ABSTRACT

Chronic kidney disease (CKD) is associated to significant infection incidence and severity, the cause of death of, approximately, 20% of end-stage renal disease patients. Close to 80% of all infections in these patients can be related to organ or tissue other than vascular access, reflecting immune system dysfunction related to several mechanisms. *Strongyloides stercoralis* is an endemic nematode found especially in tropical and subtropical areas. The clinical manifestations of *Strongyloides stercoralis* infection vary according to the acuity of infection and the host response, from asymptomatic to the disseminated presentation, frequently lethal. Risk factors for severe presentations are related to immunosuppression states. The authors report a case of a patient with advanced CKD of unknown etiology, who developed an exuberant eczema, respiratory symptoms and severe hypereosinophilia. The etiological study revealed a disseminated form of *Strongyloides stercoralis* infection with myocardia involvement, diagnosed solely by serologic testing, despite microbiological tests to identify the infective agent. In this case, the patient has evolved favorably, with remission of symptoms and cardiac features, after adequate antihelminthic treatment. The importance of parasitic colonization and its potential harm becomes clinically more relevant when patients become immunosuppressed, as in CKD progression or in the immunosuppressive therapy setting, such as solid organ transplant rejection therapy. A brief literature review related to strongyloidiasis and immunosuppression in the CKD setting is also presented.

Key-Words: Chronic kidney disease, hypereosinophilia, immunosuppression, *Strongyloides stercoralis*.

INTRODUCTION

Chronic kidney disease (CKD) is associated to significant infection incidence and severity, the cause of death for, approximately, 20% of end-stage renal disease patients, as a reflection of immune system dysfunction related to several mechanisms. *Strongyloides stercoralis* is an endemic nematode found mostly in tropical and subtropical areas. The clinical manifestations of *Strongyloides stercoralis* infection vary according to the acuity of infection and the host response, from asymptomatic to the disseminated presentation, frequently lethal. The diagnosis requires high clinical suspicion, since the available methods to identify the causative agent are either nonspecific or frequently false negative. Its isolation in cultures is particularly difficult according to its complex life cycle and to small parasitic load released in feces, and serologic tests do not distinguish acute from chronic infection. Risk factors for severe presentations include advanced age, malnutrition, diabetes mellitus, chronic renal disease, immunosuppression and organ transplantation.
While infection may be symptomatic in any immunological status, the relevance of helminthic colonization and its potential harm becomes clinically more relevant when patients become immunosuppressed, as in CKD progression, or in the immunosuppressive therapy setting, such as solid organ transplant rejection therapy. In such cases colonization may become active infection, with several degrees of severity. In these cases, if sepsis or hypereosinophilia occur, helminthic agents must be specially considered.

CASE REPORT

The authors report the case of a female African patient, 50 years old, born and living in Cabo Verde, office employee at São Vicente Island city council. She had previous history of uncontrolled arterial hypertension, with presumed renal involvement – CKD at stage 4, according to KDIGO renal function staging – and was medicated with atenolol, nifedipine, calcium carbonate and folic acid.

The patient presented with progressive worsening of generalized pruritus, asthenia, anorexia, nausea, headache and severe arterial hypertension, with no seasonal pattern identified. The symptoms developed over a period of three weeks. She was admitted at the local hospital and was considered as having uremic syndrome due to CKD progression. The laboratory results were not sent to our hospital. After symptomatic treatment, symptoms were partially alleviated and she was discharged, maintaining follow-up in outpatient consultations.

In the following two weeks after hospital discharge, the patient developed non-productive cough associated with mild dyspnea, without circadian pattern, not related to environmental changes or contact with allergenic substances. These complaints were nonresponsive to antibiotic and antitussive drugs, but remitted spontaneously.

Two months after clinical onset, systemic pruritus was now associated with diffuse and severe scratch skin lesions, despite antihistamine therapy, and blood pressure was still uncontrolled; at this time, the patient was newly admitted to the previous hospital for further study. Her blood analysis revealed creatinine 10.5 mg/dL, urea 137 mg/dL, uric acid 9 mg/dL, phosphorus 5.6 mg/dL and a normochromic normocytic anemia (hemoglobin 10 g/dL). Some viral hepatotropic infections were ruled out (B and C hepatitis serologies were negative for acute or chronic infection) as was HIV infection. The basic urinalysis revealed proteinuria (no quantitatively measured). The chest radiography did not show any relevant findings; the renal ultrasound exhibited only signs of chronic kidney disease – hyperechoic kidneys with diminished corticomedullary differentiation. The echocardiogram presented signs of hypertensive remodeled cardiopathy – left atrial and ventricular dilatation, interventricular septum hypertrophy, but still with preserved ventricular global systolic function – and mild aortic and mitral valvular regurgitation.

