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Note

Three Cases of Tuberculosis after Heart Transplantation in Spain

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Abstract Three cases are presented of tuberculosis occurring in a series of 410 heart transplant recipients in a Spanish hospital, representing a rate of 0.73%. Twenty-eight cases reported in the literature are also reviewed. In most series reported, tuberculosis occurred in a small percentage of heart transplant recipients, the average rate being 1.25%. Compared to the general population, a higher percentage (28%) of extrapulmonary and disseminated forms of the disease is seen in these patients. Although a cure without recurrence can usually be achieved with a conventional antituberculous antibiotic regimen, the disaese is still associated with a significant mortality rate of 11%. Guidelines for the early diagnosis and treatment of these patients are discussed.

Introduction

Tuberculosis (TB) is an opportunistic infection prevalent among immunocompromised patients, such as those with the acquired immunodeficiency syndrome (AIDS) or those on long-term immunosuppressive therapy for a variety of medical conditions. Among the latter, transplant recipients constitute a growing population in which early detection and therapy of infectious complications is crucial [1]. TB, a potentially life-threatening infection, has seldom been reported in heart transplant recipients. In our hospital, of the 410 patients who have received heart transplants since 1984, three have developed TB. We report on these cases here and review 28 additional cases reported in the literature.

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Case Reports

Case no. 1. A 57-year-old male underwent orthotopic heart transplantation in June 1985 for idiopathic dilated cardiomyopathy. Prior to the procedure, his skin reaction in the purified protein derivative (PPD) test measured 5 mm in diameter, a value considered to border on positive. Immunosuppression was achieved with an initial course of antithymocyte globulin, plus triple therapy with cyclosporine A, prednisone and azathioprine. The only postoperative event of note was a single episode of moderately acute rejection which resolved with an i.v. bolus of methylprednisolone. In June 1995 the patient was readmitted to hospital with a 1-month history of fever and cough. The only laboratory test results of note were as follows: hemoglobin level 9.5 g/dl, erythrocyte sedimentation rate (ESR) 34 mm, creatinine level 2 mg/dl, aspartate aminotransferase (AST) level 54 U/l, alanine aminotransferase (ALT) level 60 U/l and lactate dehydrogenase (LDH) level 796 U/l (normal <460 U/l). A chest radiograph showed a bilateral micronodular pattern. Transbronchial biopsy revealed the presence of granulomas and bone marrow biopsy the presence of both granulomas and acid-fast bacilli (Figures 1 and 2). Culture of the bronchial aspirate in Löwenstein medium yielded *Mycobacterium tuberculosis*. The patient was started on isoniazid, rifampin and pyrazinamide, and the fever resolved within 2 weeks. The chest radiograph subsequently cleared. The triple-drug therapy was maintained for 2 months, followed by isoniazid and rifampin for a total of 10 months. The dose of cyclosporine had to be increased in order to maintain appropriate levels after the administration of rifampin. Two years later, in July 1997, a pleural biopsy performed to investigate a persistent pleural effusion revealed adenocarcinoma of the lung.

Palliative care was provided and the patient died 2 months later. The autopsy examination showed no evidence of active TB.

Case no. 2. A 16-year-old patient underwent orthotopic heart transplantation in November 1989 for end-

