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Case Report

Tissue is the issue: a solitary cerebral lesion 15 years after kidney transplantation

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Abstract
Primary toxoplasmosis and reactivation of latent infections occur in solid organ transplant recipients. However, solitary cerebral lesions due to toxoplasmosis are rare. In this case, a patient presented with a haemiparesis and a cerebral lesion. We expected to find cerebral post-transplant lymfoproliferative disorder because of positive Epstein–Barr virus by polymerase chain reaction in cerebrospinal fluid, but histological findings revealed *Toxoplasma gondii* bradyzoites and tachyzoites, illustrating the necessity of obtaining material for diagnostics in immunocompromised hosts.

Keywords: brain abscess; EBV; PTLD; transplantation; toxoplasmosis

Introduction

Toxoplasma gondii is a protozoan parasite, which is known to cause opportunistic infections in the immunocompromised, as in solid-organ transplant [1, 2]. Toxoplasmosis in transplant recipients may result either from transmission with the transplanted organ from a Toxoplasma-seropositive donor to a seronegative recipient or from the reactivation of a seropositive recipient [1, 2, 3]. After a primary infection, there is a latent infection that may reactivate. Surveillance studies of renal transplant recipients based on serological evidence shows asymptomatic primary as well as latent infection in 2–14% [1–5]. Symptoms of primary *T. gondii* infection after transmission can occur until 13 months after transplantation (median 0.5–2 months) and reactivation has been described up to many years after [1, 2]. Due to difficulties in establishing a diagnosis, mortality can be high [2].

Epstein–Barr virus (EBV) is a ubiquitous DNA virus that infects up to 90% of the world's population; after primary infection, EBV establishes lifelong latency in memory B cells. In solid organ transplant patients, EBV-specific cell-mediated immunity is depressed by immunosuppression, which subsequently may lead to the development of uncontrolled EBV-driven B cell proliferation and malignant transformation, so-called post-transplantation lymphoproliferative disease (PTLD). PTLD is a serious complication of solid organ transplantation with incidence in renal transplant recipients of ~1–4%. Central nervous system (CNS) lymphoma is a rare form of PTLD and is more common after renal transplantation than after other types of solid organ transplants [6]. It is a serious and often fatal complication, with mortality rates up to 70%. Of all PTLD in solid organ transplant recipients, up to 90% is associated with EBV [7].

We report the case of a kidney transplant recipient presenting with a cerebral mass. As both blood and cerebrospinal fluid (CSF) showed to be positive for EBV DNA, CNS lymphoma was suspected. However, a brain biopsy demonstrated bradyzoites and tachyzoites probative of definite Toxoplasma disease.

Case report

A 72-year-old man was referred to our hospital because of progressive cognitive impairment noticed for a few weeks and a sudden right-sided haemiparesis after falling from his bicycle. His medical history revealed a deceased donor kidney transplantation 15 years previously, a mitral valve replacement and a mild aortic valve stenosis. Maintenance immunosuppression was stable in dose and consisted of prednisolone 7.5 mg once daily and mycophenolate 1000 mg twice daily with normal plasma levels.

In the referring hospital, CT and brain MRI demonstrated one solitary cerebral mass near the nuclei basales with a questionable ring contrast enhancement and a midline shift of 5 mm, described as probable metastasis of a tumour with unknown origin (Figure 1A and 1B). Because of the possible malignant aspect, he had been on a course of dexamethasone but his symptoms did not improve at all. He did not complain about fever, skin lesions or signs suggesting infection. Before this cognitive impairment started, his condition was normal without any episodes of flu-like illnesses. Blood cultures in the referring hospital remained negative. Physical examination showed only neurological symptoms of which a haemiparesis, impaired cognitive function and slurred speech were the most prominent. No signs of meningitis were found. There was no lymphadenopathy nor enlarged liver or spleen. Laboratory revealed no abnormal findings except for slightly elevated C-reactive protein of

