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CASE REPORT

Severe cerebral toxoplasma infection cannot be excluded by a normal CT scan

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ABSTRACT

A fatal case is reported concerning a severely immunocompromised 50-year-old female renal transplant recipient who developed fever and confusion. Cerebral imaging with contrast-enhanced computed tomography (CT) scans showed no abnormalities while subsequently performed magnetic resonance imaging (MRI) showed clear abnormalities in the basal ganglia. By that time serology and polymerase chain reaction had confirmed the diagnosis of cerebral toxoplasmosis. Because of the suboptimal sensitivity of these tests negative results should be handled with care. Once cerebral toxoplasmosis is suspected in at-risk patients, treatment should be started empirically pending the confirmation of the diagnosis. A normal cerebral CT scan does not preclude cerebral toxoplasmosis. In these situations MRI can give important additional information.

What was known on this topic?
Toxoplasmosis is a rare but feared complication after renal transplantation. The varying presentation of this opportunistic infection and the pitfalls in the diagnostic work-up make it difficult to diagnose the condition early.

What does this add?
This case clearly demonstrates the suboptimal sensitivity of CT scan to diagnose cerebral toxoplasmosis after transplantation. MRI can give important additional information and we recommend using it early.

KEYWORDS

Brain imaging, cerebral toxoplasmosis, MRI, renal transplantation, toxoplasma encephalitis

INTRODUCTION

Toxoplasmosis is a rare but feared complication after solid organ transplantation[1] with a high case-fatality rate. Unfortunately the currently used diagnostic tests are sometimes difficult to interpret especially in the heavily immunocompromised patients at risk. Because of the suboptimal sensitivity of these tests negative results should be handled with care. This fatal case shows the limitation of cerebral imaging with contrast-enhanced computed tomography (CT) scanning in this condition. We will briefly review the varying clinical presentations of this opportunistic infection and the pitfalls in the diagnostic work-up.

CASE REPORT

A 50-year-old Ghanese woman with end-stage renal disease due to hypertension received a postmortal renal transplantation in 2001. Immunosuppressive therapy consisted of prednisolone, ciclosporin and mycophenolate mofetil (MMF). Direct post-transplantation a mild acute cellular rejection was successfully treated with 1000

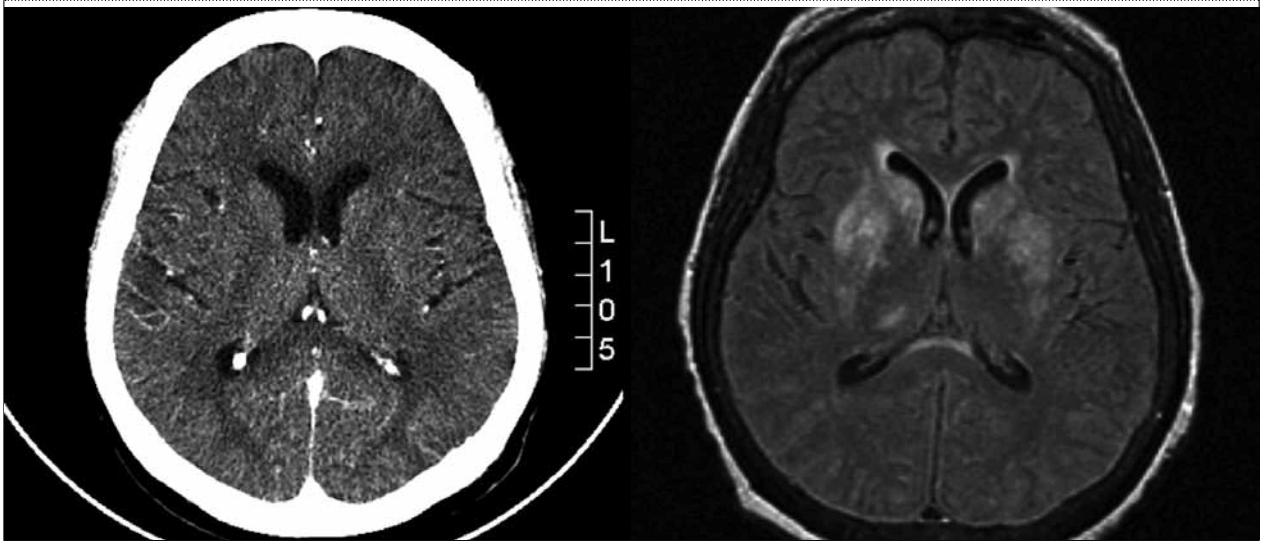
mg of methylprednisolone on three consecutive days. In 2004 it was decided to slowly taper and subsequently stop the MMF. She continued the use of ciclosporin and prednisolone in a daily dosage of 10 mg. After six months a rise in plasma creatinine level from 160 to 375 µmol/l was noted again due to acute cellular rejection. When renal function did not improve after treatment with another 3000 mg of methylprednisolone a course of antithymocyte globulin was given followed by two doses of intravenous immunoglobulins (IVIG). One day after this treatment she developed fever and mental confusion. There were no focal neurological abnormalities and fundoscopy was normal. A CT scan before and after intravenous contrast of the cerebrum did not show any abnormalities. Laboratory analysis showed thrombocytopenia (54 x 10^9/l), leucocytopenia and lymphopenia (2.3 x 10^9/l with 9.4% lymphocytes), elevated lipase (1053 U/l) and rhabdomyolysis (maximum CPK 2570 U/l). Cultures from urine, blood and bone marrow were negative as was a polymerase chain reaction (PCR) on *Mycobacterium tuberculosis*. Analysis of cerebrospinal fluid (CSF) showed a small increase in protein level of 0.87 g/l (normal value <0.5 g/l), a normal Giemsa stain and lymphocyte pleiocytosis. Ciclosporin therapy was stopped. After several days of no improvement a CT scan of the cerebrum was repeated and again showed no abnormalities. However a MRI scan of the brain, performed a day after the second negative CT scan, yielded extensive areas of marked inflammation and oedema around the basal ganglia (*figure 1*) suggestive of *Toxoplasmosis cerebri*. This diagnosis was confirmed by a rise in serum IgG for *Toxoplasma* from 220 IU/ml to 4236 IU/ml, an increase in the titre of the Sabin Feldman test from 1:512 to 1:2048 and a positive CSF PCR on toxoplasmosis. The IgG avidity was high, indicating primary toxoplasma infection had taken place longer before which was confirmed by the 1:32 titre in the Sabin Feldman test, routinely performed before transplantation. This all suggested reactivation instead of an acute infection in this case. Therapy with sulfadiazine, pyrimethamine and folinic acid was started. Despite this, the disease progressed and the patient died four weeks after initiation of therapy. Autopsy was not performed according to the wishes of her family.

