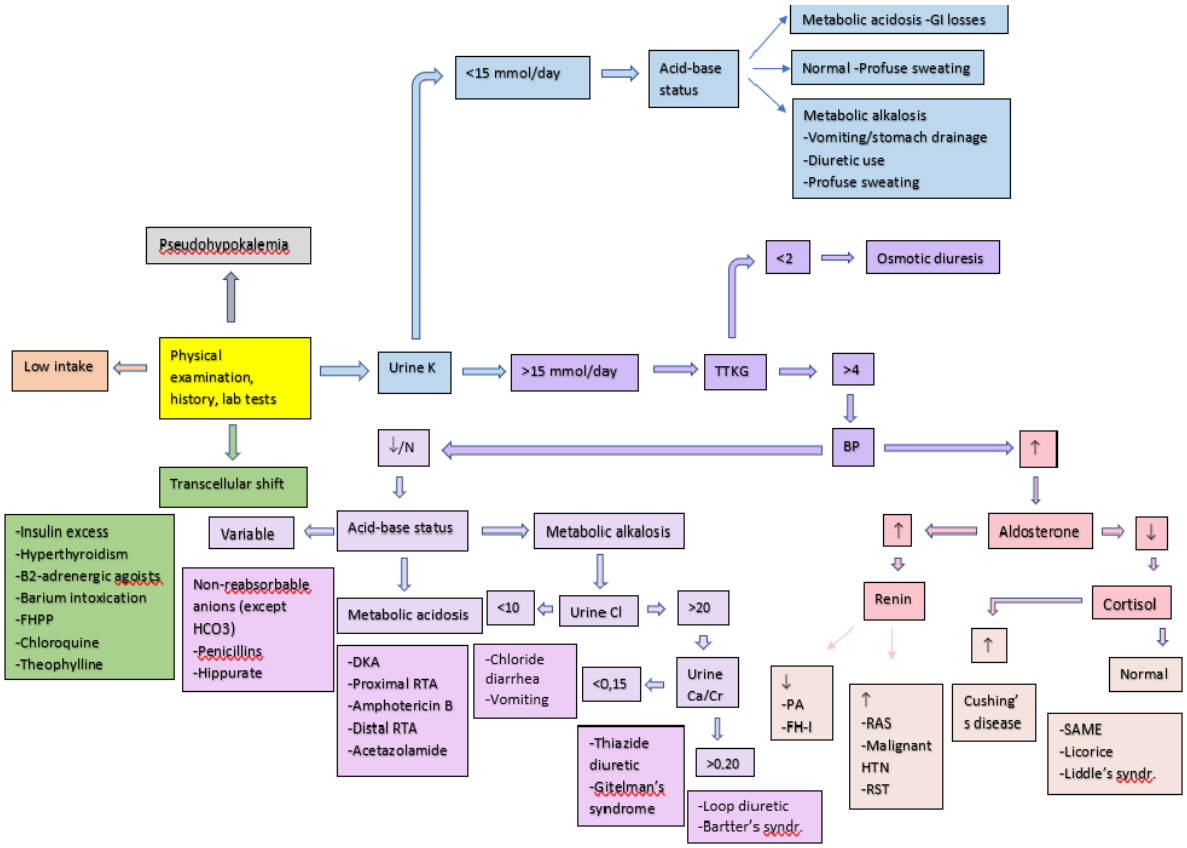

Fig. 1. BP- blood pressure, FH-I- familial hyperaldosteronism type I, DKA- diabetic ketoacidosis, FHPP- familial hypokalemic periodic paralysis, PA- primary aldosteronism, HTN- hypertension, RST- renin-secreting tumor, RAS- renal artery stenosis, SAME-syndrome of apparent mineralocorticoid excess, RTA- renal tubular acidosis, TTKG- transtubular potassium gradient.

Conclusions

Severe hypokalemia is a clinical condition with potentially life-threatening manifestations. We presented a 62-year-old woman, known with autoimmune thyroiditis with substitutive hormonal therapy, with recent history of SARS-CoV-2 severe infection with extensive residual fibrosis and bronchiectasis, with massive pulmonary embolism treated by thrombolysis, resuscitated cardiac-pulmonary arrest, prolonged septic status with multiple nosocomial infections and large spectrum antibiotherapy, post-cholecystectomy status, who developped during hospitalisation persistent hypokalemia, with a dominant renal component. Most probably, in this case more mechanisms were involved. Initially, the patient presented mixed alkalosis, the metabolic component probably in the context of vomitting and chloride loss, while the respiratory component in the context of the post-COVID-19 extensive fibrosis and bronchiectasis. Throughout the hospitalization, the alkalosis persisted as a partially compensated primary respiratory alkalosis and contributed to mantaining the hypokalemia. Also, the patient presented arterial hypotension, most probably because of sepsis (multiple persistent infections), which activates the sympathetic nervous system (intracellular shift of

potassium) and renin-angiotensin-aldosterone system (renal loss of potassium).

The patient needed high doses of intravenous potassium chloride, potassium-sparing diuretic (Spironolactone) and supplements of potassium, with a partial and late correction of serum potassium. This patient needs long-term monitorization and reassessment of other possible causes of hypokalemia, in case of persistance.

Author Contributions:

E.G. and C.D. conceived the original draft preparation. I.C., C.C., and A.P. were responsible for conception and design of the review. I.C., C.V and A.P. were responsible for the data acquisition. I.C, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. E.G., C.D., I.C, C.C., and A.P. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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