According to these findings and considering the hypothesis that the symptoms were due to end-stage chronic kidney disease, her attending nephrologist decided to initiate renal replacement therapy (hemodialysis), which allowed blood pressure control but did not improve systemic pruritus and skin lesions.

Since further evaluation and treatment were needed, the patient was transferred to our hospital, in Portugal. Her complaints had begun 3 months ago and were worsening – the pruritus during night time caused insomnia – and the patient reported a weight loss of 6 kg, corresponding to about 10% of her previous body weight.

She denied having previous allergic disease, contact with animals, recent travel or new drugs intake.

At this time, skin examination revealed an exuberant diffuse exanthema, scratch lesions with hemorrhagic spots and xerosis, not sparing any skin area. Cardiac auscultation led to the detection of a systolic heart murmur, more intense at the aortic area.

Our preliminary blood analysis confirmed the anemia – normochromic normocytic – but also showed leukocytosis (total white blood cells count: 21640x10^9/L) with absolute neutrophilia (13010x10^9/L, 60.1%) and relative plus absolute eosinophilia (6230x10^9/L, 28.8%), mild elevation of reactive C protein (1.9mg/dL) and lactate dehydrogenase (943 U/L). The white blood cells count remained elevated over time.

Considering the clinical finding of pruriginous skin rash and the presence of eosinophilia, more tests were conducted. In order to exclude drug allergy and all medication was suspended, but that did not result in any modification of complaints or skin appearance. Microscopic examination of stools and blood did not reveal parasite eggs, cysts or larvae. *Cryptococcus* and hydatid cyst serologic tests were also negative. Nevertheless, considering the false negative rate of these tests and the high clinical suspicion of parasitic infection, albendazole was prescribed, as a therapeutic trial, but that did not result in clinical improvement either.
An autoimmune panel, including rheumatoid arthritis test, autoantibody assay (anti double-stranded DNA and anti-nuclear) and complement, showed values within the normal range.

A skin biopsy was performed and only revealed signs of eczema. A transthoracic echocardiogram showed, apart from concentric left ventricular hypertrophy with preserved systolic function (ejection fraction 70%), that the myocardium had a mottled pattern, suggesting infiltrative cardiomyopathy.

After the first tests, we concluded that this patient had a systemic hypereosinophilia with skin and, possibly, myocardia involvement, so further studies were conducted.

Considering hematologic diseases, a bone marrow aspiration and biopsy were performed and revealed normocellular bone marrow, with no deviation of the myeloid/erythroid ratio, 36% eosinophil cells, at different maturation stages, and mastocytosis. Serum triptase mild elevation (15.4mcg/L) was associated to increased mast cells number.

Plasma total immunoglobulin E (IgE) was very high (2828U/L), 32 times above upper laboratory level, but available specific IgE for parasites (Ascaris and Aspergilus) were negative (<10U/L).

A computed tomography of the chest abdomen and pelvis did not reveal any occult neoplasm; it showed axillary and inguinal enlarged lymph nodes, which seemed to be reactive, cardiomegaly with a small pericardial effusion on the anterior and inferior recess, mild homogeneous hepatomegaly, with no other significant findings.

During the hospital stay, dosage and number of antipruriginous drugs were optimized: the patient needed high doses of ranitidine, hydroxyzine, loratadine, clemastine and prednisolone, with significant reduction of the pruritus, enabling progressive healing of the scattered skin lesions.

Since no etiology was found at this stage and the patient maintained fluctuant hypereosinophilia and symptoms, more serologic tests were performed, searching for rarer infections. Acute and late antibodies for infection by Ascaris, Giardia, Nocardia, Toxocara, Fasciola, Ascaris, Ancilostoma, Filaria, Enterobius vermicularis, Trichinella and Schistosoma were negative, but serologic testing for Strongiloides stercoralis was positive.

