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BRIEF REPORT

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Fatal primary multidrug-resistant tuberculosis in a heart transplant recipient

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Abstract The incidence of tuberculosis (TB) worldwide is currently on the rise, not only in the general population but also quite notably among immunosuppressed patients. Its incidence among patients undergoing antirejection therapy is considerably higher than in the general population, and heart transplant recipients have been found to carry the highest risk of TB. There are no reported data, however, on primary TB caused by multidrug-resistant (MDR) *Mycobacterium tuberculosis* (*M. tuberculosis*) in heart transplant recipients. We describe the case of a patient who developed active primary MDR TB following the reactivation of a latent tuberculous infection 6 months after transplantation. The patient was most likely infected by *M. tuberculosis* during a period of time he spent in prison 10 years before undergoing transplantation, but he never developed active tuberculosis, nor did he ever receive antituberculous medication prior to transplantation. Because of the atypical clinical presentation, establishment of the diagnosis was postponed, and the resistance pattern of the isolate grown from bronchoalveolar lavage (BAL) specimens (resistant to isoniazid and rifampicin) led to treatment failure and a fatal outcome. The adoption of the most rapid diagnostic tools for the identification of *M. tuberculosis* and for a quick screening of drug-resistant isolates is urgently needed in those centers where organ transplantation is carried out.

Key words Tuberculosis, heart transplantation · Heart transplantation, tuberculosis

Introduction

Tuberculosis (TB) has increased dramatically worldwide in the last 15 years. Many different factors contribute to this ongoing trend. Infection with human immunodeficiency virus (HIV) is the single most important factor predisposing one to the development of active TB but other less prevalent immunosuppressant conditions also play important roles in the current diffusion of the disease.

In organ transplant recipients receiving antirejection therapy, the incidence of TB has been found to be significantly higher than in the general population. Possibly due to the initial administration of more aggressive immunosuppressive regimens, patients who undergo heart transplantation have been found to carry the highest risk of TB of all transplant recipients. In terms of a standardized annual rate, TB was found to have an incidence of 320/100,000 in liver transplant recipients, of 480/100,000 in renal transplant recipients, and of 1300/100,000 in heart tranplant recipients, while the annual rate in the general population in the United States and Italy was 9.3/100,000 and 10.2/100,000, respectively, in 1994 [7–9, 12].

In the setting of transplantation, no data are currently available on one of the most alarming aspects of the recent TB resurgence, i.e., the diffusion of *Mycobacterium tuberculosis* (*M. tuberculosis*) isolates that are resis-

tant to isoniazid and rifampicin (multidrug-resistant strains; MDR), the two most active drugs for antituberculous chemotherapy.

We describe herewith a case of primary MDR TB that developed in a heart transplant recipient.

Case report

A 54-year-old HIV-negative Caucasian male underwent orthotopic heart transplantation (OHT) for dilated cardiomyopathy and pulmonary hypertension in May 1995 at the Department of Cardiovascular Surgery of the University Hospital of Verona. An intradermal test with protein-purified derivative (PPD, 5 IU) carried out 2 months before transplantation was positive, but the patient had no prior history of active tuberculosis and had never received antituberculous medication. No clues indicating past exposure to TB or clinical episodes suggesting prior active TB were recognizable in the donor's history. No abnormalities other than an enlarged cardiac profile were seen on repeated chest x-ray before transplantation. Apart from his worsening cardiac disorder, our patient had no other relevant diseases. In the patient's past history, the only remarkable event was a prolonged imprisonment that ended 10 years before transplantation.

A triple immunosuppressive drug regimen with cyclosporin A, azathioprine, and prednisone was started following OHT. A 7-day course of anti-thymocyte globulins was given in the immediate postoperative period. Six weeks after OHT, an acute rejection episode (histological grade 2) was diagnosed and successfully treated with oral prednisone for 3 days. At the end of the 6th post-transplant month, the patient was admitted to our ward with persistent fever. The physical examination was unremarkable. Cultures of blood for bacteria, mycobacteria, fungi, and CMV were negative, as were urine cultures. The chest x-ray was normal. The patient was successfully treated with vancomycin and tobramicin. Two weeks later, he was readmitted to our department for recurrent fever (maximum body temperature 39 °C), mild abdominal pain, polypnea, and tachycardia. Arterial blood gases and chest x-ray were normal. Blood, urine, and sputum samples were collected for cultures and empirical antibiotic therapy with imipenem was started. An emergency endomyocardial biopsy was negative for rejection. Over the next week of treatment, the clinical condition of the patient deteriorated with persistence of intermittent fever and polypnea. Cultures for bacteria, mycobacteria, fungi, and CMV were negative. A bronchoscopy was performed and examination of bronchoalveolar lavage (BAL) specimens showed acid-fast bacilli. The patient was then treated with rifampin, isoniazid, and pyrazinamide for 2 weeks, but no clinical improvement was observed. Culture of BAL samples showed growth of *M. tuberculosis* and the diagnosis of pulmonary TB was confirmed. The results of drug susceptibility testing (Bactec Radiometric System, Becton Dickinson, USA) showed resistance to rifampin and isoniazid, and so treatment was switched to pyrazinamide, streptomycin, ethambutol, and ciprofloxacin. The patient developed jaundice associated with progressive renal and hepatic failure and died of multiorgan dysfunction 8 months following OHT. A month before his death, the patient had been tested again for anti-HIV antibodies; the results were negative.

