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КАРБУНКУЛ ПОЧКИ У ПАЦИЕНТКИ С ПЕРВИЧНЫМ СИСТЕМНЫМ AL-АМИЛОИДОЗОМ И НЕФРОТИЧЕСКИМ СИНДРОМОМ

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Kidney Carbuncle in a Patient with Primary Systemic Al-Amyloidosis and Nephortic Syndrome

Резюме

Диагностика и лечение системного амилоидоза остается значимой клинической проблемой для врачей различных специальностей. Инфекционные осложнения и сепсис составляют до 8% причин смерти больных амилоидозом. Приведенный клинический случай демонстрирует развитие изначально имевшейся бессимптомной моноклональной гаммапатии неясного значения с исходом в системный AL-амилоидоз, течение которого осложнилось формированием карбункула почки после проведения первых циклов химиотерапии. Было установлено значительное расхождение между тяжестью общей клинической картины пациентки и изменениями в лабораторных показателях. Объективных факторов для восходящего распространения инфекции мочевыводящих путей или гематогенной диссеминации из других очагов выявлено не было, в связи с чем была предположена первичная бактериемия.

Ключевые слова: *AL-амилоидоз, карбункул, почка, нефротический синдром, МГНЗ*

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Abstract

The diagnosis and treatment of systemic amyloidosis remains a significant clinical problem for physicians of various specialties. Infectious complications and sepsis account for up to 8% of deaths in amyloidosis patients. This clinical case describes the development of an initially asymptomatic monoclonal gammopathy of unclear significance into systemic AL-amyloidosis, which was complicated by the formation of a renal carbuncle after the first cycles of chemotherapy. There was a significant discrepancy between the severity of the patient's overall clinical state and changes in laboratory parameters. There were no objective factors for the ascending spread of urinary tract infection or hematogenous dissemination from other foci, so a primary bacteremia was assumed.

Key words: *AL-amyloidosis, carbuncle, kidney, nephrotic syndrome, MGUS*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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CRP — C-reactive protein, CT — computed tomography, GFR — glomerular filtration rate, MGUS — monoclonal gammopathy of undetermined significance, US — ultrasound

Introduction

Amyloidosis is a heterogeneous group of hereditary and acquired diseases with pathogenesis based on the deposition of an insoluble fibrillar glycoprotein, amyloid, in the extracellular space [1]. There are 36 known types of human amyloidosis today; their classification is based on the structure of amyloid fibrils and their precursor proteins. Structural variants of amyloidosis are associated with both the systemic and localized nature of the disease. Amyloidosis types with immunoglobulin light (AL) or heavy (AH) chains and procalcitonin (Acal) as precursors can involve one or multiple organs in the process of amyloid infiltration [2]. Localized types are much less common than systemic types, including those in cases of AL amyloidosis [2, 3].

AL amyloidosis, previously defined as primary, is the most common type of systemic amyloidosis in developed countries with an incidence of 5-10 cases per 1,000,000 individuals annually. Its prevalence has been increasing over the past nine years [4, 5]. AL amyloidosis is significantly more common in patients aged over 65, with a slight predominance of male patients. The relative risk of AL amyloidosis is eight times higher in patients with plasma cell dyscrasia and asymptomatic monoclonal gammopathy of undetermined significance (MGUS) [6]. Abnormal clones of plasma cells that produce nephrotoxic paraprotein are not an exclusive feature of AL amyloidosis. Identification of a non-malignant clone of B-cell differentiation line generally defines a group of pathological conditions characterized by specific variants of kidney damage — monoclonal gammopathies of renal significance [7, 8].

Amyloid infiltration in AL amyloidosis can affect almost any organ; however, it mainly affects the heart, kidneys, liver, spleen, and, to a lesser extent, the gastrointestinal tract and nerve fibers, with the exception of the central nervous system [2, 9]. The clinical presentation of this disease is usually extremely obscure

and includes fatigue, weight loss, peripheral edema; dyspnea and orthostatic hypotension are often found. Symptoms highly specific for AL amyloidosis include macroglossia and periorbital purpura (raccoon's eyes), which can be observed in 15% of cases and have low sensitivity [10]. The detection of diastolic myocardial dysfunction and isolated proteinuria over 0.5 g/day without objective and common causes, i.e., a long history of arterial hypertension and/or diabetes mellitus, enables to include systemic amyloidosis in the differential diagnosis. The onset of secondary cardiorenal syndrome (type 5) is a key stage in the development of a vicious pathophysiological circle in cases of AL amyloidosis. Therefore, for most patients, myocardial damage with the development of chronic heart failure, rhythm disturbances, and amyloid nephropathy with the progression of chronic kidney disease (CKD) are the most significant issues in terms of the quality of life and poor prognosis [11].