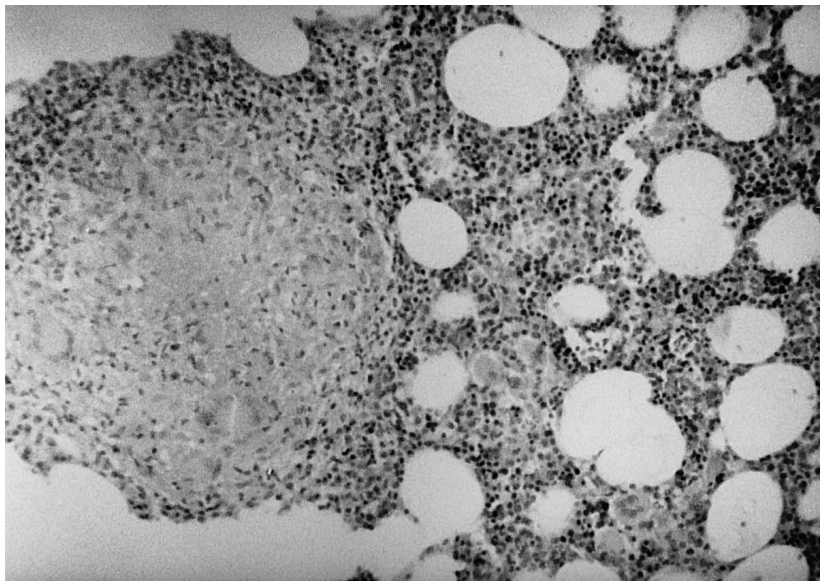

Figure 1 Bone marrow biopsy showing a tuberculoid granuloma in hematopoietic parenchyma

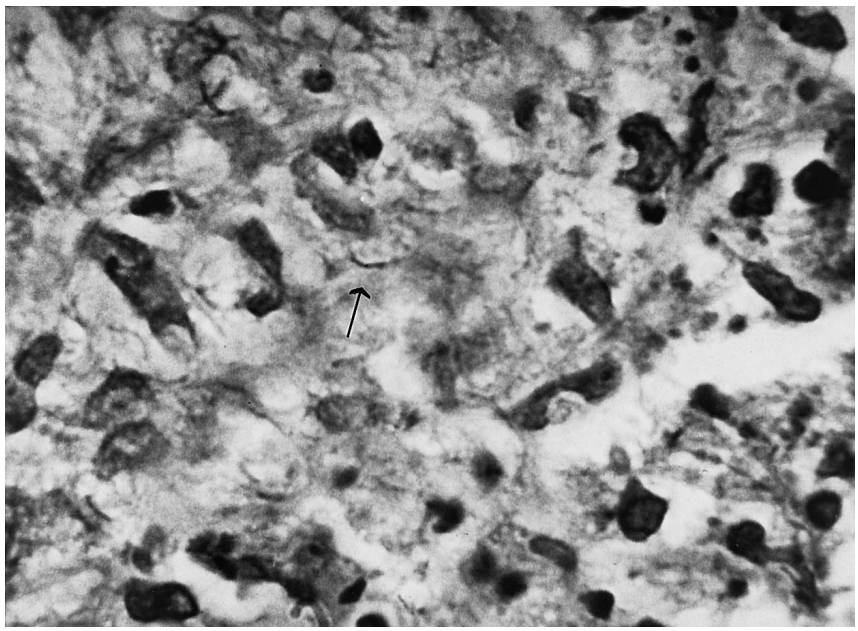

Figure 2 Acid fast bacilli inside histocytes, indicated by arrow (H&E; ×100)

stage hypertrophic cardiomyopathy. A PPD skin test was negative. The patient received OKT3 monoclonal antibodies, prednisone, azathioprine and cyclosporine. During the postoperative period he experienced seroconversion for cytomegalovirus and toxoplasma, bacteremia due to *Serratia* and an episode of acute rejection treated with steroid boluses. In January 1990 he developed fever, chills and headache. Auscultation disclosed hypoventilation at the right lung base. Laboratory tests showed a hemoglobin level of 9 g/dl, platelet count of 532 000/mm3 and ESR of 140 mm. A chest radiograph revealed a right pleural effusion. Thoracocentesis yielded an exudate containing 1775 cells/mm3 (predominantly lymphocytes) with a glucose level of 67 mg/dl, protein level of 3.4 g/dl and an adenosine deaminase (ADA) level of 73 U/l (normal <40 U/l). A Ziehl-Neelsen stain of pleural fluid was negative. On the basis of the positive ADA result, the patient was started on isoniazid, pyrazinamide and ethambutol. Fever resolved within 9 days and the chest radiograph subsequently became normal. Five weeks later culture of pleural fluid in Löwenstein medium grew *Mycobacterium tuberculosis*. The patient was maintained on the three-drug regimen for 2 months, and received isoniazid and pyrazynamide for a total of 9 months. Seven years later no recurrence of TB has occurred.