Discussion

The prognosis for MDR TB is unfavorable in immunosuppressed patients. The only chance of achieving a better outcome is to ensure an early diagnosis and the prompt initiation of effective antituberculous chemotherapy [6]. Since MDR TB is a transmissible but preventable disease, it is of some interest to explore the epidemiological profile of the disease in our patient.

Before undergoing OHT, the patient showed a positive response to PPD, which suggests that active TB resulted from the reactivation of a latent, previously acquired infection. With regard to the pattern of resistance to antimicrobials of the *M. tuberculosis* isolate concerned here, it should be noted that our patient had never received any antituberculous medication in the past. Consequently, the selection of such a MDR *M. tuberculosis* strain must have been determined before it was transmitted to him.

The patient's past history included only one circumstance that carried any risk of exposure to MDR strains of *M. tuberculosis*, namely a 3-year period of imprisonment a decade before he underwent OHT. Most prison inmates come from the lowest socioeconomic levels of society, where tuberculous infection reaches its highest levels of prevalence, and given the current overcrowded conditions, a great number of people are potentially exposed to active TB cases while in prison. Furthermore, conditions favoring the selection of MDR TB are clearly present in prison, where the level of preventive care and medical assistance is often less than ideal [1]. In this setting, early diagnosis, isolation precautions, and supervised treatment – all essential steps in the prevention of MDR – are seldom feasible at the level required, thus allowing MDR *M. tuberculosis* strains to emerge and spread among susceptible individuals.

Although no information was available regarding TB cases among prison inmates of our patient, since no other suggestive epidemiological elements were present in his past history, it seems likely that our patient acquired his MDR tuberculous infection while in prison and that active disease developed only 10 years later, when antirejection immunosuppressive therapy aflowed TB reactivation.

Current knowledge of primary MDR TB is mostly focused on highly susceptible immunocompromised subjects (most of them with advanced HIV infection) who developed the disease shortly after having been exposed in congregate settings; there is very little data available on the reactivation of a latent MDR tuberculous infection long after transmission, as the latter seems to be quite a rare event.

Based on clinico-epidemiological data [4] and on recent genetic studies on MDR strains of *M. tuberculosis* [5], it has been suggested that the latter may be less virulent than drug-sensitive isolates. This could explain why

active TB following transmission of MDR bacilli almost exclusively occurs in immunocompromised subjects. With the increasing size of the immunocompromised population, a parallel rise in MDR TB cases is being recorded, suggesting that the potential future diffusion of MDR tuberculous infection is greater than has been anticipated thus far. This is of particular importance for organ transplant recipients whose immunosuppressed condition is amenable to long-term control and does not have as poor a short-term prognosis as patients with AIDS.

Since the clinical presentation of active TB tends to be atypical in immunocompromised patients, as it was in our case, the highest awareness of a possible tuberculous etiology should be maintained in the diagnostic work-up, and modern diagnostic technologies must be made available for early recognition of TB and, in particular of MDR TB.

The newest methods of detection of *M. tuberculosis* offer the advantage of being able to more quickly identify tuberculous bacilli in human specimens; apart from the still investigational method based on the polymerase chain reaction (PCR) [2], the radiometric detection of *M. tuberculosis* growth in culture vials may anticipate the diagnosis by days or weeks, as compared to conventional methods [10]. For MDR strains, a new molecular device has been developed [11] and marketed for the rapid genetic identification of rifampicin-resistant *M. tuberculosis* as early as in sputum specimens [3]. This method is able to rapidly identify the genetic mutations responsible for *M. tuberculosis* resistance to rifamipicin in as many as 97 % of cases. Since resistance to rifampin almost invariably implies the coexistence of resistance to isoniazid, this quickly available information allows for the early initiation of antituberculous chemotherapy with an alternative and more appropriate regimen.

While the routine use of these rapid diagnostic technologies is questionable in common hospital practice, their adoption at a negligible additional cost should become mandatory in all centers where organ transplantation is carried out.

We believe that, in order to guarantee the best chances of success for a therapeutic option as important and costly as transplantation, all of the most advanced technologies allowing for the quickest diagnosis of life-threatening infections should be available for post-transplant clinical management. Having made such an extreme therapeutic effort for a patient, it would be unforgivable to lose him due to an avoidable, diagnostic delay.

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