Considering previous treatment failure with albendazole and the severity of the disease, treatment with evermectin (12mg once a day, for 2 consecutive days, per os) was prescribed. As a result, complaints subsided completely and skin lesions resolved progressively, both in texture and color. Laboratory abnormalities normalized almost entirely: eosinophil blood count decreased into the normal range (0.21x10^9/L), as well as triptase (8.6 mcg/L), but the patient kept severe serum IgE elevation (3122U/mL), although she remained asymptomatic.

During follow up, microscopic examination of the stools was repeated but identified only Giardia intestinalis specimens; tinidazol (2 gr, single dose, per os) was prescribed, allowing infection resolution.

The infiltration pattern of the myocardium, observed on transthoracic echocardiogram, disappeared; it was confirmed by repeat testing 40 days after evermectin treatment.

### MINI-REVIEW

#### CKD and Immunodeficiency

CKD is a very complex syndrome with multiple organ involvement; it is associated with systemic inflammation and acquired immunodeficiency simultaneously, promoting, among other complications, cardiovascular disease and infections, namely viral or helminthic. Several investigations have been performed in this area, especially on microbiome, pursuing potential mechanisms that would explain the relationship between these conditions. A paper from Anders and colleagues proposed that uremia and secondary gut dysbiosis acts as a trigger to systemic inflammation and immune activity suppression.

A study from Gil and colleagues performed in Brazil found a high prevalence of parasitic infection in hemodialysis patients, without a clear relationship between symptoms and the type of parasite or with multiple parasitic infections.

On the other hand, other work groups established differences on differential white blood cell (WBC) count in CKD patients. Agarwal and Light compared patients with and without CKD and found that those with CKD had more eosinophils and granulocytes and fewer lymphocytes in differential blood cell counting; the same authors observed also that there is a greater variation in leukocytes over time and that both granulocyte and monocyte spikes were independently associated with...
end-stage renal disease (ESRD) and death, although no specific cause was identified for these variations.8

Considering data from microbiome changes with CKD and along its progression, the peripheral WBC modifications observed in these patients can be explained by some hypothetical mechanisms: they may be related to latent and indolent infections, or colonization by harmless agents to the immunocompetent patients, that break mucosal barriers, but also with chronic inflammatory status arising from the renal illness itself and permanent microbiologic invasion with incomplete depuration.

■ Eosinophilia

Eosinophilia is defined as eosinophil counting on peripheral blood superior to 0.5x10⁹/L, being classified as mild, moderate or severe, according to countings – 0.5-1.5, 1.5-5 or higher than 5x10⁹/L, respectively. Hypereosinophilia is considered when eosinophil peripheral blood counting exceeds 1.5x10⁹/L; this cut-off establishes more probability to organ and tissue damage, regardless underlying etiology. The most frequent causes of eosinophilia include helminthic parasite infections, atopic and allergic diseases and adverse drug reactions; unusual situations have been associated to neoplastic diseases, namely hematologic or paraneoplastic, autoimmune or immunodeficiency disorders.

Roufosse and Weller proposed a practical approach to hypereosinophilic patients; according to them, the cause and the complications eosinophil-mediated, requiring urgent lowering strategies, should be assessed simultaneously, suggesting that, patients with rapid eosinophil lowering requirement, should be given corticosteroids nevertheless other treatment measures.

Since more studies are necessary to a better understanding of WBC count variations on CKD patients, hypereosinophilia, especially severe, is being considered as in non-CKD patients.

■ Strongyloidiasis

Strongyloidiasis is an intestinal helminthic parasitic infection caused by two species of Strongyloides; S. stercoralis (SS) is the most important and common in humans, the principal host. Other mammals, such as cats or dogs, may harbor the worm and serve as reservoir hosts. Its life cycle is complex and unique among intestinal nematodes.