Case no. 3. A 50-year-old man underwent orthotopic heart transplantation for end-stage ischemic cardio-

myopathy in November 1996. Earlier, in June 1996, his chest radiograph showed a nodule measuring 2.5 cm in the left upper lobe and a smaller nodule in the lingula. A sputum smear revealed acid-fast bacilli and culture of a sputum specimen on Löwenstein medium grew *Mycobacterium tuberculosis*. Transthoracic aspiration only yielded a necrotic sample with scant cell remnants.

The patient was treated with isoniazid, rifampin and pyrazynamide for 2 months and received a 3-month course of isoniazid and rifampin before transplantation. A sputum smear was negative for acid-fast bacilli 2 months after initiation of therapy and was still negative immediately before transplantation. After the procedure, the patient received OKT3 monoclonal antibodies, prednisone, azathioprine and cyclosporine. The antituberculous regimen with isoniazid and rifampin was continued. Acute rejection episodes in December 1996 and January 1997 were treated with steroid boluses. In January 1997 the patient underwent pericardiectomy for constrictive pericarditis. There was no evidence of TB in the explanted pericardium. In May 1997, the patient was asymptomatic but a chest computed tomography (CT) scan revealed that the left upper lobe nodule had grown larger. Laboratory results were normal. Fine needle transthoracic lung aspiration was performed (while the patient was receiving antituberculous drugs), revealing abundant acid-fast bacilli, although a culture was negative after 8 weeks. In June 1997 the patient was admitted to hospital again with generalized weakness, hyperkalemia and renal insufficiency, adverse effects of high cyclosporine levels (690 ng/ml) after rifampin was stopped unintentionally while maintaining the same cyclosporine dose. At present, the patient is in good condition and receiving isoniazid and rifampin.

Discussion

Our three cases can be added to the existing list of 28 cases of TB in heart transplant recipients reported in the literature [2–13]. Only partial information is provided in many reports, but we have analyzed all available data.

There is a marked geographic variation in the incidence of TB, which seems to be more prevalent in the Mediterranean countries than in northern Europe and the USA. The incidence of TB observed in the general population in our region is 40 to 45 cases per 100 000 population [14]. The prevalence of TB after cardiac transplantation in our hospital was 0.73%, an almost 20-fold increase. Published reports show an incidence after heart transplantation ranging from 0 to 3.3% (average 1.25%) [4–6, 10–13, 15]. In comparison, the mean rate of TB among renal transplant recipients is 4.5%, ranging from 0.5% up to 11.5% in endemic areas [16–20]. Liver transplant recipients have a mean incidence of TB of 0.8%, with a range of 0.4% to 1.2% [21–24]. The incidence in lung transplant recipients is 2.2% [25–27].

A general review of TB in heart transplant recipients shows that the mean age is 47.7 years (range 8 months to 71 years). The gender of patients was mentioned in 16 cases, 5 females and 11 males. The underlying diseases before transplantation reported in 16 patients were idiopathic dilated cardiomyopathy in 13, ischemic heart disease in 2 and valvular disease in 1 [2, 3, 7, 10, 11]. In one study a trend towards infectious complications after heart transplantation was found in recipients with dilated cardiomyopathy [28].

The interval between heart transplantation and development of TB ranged from 0.8 to 120 months (median 4 months), 58.8% of cases being diagnosed in the first 6 months, when immunosuppresssive therapy was most intensive.

