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CASE REPORT

Toxoplasmosis-associated hemophagocytic syndrome in renal transplantation

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Summary

Toxoplasmosis is an infrequent, often difficult to diagnose and potentially lethal disease in kidney transplant recipients. Among reported cases, a few were associated with hemophagocytic syndrome (HPS), a rare condition characterized by widespread proliferation of macrophages phagocytizing blood elements, accompanied by fever and pancytopenia. We report here the case of a patient who received a *Toxoplasma gondii* positive kidney allograft and developed invasive toxoplasmosis 10 days after surgery, with high fever, skin rash, arthralgias, and renal failure, followed by pneumonia, anemia, thrombocytopenia, liver dysfunction, and encephalitis. Mislead by the absence of Toxoplasma on blood smears, alveolar fluid, renal graft biopsy, and negative brain computed tomography, confusion with serum sickness, and simultaneous herpetic infection, we failed to make the right diagnosis and the patient died with septic shock 11 days later. An HPS was revealed by a late bone marrow analysis. This may well be the fourth case ever reported of toxoplasmosis-associated HPS in renal transplant recipients.

Introduction

Toxoplasmosis is seldom seen in renal transplant recipients, usually transmitted by the donor's kidney, occurring in the early high-immunosuppression post-transplant phase. Unless promptly treated, it is lethal in most cases [1]. Its diagnosis may be difficult. Fever and neurologic signs may be suggestive for the disease, and confirmation requires thorough search for the parasite and for specific antibodies. Only a few cases of toxoplasmosis in renal transplant patients were reportedly associated with hemophagocytic syndrome (HPS), a rare but serious condition characterized by extensive macrophage activation and proliferation, with phagocytosis of hemopoietic cells, fever, pancytopenia, and liver dysfunction [2].

Case report

MF, a 38-year-old Caucasian male with end-stage renal disease (ESRD) secondary to reflux nephropathy, received a kidney allograft from a 26-year-old male cadaveric donor. The recipient had blood type B and human leukocyte antigen (HLA) type A2-A3 B7-B27 DR2-DR8. The donor had blood type O and HLA type A11-A19(2) B5-B7 DR2-DR7 and his serology was hepatitis B surface negative, human immunodeficiency virus negative, cytomegalovirus negative and Toxoplasma positive (with extremely high titers of both IgM and IgG anti-Toxoplasma antibodies). Immunosuppression was induced with ATG, methylprednisolone and azathioprine. The graft functioned properly, with a 0.9 mg/dl (81 μmol/l) serum creatinine (sCr) on day 10.

At that point the patient developed high fever (40 °C), skin rash and arthralgias, together with a fall in serum C3c and C4. Suspecting serum sickness, we stopped ATG immediately. Otherwise, we found no clinical evidence of infection whatsoever; urine and blood cultures were negative. The graft function worsened, with sCr raising to 3.8 mg/dl (335 μmol/l) on day 12, while the platelet count fell to 80 000/mm^3.We ruled out disseminated

intravascular (i.v.) coagulation, for serum D-dimers and fibrin degradation products were low, as well as microangiopathic hemolytic anemia, as there were no schistocytes on the blood smear and serum haptoglobin level was normal. The search for anti-platelet antibodies was negative. Graft ultrasound showed no abnormality. A biopsy on day 12 found endocapillary glomerulonephritis with C3 vascular deposits. Maintaining the diagnosis of serum sickness, we administered corticoids in i.v. boluses on three consecutive days.