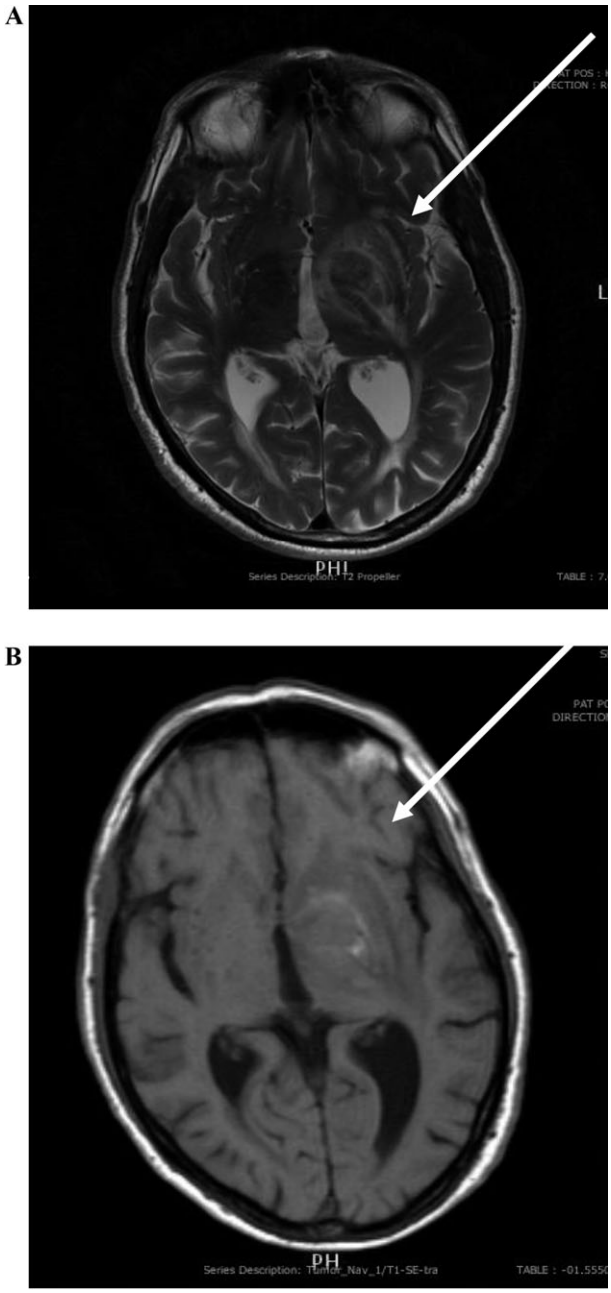

Fig. 1. (**A**) MRI cerebrum (T2) showing cerebral mass near nuclei basales. (**B**) MRI cerebrum (T2) also showing cerebral mass.

13 mL/L (normal value < 5 mL/L). Chest radiography was normal. Further blood cultures and cytomegalovirus viral load in whole blood remained negative. Yet, up to 40 700 copies/mL EBV DNA were detected by reverse transcription–polymerase chain reaction (RT–PCR) in whole blood. In the CSF besides a white blood count of 22 × 10^6/L (mainly lymphocytes with a few monocytes), no protein and a glucose 3.5 mmol/L, also 7160 copies/mL EBV DNA could be detected. These positive EBV viral loads provided a high suspicion of EBV-driven CNS lymphoma, mainly because of the clinical symptoms and radiological symptoms, which made an infectious origin less likely.

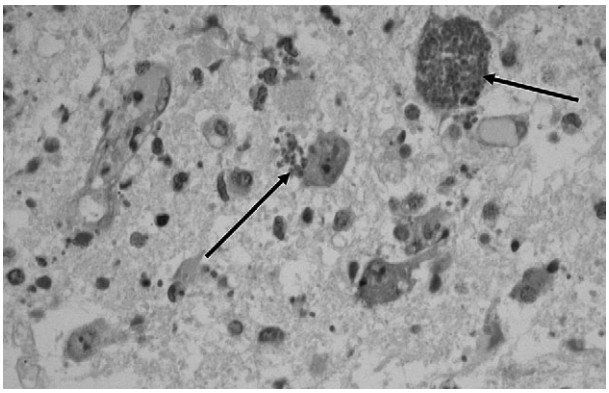

Fig. 2. Bradyzoites and tachyzoites in brain biopsy.

However, immunophenotyping of the CSF showed mainly T cells, without markers of bone marrow diseases or CD20-positive B cells. Doubt was cast and a stereotactic brain biopsy was performed after a PET scan, which did not answer our differential diagnosis between malignant or infectious cause. However, the biopsy showed *T. gondii* tachyzoites and bradyzoites, without any signs of malignancy and PTLD (Figure 2). Unfortunately, *T. gondii* serology at time of transplantation had not been performed, but subsequently, high antibodies against *T. gondii* (negative IgM, IgG > 300) and *T. gondii* DNA in CSF using RT–PCR could be detected. The patient was treated with oral trimethoprim-sulfamethoxazole (co-trimoxazol) 960 mg three times daily for 6 weeks, improving the neurological symptoms.

