Teaching Point
(Section Editor: A. Meyrier)

Unclear fever 7 weeks after renal transplantation in a 56-year-old patient

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Keywords: aspergillosis; caspofungin; kidney transplantation; thyroiditis; voriconazol

Introduction

Opportunistic infections may assume rare and deceptive localizations, as illustrated by the following case.

Case report

A 56-year-old male patient with end-stage renal disease, due to focal sclerotic segmental glomerulonephritis, underwent renal cadaveric transplantation after 2 years of haemodialysis (full-house HLA-match, donor age 48 years, donor and recipient cytomegalovirus (CMV) negative, cold ischaemia time 16 h). Due to initial graft non-function, alternate-day haemodialysis was continued for the following 3 weeks until the kidney function gradually improved. The immunosuppressive treatment consisted of prednisone, ciclosporin and mycophenolate mofetil. Five weeks after transplantation, pp65-antigenaemia was detected. Although clinical symptoms were absent, daily treatment with 150 mg gancyclovir p.o. over 3 weeks was initiated. The pp65-antigenaemia disappeared. In the seventh week post-transplant, the patient presented with fever (38.7°C), an elevated white blood cell count (12.0 G/l) (normal range 4.3–10.0) and an increased C-reactive protein (CRP) level (162 mg/l) (normal range <5).

Microbiological testing revealed Stenotrophomonas maltophilia in cultures obtained from the surgical site. Under treatment with 250 mg levofloxacin p.o. per day, laboratory signs of inflammation persisted. Since a thorough diagnostic work-up for the underlying infection did not lead to a sufficient diagnosis, an inflammation scintigraphy with 99mTc-labelled antineutrophilic antibodies was performed 12 weeks after transplantation. The scan revealed accumulation of granulocytes in the left lobe of the thyroid gland. At physical examination the thyroid gland was slightly enlarged and indolent. Ultrasonography showed multiple liquid abscess formations (Figure 1). Fine needle aspirates yielded Aspergillus fumigatus hyphae. Neither clinical examination nor chest radiography or magnetic resonance imaging exhibited signs of disseminated Aspergillus infection. Aspergillus antigenaemia could not be detected by serological ELISA-screening for galactomannan antigen. The triple immunosuppressive treatment with ciclosporin, mycophenolate mofetil and prednisone was discontinued and replaced by prednisone monotherapy for the following 3 months. Antifungal treatment with caspofungin was initiated. After an initial reduction of the inflammatory parameters however, the CRP level stabilized at above 60 mg/l at week 19, and repeated fine needle aspirates of the thyroid gland were still positive for Aspergillus. After voriconazole was added to caspofungin, the sonographic findings improved and inflammatory parameters normalized. On the day of discharge, 6 months after transplantation and 3 months after the development of the mycotic thyroiditis, fine needle aspirates of the left thyroid lobe still revealed minor growth of Aspergillus. However, CRP had dropped to a level <5 mg/l. After discharge, the treatment with voriconazole was continued for the following 4 months until subsequent aspirations became negative at month 10. After discharge, mycophenolate mofetil was included in a daily dosage of 1000 mg and prednisone was reduced.

Comment

The incidence of fungal infections in transplant recipients is lower than that of viral or bacterial infections. However, invasive pulmonary aspergillosis is a common infection in transplant recipients and is associated with a high mortality [1,2]. Apart from intensive immunosuppressive therapy, acute transplant...
Aspergillus is a ubiquitous saprophyte and possesses angio-invasive properties, which enable the fungus to disseminate via haematogenous spread. In the majority of cases the primary site of infection is the lung, but metastatic colonization can be found in virtually any organ. The clinical course of invasive aspergillosis is often fulminant, causing central nervous system invasion and sepsis [1].

Aspergillus thyroiditis usually presents with focal abscesses, haemorrhagic lesions or diffuse infiltration. Involvement of the thyroid gland at autopsy findings is reported in 9–15% of patients with disseminated disease [4]. Isolated infection of the thyroid gland without signs of disseminated disease has been reported only exceptionally in the literature. All previously reported cases exhibited an immunocompromised setting, e.g. non-Hodgkin’s lymphoma, lupus erythematosides or chronic granulomatous disease [5–7]. To our knowledge, no case report describing the survival of isolated Aspergillus thyroiditis in a renal transplant recipient has ever been published.

Considering the potential life-threatening clinical course of Aspergillus infection and the cryptogenicity of the infectious mode, it is important to establish a quick and efficient clinical diagnostic work-up. With a negative predictive value of 95%, serological Aspergillus galactomannan screening by ELISA can virtually exclude disseminated aspergillosis [8]. Obtaining a diagnosis can become more difficult in localized cases, which, as in our case, may not develop detectable antigenaemia. If the site of infection is primarily undetectable, granulocyte scintigraphy may be a valuable diagnostic tool. In case of thyroidal localization, fine needle aspiration is mandatory to differentiate other possible causes of inflammation.

Nephrotoxicity limits the administration of amphotericin B. This is especially true for renal transplant recipients with prolonged post-operative allograft malfunctioning, as seen in the present case [9]. Lipid formulations of amphotericin B (1 × 1 mg/kg i.v. up to 3 mg/kg i.v. daily) are reported to show decreased rates of side effects and probably an even higher efficacy [9]. Therapy with voriconazol (d1: 2 × 6 mg/kg i.v.; d2: 2 × 4 mg/kg i.v. or d1: 2 × 400 mg p.o.; d2: 2 × 200 mg p.o.) was reported to be superior to amphotericin B in invasive aspergillosis mono-therapy [10] and caspofungin (d1: 1 × 70 mg i.v.; d2: 1 × 50 mg i.v.) was found to be an effective ‘rescue’ therapy [11]. Similar to the present case, combination therapy (amphotericin B plus caspofungin or caspofungin plus voriconazole) might ultimately be the treatment of choice in the future [12,13].

Drug interactions between immunosuppressive and antifungal drugs are a therapeutic challenge in allograft recipients. They warrant a careful monitoring of ciclosporin or tacrolimus blood levels. With respect to the choice of immunosuppressive agents, there is currently insufficient data in favour of a particular mono- or combination therapy in renal transplant recipients with aspergillosis. However, most centres follow a policy of a substantial reduction of immunosuppression in severe aspergillus infections in renal transplant recipients.

**Teaching points**

(i) The differential diagnosis of localized aspergillosis can be difficult due to non-specific and moderate clinical signs. In these cases, 99mTc-leucocyte scintigraphy may be a valuable diagnostic tool.

(ii) In localized aspergillosis, systemic antigenaemia as detected by galactomannan screening may not develop.

(iii) Taking their low renal toxicity and high antifungal efficacy into account, voriconazol, caspofungin or a combination of both might be considered as the first-line treatment of aspergillosis in renal transplant recipients.

**Conflict of interest statement:** None declared.

**References**


Received for publication: 13.9.05
Accepted in revised form: 25.4.06