DISCUSSION

Our patient suffered from a disseminated *Toxoplasmosis gondii* infection due to reactivation after antithymocyte globulin treatment for a late allograft rejection. Neurological symptoms as well as the signs of rhabdomyolysis and pancreatitis fit with this infection. Extracerebral toxoplasmosis can involve any organ system with eye and lung involvement (approximately 50 and 25% of cases, respectively) as the most frequently involved organs.[2] Pancreatic infection in patients with acquired immunodeficiency syndrome (AIDS) with extracerebral toxoplasmosis was found in 26% of cases at autopsy.[3]

In 1996 Renoult *et al.* described six cases and reviewed 25 cases of *T. gondii* infection complicating renal transplantation.[4] The majority of these infections occurred within three months post-transplantation and were assumed to be donor-derived. Late infection was seen in a minority of cases. Twelve of the 31 patients received antilymphocyte therapy. In this series focal neurological

Figure 1. *Contrast-enhanced CT scan of the brain without significant abnormalities (left picture) and MRI in 'FLAIR-setting', showing diffuse abnormal signal around the basal ganglia (right picture) a predilection localisation for toxoplasmic encephalitis in severely immunocompromised patients*



signs were rare. Co-infection with viruses of the herpes virus group occurred in half of the patients. The outcome of symptomatic toxoplasmosis after renal transplantation seems poor. Of these 31 patients reviewed, 20 (64%, all but one left untreated) died. However, ten of the 11 patients given specific treatment survived, indicating that early diagnosis and therapy are essential.

Toxoplasmosis should be considered in the differential diagnosis of fever, sepsis, pneumonia or encephalitis in transplant recipients. Diagnosis can be established by cerebral imaging in combination with serological tests, direct detection of the parasite by staining or quantitative PCR. MRI scanning of the brain seems much more sensitive than CT scanning. In a prospective study of 50 patients with AIDS and neurological symptoms, relevant abnormalities in 40% of the patients were seen on MRI and not on CT.[5] Discrete abnormalities on MRI not seen on contrast-enhanced CT scan represented significant encephalitis at autopsy.[6] Compared with patients with AIDS, patients who develop cerebral toxoplasmosis after transplantation seem less likely to show ring enhancement or oedema on cerebral imaging.[7]

Serological tests usually suffice to establish the diagnosis in immunocompetent patients.[8] IgG antibodies rise one to two weeks after infection and continue to do so until six to eight weeks after primary infection. Tests for avidity of IgG antibodies have become standard to discriminate between recently acquired infection and those obtained in the more distant past. High avidity antibodies are seldom found in the first four months of infection. In the case described, the IgG aviditiy of the serum sample was high indicating an infection in the past, which was confirmed by low positive IgG values on pretransplantation testing. In addition to IgG, IgM can be used to determine if the infection is recent or more distant.[9] In immunodeficient patients antibody titres are much more difficult to interpret. Repeatedly negative IgG to toxoplama virtually excluded toxoplasmosis. Any positive IgG titre, both low and high, can be associated with reactivation of toxoplasmosis in immunocompromised patients. A rise in IgG to toxoplasma, as in the patient described in this study, can indicate clinical reactivation and warrants special attention, especially in case of unknown clinical findings. Rising of IgG antibody titres can also be observed without clinical importance. Proper interpretation of PCR tests is difficult, with different sensitivity and specificity results being reported from different laboratories using the same PCR probes.[9] A positive PCR on CSF, as in the patient described, is a strong indication of cerebral toxoplasmosis. False-negative PCR results on CSF in cases with cerebral toxoplasmosis are, however, not uncommon. A recent letter in this journal concerning a fatal case of disseminated toxoplasmosis after liver transplantation reported that real-time PCR on plasma could be helpful to detect this condition.[10] Direct examination with a Giemsa stain or immunoperoxidase is possible but has a low sensitivity.

CONCLUSION

Once cerebral toxoplasmosis is suspected in at-risk patients, treatment should be started empirically pending the confirmation of the diagnosis.[11] A normal cerebral CT scan does not preclude cerebral toxoplasmosis. In this situation MRI can give important additional information.

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