The diagnostic algorithm in cases of suspected AL amyloidosis primarily includes serum or urine immunofixation for paraprotein in order to exclude plasma cell dyscrasia. Final verification of the diagnosis is based on morphological examination. The sensitivity of rectal or gastric mucosa biopsy is about 75–80%, and it is second only to percutaneous renal biopsy with sensitivity and specificity close to 100%. Subcutaneous adipose tissue (SAT) aspiration is less invasive and is the most preferred method. Detection of amyloid protein in subcutaneous fat aspirate in a patient with known plasma cell dyscrasia is sufficient for the final confirmation of the diagnosis of amyloidosis [12, 13]. The disadvantage of this biopsy site is the impossibility of typing amyloid fibrils, which does not allow excluding ATTRwt-amyloidosis without immunohistochemical examination or laser microdissection. The sensitivity of SAT aspiration is significantly lower in the presence of a low "amyloid load" of the whole body [13, 14].

Despite the established correlation between MGUS and amyloidosis and recommendations for screening monoclonal gammopathies in risk groups, many patients are diagnosed with amyloidosis when amyloid infiltration of the heart and kidneys becomes clinically significant. Mortality among patients with MGUS is largely determined not only by the progression of amyloidosis but also by the high risk of malignant paraproteinemias (multiple myeloma, Waldenstrom macroglobulinemia), rapidly progressing coronary heart disease, and, not least, severe bacterial and viral infections [15]

In the given clinical case, we describe the history of the development of AL amyloidosis with underlying chronic glomerulonephritis with MGUS with the course complicated by a renal carbuncle of unknown etiology.

Case report

Patient N., female, 62, was urgently hospitalized in the Internal Medicine Department of a multidisciplinary hospital with complaints of high body temperature of up to 39°C accompanied by shaking chills, sweating and general weakness.

She considers herself ill since 2016 when she was diagnosed with chronic glomerulonephritis with severe urinary syndrome and monoclonal gammopathy of unknown origin with preserved renal function: glomerular filtration rate (GFR) according to CKD-EPI 104 ml/min/1.73 m^2.

She was followed up by a hematologist and a nephrologist. On February 14, 2018, she visited the Treatment and Rehabilitation Center for swelling of the right lower limb; occlusive thrombosis of muscular venous sinus, of the right posterior tibial vein with flotation into popliteal vein was revealed. Anticoagulant therapy was started — enoxaparin 80 mg twice a day, with further dose adjustment. Control examination on March 29, 2018, demonstrated positive changes with complete recanalization of thrombus. In June 2018, due to persisting complaints of leg edema, she was hospitalized for examination: with underlying exacerbation of chronic glomerulonephritis accompanied by nephrotic syndrome (daily proteinuria — 7.3 g/day, total cholesterol — 11.8 mmol/l), cryoglobulinemia was revealed, GFR CKD-EPI 96 ml/min/1.73 m^2. After transfer to the Nephrology Department, upon further examination, the following diagnosis was made: primary AL amyloidosis with damage of kidneys (nephrotic syndrome with preserved kidney function), gastrointestinal tract, nervous system, adrenal glands. CKD C1 A4 (GFR CKD-EPI 91.6 ml/min/1.73m^2). The diagnosis was confirmed by a puncture biopsy of the right kidney. The results of the histological exam of the rectal and gastric mucos membrane for amyloid were negative. After stabilization of the condition, four courses of chemotherapy were carried out according to the bortezomib-melphalan-dexamethasone scheme (cycle of 28 days). Two weeks before the current hospitalization, she was discharged from the Nephrology Department in satisfactory condition after the last treatment course.

The current deterioration was acute and manifested as a febrile fever that persisted for five days, with no catarrhal respiratory signs. Self-administered antipyretic therapy (indomethacin 100 mg per rectum) had no significant effect; therefore on November 18, 2018, the patient called an ambulance team and was hospitalized for examination and treatment.

Patient's life history: retired, lives with her husband and children, denies bad habits. No history of allergies. Epidemiological history was unremarkable.