However, fever persisted and renal function continued to deteriorate. A second graft biopsy revealed clearly improving glomerular lesions, but newly added severe tubular necrosis. Liver dysfunction developed next, with high serum aminotransferases, lactacte dehydrogenase (LDH) and conjugated bilirubin, and low fibrinogen. Simultaneously, the occurrence of labial herpes, a positive herpes virus serology conversion and a mental deterioration made us consider herpetic encephalopathy, so we started acyclovir i.v. and fluconazole i.v. Cerebral computed tomography (CT), as well as abdominal CT, were unremarkable. The patient later developing pulmonary rales, his chest CT showed diffuse alveolitis and bilateral pleural effusion, but fiberoptic bronchoscopy with alveolar lavage and bronchial brushing failed to detect any germs. On day 19 the patient's general status dramatically altered, as he developed acute pulmonary edema, respiratory failure and shock. He was transferred to ICU and received assisted ventilation. A cardiac event was ruled out, for electrocardiogram, echocardiogram and pulmonary capillary wedge-pressure were normal. Sepsis was once again considered, and broad-spectrum antibiotherapy was started, with imipenem/cilastatin, amikacin, vancomycin and spiramycin.

On day 21, unfortunately, the patient died. The bone marrow biopsy, performed earlier, made a late diagnosis of toxoplasmosis. The myelogram showed, in fact, a large number of intracellular and extracellular *Toxoplasma gondii* trophozoites. It also revealed a hemophagocytic phenomenon: numerous macrophages containing phagocyted, slightly altered blood cells inside the cytoplasm. The protozoan was simultaneously found on the peripheral blood smear. Retrospectively, we searched the patient's toxoplasma serology on his previous blood samples: it had been negative before transplantation, but it had turned positive for both IgM and IgG on day 20. The autopsy revealed pulmonary congestion, multiple infarctions (in the right lung, in the kidney graft, and in the liver), and multiple serous effusions (pleural, pericardial, and peritoneal). Toxoplasma trophozoites were found in the lungs, heart, liver, and brain, but not in the kidney allograft (Table 1).

Table 1. Evolution of the main laboratory parameters.

Parameter	Day 0	Day 7	Day 14	Day 21
Serum creatinine (μmol/l)	418	75	587	551
Hb (g/dl)	10,1	8,2	7,3	6,8
WBC (10^3/mm^3)	7,7	6,4	5,6	7,4
Platelet count (10^3/mm^3)	230	283	48	18
Prothrombin index (%)	100	91	83	61
ALAT (U/l)	5	6	148	283
LDH (U/l)	319	228	1410	2270
Fibrinogen (mg/dl)	272	200	204	165

ALAT, alanine amino transferase; LDH, lactacte dehydrogenase.

Discussion

This case demonstrates the difficulties in diagnosing toxoplasmosis, particularly when occurring in early postrenal transplant, and the devastating course this disease may take in this setting, including the rare, but extremely severe complication of HPS.

Organ transplantation is a common route of transmission of *T. gondii* in humans [3]. Unlike immunocompetent individuals, immunosuppressed patients are prone to develop disseminated infections. Most cases of invasive toxoplasmosis have been reported in heart and bone marrow recipients [4]. In renal transplantation the disease is rather rare. In a literature survey, Renoult *et al.* [1] found not more than 31 case reports. Toxoplasmosis was transmitted by the donor in at least one third of these cases, as well as in our patient. He developed the disease very early after transplantation, which points out the role of intense immunosuppression and of ATG treatment as risk factors [5].

Invasive toxoplasmosis commonly presents with fever, leukopenia and thrombocytopenia, augmentation of liver enzymes, neurological signs and pneumonia [5], but these findings are nonspecific. In our patient, the onset of the disease mimicked serum sickness. Indeed, this condition may be induced by ATG and may present with fever, skin rash and arthralgias, classical pathway activation of complement with low serum C3 and C4, and endocapillary glomerulonephritis with C3 deposits. The transplanted kidney is generally unaffected [6], so renal biopsy is usually not helpful. Concomitant infections, like herpes in our case, were found in more than half of the reported patients [1]. We can assume that such infections, either favoring or favored by invasive toxoplasmosis, may not only worsen its course, but also may mask and delay its diagnosis.