Due to subclinical behavior of SS infection, the true prevalence is underestimated. Outside endemic areas, the highest prevalence is reported in long-term institutionalized care subjects, prisons, refugees or immigrants from tropical or subtropical countries and people who were in southwest Asia during World War II and the Vietnam War.9

Human infection occurs after penetration of larval forms on skin or mucosal tissues from contaminated soil or by fecal-oral route (autoinfection mechanism), allowing continuous infection for several years after initial inoculation. Most infected patients do not experience significant complaints; in symptomatic patients, the most common clinical manifestations are vague. In acute infection, symptoms are mostly related to gastrointestinal tract – anorexia, nausea, vomiting, epigastric cramping, diarrhea, constipation, indigestion – and respiratory tract – mild cough and wheezing – whereas chronic infection is characterized by skin involvement – itch and excoriation secondary to pruritic papulovesicular lesions.10

Several immunosuppressive conditions, especially when related to cell-mediated immunity impairment, have been associated to development of hyperinfection syndrome.7,14 In these cases, a massive dissemination of larval forms occurs to extraintestinal organs – lungs, liver, heart, central nervous system and endocrine organs, and defines disseminated form of strongyloidiasis. In this severe form, translocation of enteric bacteria may also occur, leading to polymicrobial bacteremia and organ specific infection. The severity of symptoms becomes higher and fever and neurologic manifestations – altered mental status, focal seizures, meningitis, brain abscess – are also present.7,10,12,13

Given the paucity and non-specificity of clinical presentation, a high level of suspicion is required for diagnosis. Microscopical stool observation can lead to larvae identification, but is a rare finding, given the intermittence and low burden of parasites elimination in feces. This problem can be partially overruled by 7 consecutive stool sampling, increasing sensitivity to more than 90%. Serodiagnosis is not readily available but ELISA (immunoglobulin G) for larval forms can be helpful to reach diagnosis when stool tests are negative.15 Despite ELISA high negative predictive value (98%), ELISA can be negative in immunocompromised hosts; false positives can also occur in other helminthic infections and does not distinguish past and present infection.11,12,16

If these tests fail to make the diagnosis, duodenal endoscopy with biopsies, sputum, bronchoalveolar
fluid, urine, cerebrospinal fluid should be collected to search for filariform or rhabditiform larvae. Skin biopsies are neither necessary nor sufficient because parasites are rarely visualized; although, in severe infection, the biopsies should be obtained on purpuric eruptions, since those lesions contain the largest amount of larvae16.

Recommended treatment includes supportive measures and anthelmintic therapy. Strongyloides infections should be treated even in the absence of symptoms as hyperinfection syndrome carries a high mortality rate5,17.

First-line anthelmintic is ivermectin (200 mcg/kg, administered on two consecutive days or two weeks apart) owing to its superior efficacy and fewer side effects compared to benzimidazoles. In hyperinfection and disseminated disease, ivermectin should be administrated daily until symptoms resolution and until larvae become undetected for at least 2 weeks, associated or not to albendazole. Immigrants from endemic areas for loiasis should be screened for high levels of microfilaremia since ivermectin therapy can precipitate encephalopathy17.

Among immunosuppressive agents, only cyclosporine A (CyA) evidenced anthelmintic activity; to date, no cases of severe SS infections have been reported in transplant recipients under CyA treatment14,17. Even so, no recommendation has been made to include CyA as regular therapy for SS infections.

Regardless the good prognosis and mild severity of acute and chronic strongyloidiasis in immunocompetent hosts, severe strongyloidiasis carries a high mortality rate (>80%), frequently due to late diagnosis and to the host immunocompromised status, allowing Gram-negative severe infections.

Screening for transplant candidates

Patients with end-stage renal disease are frequently candidates for renal transplantation. The resolution of uremia improves the inherent immunological impairment of CKD itself but, still, pharmacological immunosuppression determines hosts’ cell-mediated defense mechanisms. As noted above, carriers of intestinal parasites with pathogenic potential, even when asymptomatic prior to transplant, can develop severe clinical manifestations after transplantation, complications that may influence transplantation success. Considering also the high prevalence of intestinal parasites and the dissociation between symptoms and infection in CKD patients, some reviewers have already suggested incorporating stool tests in routine pre-transplant screening.

In our opinion, considering the demographic characteristics of Portuguese kidney recipient candidates, namely the high number of immigrants or cohabiters from endemic countries, the screening before transplant for asymptomatic SS infection and SS eradication should be seriously considered, particularly on those with multiple risk factors for helminthic infection. Furthermore, preventive measures for the colonization through the fecal-oral contamination route should be enhanced18-20.

Disclosure of potential conflicts of interest: none declared.

References


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