Comorbidities:

– arterial hypertension for 20 years with maximum values of 180/100 mm Hg. Constant medication therapy with amlodipine 5 mg, valsartan 80 mg per os helps to maintain target blood pressure values (120/70 mm Hg); the patient also constantly takes atorvastatin 10 mg, rabeprazole 20 mg, rivaroxaban 20 mg once daily
– bilateral gonarthrosis since 2004. In 2015, arthroscopic debridement, meniscectomy of left knee joint was performed, in 2016 — total arthroplasty of left knee joint, in 2017 — total arthroplasty of right knee joint with a satisfactory result.

Objective status on admission: condition of moderate severity. Clear consciousness. Active position. T = 38.7° C. Skin, visible mucosae are pale, no rash. Harsh breathing is heard in lungs, no wheezing, respiratory rate 18 per minute. Heart sounds are muffled, rhythmic, heart rate (HR) — 80 bpm, blood pressure — 118/78 mm Hg. Abdomen is soft, painless in all parts on palpation. No peripheral edemas. Costovertebral angle tenderness was absent on both sides. Urination is free, painless.

CBC on admission — mild leukocytosis 10.9×10^9/l, no anemia. Blood biochemistry revealed hypoalbuminemia, hypercholesterolemia, hyponatremia, and mild hypokalemia, as well as increased C-reactive protein (CRP) level: total protein — 50 g/l, albumin — 26.5 g/l, urea — 8.0 mmol/l , creatinine — 91 μmol/l, **glucose — 10.64 mmol/l, total cholesterol — 5.94 mmol/l**, total bilirubin — 3.8 μmol/l, AST — 43.2 U/l, ALT — 44.2 U/l, **potassium — 3.41 mmol/l, sodium — 132.6 mmol/l, CRP — 153.3 mg/l**, procalcitonin < 0.5 ng/ml. N-terminal pro-brain natriuretic peptide **(NT-proBNP) — 292 pg/ml**. Coagulogram: increased concentration of fibrinogen to 5.28 g/l. Clinical urinalysis: proteinuria (1.0 g/l), leukocyturia (80 — 100 per HPF) and erythrocyturia (100 — 120 per HPF). Urine analysis by Nechiporenko: RBC 37.500 — U/ml, WBC — 77.500 U/ml.

According to the results of computed tomography (CT), no reliable data for inflammatory changes in lungs were obtained; a region of decreased pneumatization of ground-glass opacity was revealed in S1+2 of left lung.

Echocardiography: slightly increased left atrial cavity up to 4.0×5.0 cm (normal: 3.9×4.8); LV parameters: end diastolic dimension — 4.6 cm (normal: 3.8 — 5.5), end systolic dimension — 3.0 cm (normal: 2.2 — 4.0), posterior wall — 0.9 cm (up to 1.1); dimensions of right atrium in 4-chamber view — 3.2×4.3 cm (normal: 3.8×4.6); average diameter of right ventricle in 4-chamber view — 2.3 cm (normal up to 3.6); diastolic size of interventricular septum — 1.0 cm (normal up to 1.1). Global myocardial contractility is satisfactory, ejection fraction — 63%. Type 1 left ventricular diastolic dysfunction. Grade 1 mitral regurgitation. Grade 1 tricuspid regurgitation. Atrial septal aneurysm.

Electrocardiography: sinus rhythm, HR — 83 per minute, normal QRS axis, no acute focal lesion.

Abdominal ultrasound: moderate hepatosplenomegaly. Liver is enlarged due to the right lobe (vertical oblique size of right lobe — 20.5 cm, height of left lobe –5.0 cm), with sharp and even contours; its lower edge is somewhat rounded and localized at the level of navel. Liver tissue of a homogeneous fine-grained structure, of normal uniform echogenicity, with no focal changes, vascular pattern without changes. Portal and splenic veins are not dilated — 12 mm and 7.5 mm, respectively. Spleen is elongated, moderately enlarged, 14.6×4.2 cm, homogeneous, of normal echogenicity.