Unfortunately, in the course of his disease, he developed massive gastrointestinal bleeding because of stomach ulcers twice, which necessitated admission to the intensive care unit.

He had not regained his prior condition when he was referred to a nursing home and was re-admitted for pneumonia within a few weeks. His condition detoriated quickly and he died within 3 months after diagnosis of cerebral mass lesions due to toxoplasmosis. Unfortunately, no CT cerebrums were done after we started treatment and autopsy was refused.

Discussion

In this case, a CNS lymphoma was suspected because of detection of EBV DNA in cerebrospinal fluid. Yet, a brain biopsy showed tachyzoites and bradyzoites, which fits the diagnosis of toxoplasmosis. This underscores the significance of establishing a diagnosis with biopsy-proven evidence.

In immunocompetent hosts, a primary Toxoplasma infection is symptomatic in only 10–20% and serological evidence of latent infections in general exceeds 50% but may vary considerably among different geographic areas.

The clinical presentation of toxoplasmosis in solid-organ transplant recipients varied in the past; diagnosis was usually based on serological evidence [3]. Fever occurs in 80%, followed by pulmonary complaints and often neurological signs. Seizures may be the first clue for disseminated cerebral toxoplasmosis [2, 3, 8]. CT or MRI is preferred for showing

cerebral involvement, demonstrating intracranial mass lesions, focal necrosis, oedema or diffuse encephalitis [1, 2, 8].

Toxoplasmosis has a predilection for periventricular areas where tissue damage and necrosis may account for penetration and release of *T. gondii* into ventricular fluid, but it may not pass to the arachnoid space [5]. A lumbar puncture will seldom establish the diagnosis and as immunosuppression in transplant recipients also impairs serological diagnosis, demonstration of parasites in body fluid or tissue is the mainstay of diagnosis [1]. Microscopic examination of Giemsa-stained smears of bone marrow or bronchoalveolar lavage fluid is simple, quick and provides definitive proof [1, 2]. Unfortunately, sensitivity is low.

In toxoplasmic encephalitis, the value of cytological examination of CSF is unclear and direct identification of *T. gondii* in CSF is extremely rare [5]. PCR techniques offer the most sensitive technique, which also allows quantification of *T. gondii* DNA to monitor treatment efficacy as well. A negative PCR result has a good negative predictive value but does not rule out the diagnosis [1].

Significant increase of antibody titres or a positive PCR result should raise suspicion of reactivation but are often seen without clinical symptoms or illness [1,2]. In our case, we found a co-existence of EBV DNA together with Toxoplasma. This phenomenon is rare, but a few more cases in which these micro-organisms were concomitantly found in CSF have been described in the literature.

In 1993, Cinque *et al.* [9] frequently found a combination of pathogens in cerebral diseases in HIV patients and therefore, they advised a combined use of EBV PCR with other assays, especially for Toxoplasma. This co-existence was confirmed by Tachikawa *et al.* [10], who performed PCR on 37 postmortem CSF samples of HIV patients and found a positive PCR for both EBV and Toxoplasma, while only the first was suspected.

Causes for this co-existence are not yet unravelled but it seems that exposition to many other infectious and parasitic diseases impair the EBV-specific immune responses thus increasing the number of EBV-carrying B cells in the circulation [11]. As Toxoplasma is also known to impair immunosurveillance, an equivalent mechanism could apply for already latent EBV. In addition, transplant recipients experience protracted episodes of impaired EBV immunosurveillance and reactivation, causing amplification of the EBV viral load and subsequently the number of EBV-carrying cells [9,11].

For encephalitis due to toxoplasmosis, treatment used to be a combination of pyrimethamine–sulfadiazine, but recently, it is demonstrated that trimethoprim–sulfamethoxazole provides the same efficiency, has less serious side effects and is well tolerated, even at high dose [12].

Mainly due to patient and doctor delay and difficulties in gaining tissue to establish a biopsy-proven diagnosis, prognosis of toxoplasmosis encephalitis can be poor. In contrast to the HIV-positive patient where mortality is high, treatment in transplant recipients is fairly easy, well tolerated and shows a clinical improvement of 71–100% of patients [12]. A small risk of relapse exists but is mostly influenced by poor adherence to treatment of prophylaxis [12].

Conclusions

Brain abscesses caused by *T. gondii* or toxoplasmosis encephalitis are not commonly seen after renal transplantation, but once the diagnosis is established, treatment is generally well tolerated and mortality can be diminished. Therefore, it is of utmost importance to gain biopsy-proven evidence, even when this is difficult to obtain. Although PCR has made a difficult diagnosis easier, tissue still stays the issue.

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