The long interval between heart transplant and the development of TB in two cases (3.4 and 10 years, respectively) indicates the persistent risk of TB even in patients on low-dose maintenance immunosuppression. Treatment for severe rejection correlates with a higher risk of infection [28]. Two of our patients were treated with steroid boluses for episodes of acute rejection during the 6 months prior to diagnosis of TB. In the literature rejection was reported to occur shortly before TB in seven patients [7, 10, 11]. While steroids, azathioprine and antilymphocyte globulin favour dissemination of infection in mice, the role of cyclosporine has yet to be defined [29]. The prevalence of TB in one patient series where heart transplant recipients did not receive monoclonal or polyclonal antibodies did not differ from that in other series [11].

It is assumed that reactivation, rather than primary infection, is the main pathogenetic mechanism in heart and renal transplantation patients [10, 20]. Nevertheless, we found only three patients with evidence of previous TB infection: our cases no. 1 and 3, and an additional case reported in the literature [10]. Allografts were found to be responsible for the transmission of infection to renal and lung transplant recipients in several reports [13, 20, 26].

The clinical presentation was extrapulmonary in two of our patients (pleural and disseminated infection, respectively), as in 12 of the 20 cases in the literature for which this information was available (Table 1). While the frequency of disseminated disease in the normal population is 1%, in patients on immunosuppressive therapy the risk is increased up to 40-fold [1]. Disseminated infection was observed in 28% of heart transplant recipients, and the rate was even higher in

Table 1 Clinical manifestations, management and outcome of tuberculosis in 28 heart transplant recipients reported in the literature

Reference	Site	Fever	Diagnostic specimen	Treatment	Outcome
2	lung	NR	BAL	INH, RIF, ET	alive
3	meninges	NR	NR	NR	died of TB
4	lung	NR	NR	INH, RIF, ET, STR	alive
	lung	NR	NR	INH, RIF, ET, STR	alive
5	disseminated	NR	NR	NR	NR
	lung	NR	NR	NR	NR
6	lung	NR	autopsy	None	died, not of TB
7	disseminated	yes	bone marrow biopsy/ sputum	INH, RIF, ET	alive
8	mediastinal lymph node	yes	lymph node biopsy	NR	alive
9	lung	NR	sputum	INH, RIF, ET	NR
10	disseminated	yes	thoracotomy/	INH, ET, STR, PZ	alive
	urinary	yes	blood		
	pleural	no	urine	INH, ET	alive
			thoracocentesis	INH, ET	alive
11	lung	no	–	INH, RIF, ET	alive
	disseminated	yes	–	INH, RIF, ET, PZ	alive
	disseminated	yes	–	INH, RIF, ET, PZ	died of TB
	lung	yes	–	INH, RIF, PZ	alive
	urinary	no	urine	INH, ET, PZ	alive
	lung	no	–	INH, RIF, PZ	alive
	urinary	no	urine	INH, RIF, ET	alive
12	NR	NR	NR	NR	3 alive 1 died of TB 2 died, not of TB
13	lung	NR	BAL	INH, RIF, ET	alive
	disseminated	NR	TBB	INH, ET	alive
Present report	disseminated	yes	TBB, bone marrow	INH, RIF, PZ	alive
	pleural	yes	thoracocentesis	INH, ET, PZ	alive
	lung	no	TT needle aspiration	INH, RIF, PZ	alive

NR, not reported; BAL, bronchoalveolar lavage; TBB, transbronchial biopsy; TT, transthoracic; INH, isoniazid; ET, ethambutol; RIF, rifampin; STR, streptomycin; PZ, pyrazinamide

renal transplantation, being 38.7% overall (64.3% in one series) [20]. Five heart transplant recipients with TB were asymptomatic at onset. Two of our patients had fever, a finding observed in 9 of 14 patients for whom this information was reported [7, 8, 10, 11].

Fever was the most commonly reported symptom of TB in renal transplant recipients (52%) [1], and in patients on immunosuppressive therapy for reasons other than transplantation (63%) [30].