Ultrasound of kidneys and ureters on admission: kidneys are located symmetrically and typically, with sharp and even contours, moderately enlarged — mostly, right kidney: right kidney at least 13.5×7.5×6.0 cm, left kidney 13.0×6.4×5.3 cm. Renal sinuses are not dilated, of normal structure and echogenicity on the left side. In the renal sinus of right kidney, single oblong cysts with the largest size up to 1.5 cm were found. In different segments of the right kidney, there are single (at least, three) simple cysts, the largest one of irregularly rounded shape, the largest size is up to 2.0 cm, localized in the anterior middle segment of the kidney; the largest size of other cysts does not exceed 1.0 cm. In the lower segment of left kidney, a simple cyst with a diameter of 0.6 — 0.7 cm was found (2.0 — 2.5 cm in different segments). There is slightly increased echogenicity of renal parenchyma and decreased size of several pyramids. Pelvicalyceal system was not dilated, no calculi found. Ureters are not dilated, with active peristalsis, no calculi in the examined areas. Conclusion: ultrasound presentation of bilateral cysts with underlying moderately pronounced nonspecific diffuse changes in kidneys.

Due to signs of systemic inflammatory reaction syndrome of unclear etiology in the absence of an objective focus of infection, empiric antibacterial therapy with levofloxacin 500 mg i/v drip was started. In addition, the patient received albumin 10% — 100 ml, enoxaparin sodium 40 mg subcutaneously once a day, omeprazole 20 mg twice a day, spironolactone 25 mg twice a day per os; when body temperature increased to 38°C — paracetamol 1000 mg — 100 ml.

In the course of ongoing therapy on day 2 after hospitalization, laboratory tests revealed negative changes: leukocytosis 13.7×10^9/l with a neutrophilic shift to the left, mild normochromic normocytic anemia (hemoglobin — 108 g/l, RBC 3.7×10^{12}/l, hematocrit — 37%, MCV — 87 fl, MCH — 29.4 pg, MCHC — 38 g/l),

erythrocyte sedimentation rate (ESR) — 72 mm/h, proteinuria — 2.8 g/l. No clinical changes since admission.

Due to no effect of therapy and a high risk of sepsis (ESR — 78 mm/h, CRP — 165.6 mg/l, procalcitonin — 10 ng/ml), levofloxacin was replaced with meropenem 2000 mg 3 times a day i/v drip.

On day 3, along with stable clinical presentation, slight positive changes of laboratory parameters were registered: CRP — 133.4 mg/l, potassium — 4.43 mmol/l, sodium — 143.3 mmol/l, lactate dehydrogenase — 524 U/l, urea — 7.0 mmol/l, creatinine — 81 μmol/l, hemoglobin — 107 g/l. Fecal occult blood test — negative. Blood and urine cultures — negative.

On November 21, 2018, CT scan of abdominal organs with intravenous enhancement was performed: in the parenchyma of the middle segment of right kidney, a lesion of reduced fluid density is visible, with ill-defined contours, 2.7×2.4×2.3 cm; in the arterial phase, there is decreased vascularization of the surrounding parenchyma with impaired corticomedullary differentiation. When compared with the results of native CT of thoracic organs from November 18, 2018, there was an increase in the size of the cyst in the right kidney from 1.6×2 cm to 2.4×2.7 cm (determined at the edge of visualization area); there is also an area with decreased corticomedullary differentiation in the lower segment of the right kidney, in the arterial phase, with ill-defined contours, about 3×3.6 cm in size. CT presentation corresponds to a carbuncle with signs of developing abscess. The diagnosis was confirmed by a control ultrasound of the right kidney. The patient was transferred for further treatment to the Urology Clinic of Sechenov First Moscow State Medical University. During observation period, the patient's condition remained stable. During transfer, there were no signs of heart failure, the patient was hemodynamically stable.

Final clinical diagnosis.

Main: Primary AL amyloidosis with damage of kidneys (nephrotic syndrome), gastrointestinal tract, nervous system, adrenal glands. Condition after chemotherapy with bortezomib-melphalan-dexamethasone (4 courses).

Complications: Carbuncle of right kidney. Systemic inflammatory response syndrome. Mild normochromic normocytic anemia of mixed genesis. Chronic kidney disease stage 2 (GFR CKD-EPI 67 ml/min/1.73m^2).

Secondary: Hypertensive disease stage II, grade 3 (achieved grade of AH 1), risk of cardiovascular complications is very high. Occlusive thrombosis of the muscular venous sinus of the right lower leg in recanalization stage. Condition after total arthroplasty of left and right knee joints 2016 — 2017

Discussion

Based on the examination and the patient's medical history, no objective data for acute or chronic urinary tract infection were revealed, making it unlikely that renal carbuncle will develop with underlying pyelonephritis. Hematogenous dissemination was not confirmed due to the absence of other foci of infection. One should take into account the high risk of previous bacteremia due to repeated venipunctures during the last four months with the development of immunosuppression during chemotherapy. It is possible that acute focal bacterial nephritis was the starting point for the development of renal carbuncle. In the case of an abscess, an intervention to drain and sanitize the focus in the right kidney with sampling for histopathological and bacteriological tests is critical not only for a favorable outcome for the patient but also for determining the etiology of renal carbuncle.