Therefore, the diagnosis of toxoplasmosis remains difficult and in most reported cases it was not considered during life. In a renal transplant patient with unexplained fever and neurological symptoms, toxoplasmosis should be positively considered. The diagnosis may be made

directly, by isolation of the parasite from infected tissue (e.g. cerebral or lymph nodes biopsies) or from body fluids (e.g. blood, bone marrow aspirate, cerebrospinal fluid or bronchial lavage fluid) or by detecting circulating Toxoplasma antigens, by IgM immunoblot assay or by PCR DNA amplification, and indirectly, by detecting changing titers of specific IgG, IgM, and IgA antitoxoplasma antibodies [5]. We unfortunately did not find the parasite in the blood, or in the bronchial lavage fluid. We avoided performing a lumbar or a pleural puncture, fearing the bleeding risk from thrombocytopenia. The CT scan did not help either, but magnetic resonance imaging (MRI) is actually considered the best diagnostic technique for toxoplasmic encephalitis, as it may detect lesions not visualized on CT scan; it typically reveals 'target'-like ring-enhancing masses and hypodensity areas, most often in the basal ganglia or corticomedullary junction [4,6]. Bone marrow aspirate and search for Toxoplasma serology were considered too late.

The fatal outcome of our patient is not surprising. In the review by Renoult *et al.* [1] the mortality rate exceeded 64% and, if untreated, toxoplasmosis was lethal in all but one case. We believe that the particular virulence of the Toxoplasma clone found in our patient may also have had a deleterious role. Indeed, its inoculation in mice resulted in death of all infected animals (DL50 = DI50), with no anti-toxoplasma antibodies having been developed by any of them. The isoenzyme typing of the clone revealed a zymodeme type 1, which is known as a virulent one and is rather rarely found in humans. Most Toxoplasma clones isolated in France induce chronic toxoplasmosis in humans and are asymptomatic in mice.

Hemophagocytic syndrome, first described by Risdall *et al.* [7] in 1979 in a series of 19 patients, is a rare clinicopathological entity, characterized by an activation of the monocyte–macrophage system, with widespread nonmalignant proliferation of tissue macrophages and phagocytosis of blood elements [8]. HPS may be either primitive (also known as 'familial erythrophagocytic lymphohistiocytosis', autosomally inherited) or reactive, secondary to infections (mostly viral), tumours or autoimmune diseases. The main clinical features of HPS are fever, skin rash, pulmonary infiltrates, and liver, spleen and lymph-node enlargement. Laboratory findings commonly comprise blood cytopenias, abnormal liver function tests, low coagulation factors V and fibrinogen, hypertriglyceridemia and high serum ferritin. Bone marrow analysis showing macrophage hemophagocytosis is the most conclusive test for a positive diagnosis [2,9]. Our patient did exhibit fever and skin, lung and liver involvement, associated with anemia, thrombocytopenia and hemophagocytosis in the bone marrow, but he had no hepato-, spleno- or adenomegaly and no leukopenia. Ferritin and triglycerides were not measured. HPS has a poor prognosis and no specific treatment besides that of the underlying disease. Although most authors believe that immunodepressed patients are more prone to develop HPS, this syndrome has rarely been reported in renal transplant patients. However, it is probably under diagnosed, as its features are variable and nonspecific [2]. Recently, Karras *et al.* [2] reported 17 cases (the largest series) and reviewed other 34 case reports of HPS in renal transplant recipients (of which 13 belonged to the Risdall *et al.* 1979 series). Among these 51 cases, only three had toxoplasmosis as the underlying condition. Thus, our case may be the fourth ever reported.

In conclusion, toxoplasmosis in a renal transplant recipient may not be diagnosed, if unsuspected, as the parasite may not be found on kidney biopsies, blood smears or alveolar lavage fluid, cerebral CT may be negative, and the disease may resemble to or associate with other conditions. Suspicion must be raised whenever fever and/or neurologic troubles occur. Bone marrow aspirate, MRI and search for toxoplasma antigens and serology are usually necessary for diagnosing toxoplasmosis. HPS, although rare, may complicate toxoplasmosis and it may also be misdiagnosed, unless suspected. Bone marrow analysis is conclusive in most cases.

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