The diagnosis in our three patients was established on the basis of invasive methods, as in 7 of the 11 patients for whom this information was available in the literature. An additional case was diagnosed, at autopsy. ADA is an enzyme that predominates in T lymphocytes, its concentration increasing when cell immunity is stimulated . The value of this test in transplant recipients, whose T lymphocytes are the main target of immunosuppressive therapy, has not been studied. Our patient with pleural TB had elevated ADA levels in pleural fluid, a finding also reported in two other patients with TB effusions (one pleural and one pericardial) [10]. Interestingly, five cases of non-tuberculous pleural effusions in heart transplant recipients in our patient series had normal ADA levels (<40 U/l), which suggests the test might be of diagnostic value in transplanted patients.

Treatment of TB in transplant recipients is controversial. Rifampin acts as a microsomal enzyme inducer with particular affinity to cytochrome P-450IIIA in the liver, which is the major cyclosporine-metabolizing enzyme system [31]. Concurrent administration of rifampin and cyclosporine increases metabolism and decreases bioavailability of the latter. Blood levels of cyclosporine do not show good correlation with the dose received, because of wide intrapatient and inter-

patient variability in the pharmacokinetics of the drug. Significant extrahepatic metabolism of cyclosporine has also been shown to exist. The presence of P450IIIA enzymes in the intestinal mucosa suggests that substantial intestinal metabolism of cyclosporine may contribute to the first-pass metabolism of orally administered drugs [32].

Two of our patients were treated with a standard antituberculous regimen including rifampin; we thus concomitantly increased the dose of cyclosporine 2.5-fold.

The only adverse effects observed were related to rebound of the cyclosporine concentration following withdrawal of rifampin in one patient.

In the literature, the dose of cyclosporine is generally increased 2.5- to 5-fold in order to obtain therapeutic levels [4, 11, 33–35]. Rifampin has been employed by different investigators without major adverse effects on the allograft [7, 16, 25, 33]. However, other investigators reported episodes of acute rejection among heart transplant recipients; one of the patients died 16 days after starting rifampin [2, 11, 13, 34, 35]. The diversity of effects reported may be related to interpatient pharmacokinetic variability, as mentioned above. Commonly accepted guidelines for treatment with rifampin include increasing the cyclosporine dose 3- to 5-fold and the frequency of administration to three times a day [33]. Daily monitoring of the cyclosporine concentration is warranted until the steady-state is reached. The main sign of a clinical response in our first two patients was the subsidence of fever within 2 weeks. There were three deaths related to TB among the 27 heart transplant recipients whose outcome is specified in the literature, representing a mortality rate of 11%.

The results of skin tests prior to infection have not been reported in most series of heart transplant recipients with TB. PPD was tested in 62 of our heart transplant patients, 24 of them being positive (38%). Of these patients, nine had clinical or radiological evidence of previous TB and received prophylactic isoniazid; none of them developed active disease. One of our 15 PPD-positive patients (case no. 1) who did not receive prophylaxis developed TB.

Isoniazid prophylaxis is recommended by the American Thoracic Association for every immunosuppressed patient with a positive skin test [36]. Nevertheless, routine isoniazid prophylaxis is not widely practised due to the low incidence of TB in Western countries.

No recurrences of TB have been reported among heart transplant recipients after treatment, a finding consistent with the results of a study of TB in immunocompromised patients in whom no relapses were observed during a follow-up period of 17 months (range: 4 months to 7 years) [30].

In conclusion, TB should be highly suspected in heart transplant recipients who develop fever. It should be taken into consideration that extrapulmonary and disseminated forms are frequent. The PPD skin test should be performed before transplantation whenever possible. In the case of a positive result, isoniazid prophylaxis should be implemented once active TB has been ruled out, particularly when the recipient has concurrent risk factors such as evidence of pulmonary sequelae of TB on chest films, inadequately treated TB, recent conversion, contact with an active case or reception of an allograft from a positive donor.

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