The described clinical case includes two clinically important issues: diagnosis of suppurative diseases of renal parenchyma, as well as the significance of MGUS for the risk of systemic amyloidosis.

Renal carbuncle and abscess are relatively rare pathologies — about 5-10 cases per 10,000 hospitalizations. Before the widespread use of ultrasound and CT, mortality in certain patient groups was as high as 50%. But even now, with the widespread use of imaging techniques in modern diagnostic algorithms, mortality remains at 9–10% [16]. This is largely due to nonspecific symptoms at the disease onset and to its long course when complaints and physical examination results usually do not indicate the severity and extension of purulent fusion of kidney tissue. The greatest danger for such patients is the high risk of urogenic sepsis. Persistent fever, high CRP level, urinary syndrome, and unsatisfactory effect of empiric antibiotic therapy suggest a purulent and inflammatory process in the kidney, but these are not prerequisite criteria. CT remains the most sensitive method for making the final diagnosis [16].

The main pathogenetic mechanism of renal carbuncle is the ascending extension of the pathogen along the urinary tract, in particular, with pyelonephritis. The hematogenous mechanism is much less common and is directly associated with secondary or primary bacteremia. The best described are cases of secondary bacteremia with the development of a kidney abscess during the removal of a microbial embolus from a detected focus of infection in another organ. Primary bacteremia remains a subject of discussion since, in the overwhelming majority of cases, the port of infection cannot be defined; such cases are classified as a renal abscess or carbuncle of unknown etiology [17]. In some cases, renal carbuncle may not be a primary morphological

element but the next stage in the development of acute focal bacterial nephritis [18].

In urological practice, most patients with renal abscess or carbuncle have one or more predisposing factors: nephrolithiasis, congenital renal anomalies, recurrent urinary tract infections, diabetes mellitus, autoimmune diseases [16]. Several clinical cases include the development of a renal abscess in patients with drug addiction and multiple injections. A case of multiple aseptic abscesses in a patient with MGUS accompanied by a clinical presentation typical for bacterial infection, is of particular interest [19].

According to the results of retrospective studies, patients with MGUS have twice the risk of developing spontaneous viral and bacterial infections compared to the general population. Within ten years from their diagnosis, patients with MGUS have a high risk of developing pneumonia, osteomyelitis, pyelonephritis, and septicemia [20]. Chemotherapeutic treatment of patients with amyloidosis can play a significant role in the development of an infectious process. Basic chemotherapeutic regimens used in the management of plasma cell dyscrasias often inevitably lead to the development of immunosuppression, which contributes not only to possible bacteremia but also to infectious complications. Analysis of literature data revealed no systematic reviews or clinical cases describing renal carbuncle or abscess in patients with systemic amyloidosis. In this regard, data required for an objective assessment of the risk of severe suppurative diseases in patients with already developed AL amyloidosis are extremely limited.

Due to the possibility of a long course of previous asymptomatic MGUS and nonspecific clinical presentation at the onset of AL amyloidosis, the diagnosis is established on average 12 months after the first manifestation of symptoms [4, 6]. Several laboratory panels were developed for screening for MGUS but they are not widespread and, in most cases, are used only when there is clinical evidence to suspect MGUS [21]. A five-year randomized population-based study on screening the population of Iceland aged over 50 for monoclonal gammopathy is in its final stage. At present, this is the only global study seeking to create an optimal strategy for diagnosing and monitoring patients with known MGUS, assess the effect of screening for MGUS on overall survival, and develop a model for determining the risk of progression [22].

Conclusion

MGUS and amyloidosis remain an important interdisciplinary issue, since the clinical manifestations of the disease are diverse, and different specialists can encounter them in their practice. Considering the regular development of nephropathy and cardiomyopathy in systemic amyloidosis, one should also take into account the possible risks of infectious complications associated both with the course of underlying disease and with the therapy performed. Prevention of bacteremia can reduce the potential risks of poor outcomes for patients with amyloidosis. Implementation of effective screening programs will allow detecting systemic forms of amyloidosis at early stages, which will help reduce the number of deaths from amyloidosis and its complications.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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