Tenosynovitis of the Wrist Due to Resistant \emph{Mycobacterium tuberculosis} in a Heart Transplant Patient

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Tubercular tenosynovitis is now rare, which can delay diagnosis of this disease. We report a case of tenosynovitis of the wrist in a heart transplant patient caused by an isoniazid- and streptomycin-resistant \emph{Mycobacterium tuberculosis} strain. Despite immunosuppression therapy, which can lead to a smoldering evolution, molecular biology analysis of biopsies allowed a rapid diagnosis.

\section*{CASE REPORT}

A 60-year-old man presented with a history of left wrist pain with marked swelling of the hand that had lasted for ca. 2 months. This patient had received a heart transplant for cardiomyopathy 6 months earlier. The immunosuppression regimen was a combination of corticotherapy and cyclosporine (150 mg twice daily [BID]). The initial evolution of the heart transplant was considered satisfactory. A rejection episode documented by an endomyocardial biopsy resulted in an increase in the cyclosporine dosage (225 mg BID). Wrist pain appeared 4 months after transplantation and increased gradually. The patient was treated with local and then systemic nonsteroidal anti-inflammatory drugs without success. He showed no signs of fever or sweating. There was a clear increase in physical asthenia and a significant functional limitation related to the swelling of the wrist, which gradually spread to the forearm. The physical examination revealed a major synovitis of the left wrist and a left axillary adenopathy. A normal venous echodoppler eliminated a diagnosis of deep venous thrombosis of the upper limb. An osseous scintiscan with \textsuperscript{99}Tc-methyl diphosphonate resulted in hyperfixation at early vascular times, which was compatible with reflex sympathetic dystrophy syndrome. There was no biological inflammatory syndrome (C-reactive protein, 11 mg/liter; fibrinogen, 4.8 g/liter). A diagnosis of gout was discarded because hyperuricemia was lacking. A synovectomy of the flexor tendons of the wrist performed after 2 months of evolution revealed a major synovitis of the flexors with nerve involvement but no spreading to adjacent bone.

Acid-fast bacilli were observed by microscopic examination in the first sample of the two synovial biopsies. Amplification and hybridization of nucleic acid extracted from the two biopsies (InnoLipa Mycobacteria v2; InnoLipa, Ghent, Belgium) showed the presence of \emph{Mycobacterium tuberculosis}. The diagnosis was confirmed by histopathology (Fig. 1), which revealed specific inflammatory lesions with large granulomas of epithelioid cells and multiple giant cells with central caseous necrosis. Visible colonies appeared on the growth medium at day 21 for the first sample and on day 41 for the second. Identification by gas chromatography (MIDI Microbiological Identification System, Newark, N.J.) confirmed the diagnosis of \emph{M. tuberculosis}.

Antituberculous treatment was started as soon as the identification of \emph{M. tuberculosis} was confirmed by amplification and hybridization of the nucleic acid extract. A four-drug regimen (rifampin [600 mg], isoniazid [300 mg], ethambutol [1,200 mg], and pyrazinamide [2 g] once daily) was justified by immunodeficiency of the patient and a history of multiple, very long stays in sub-Saharan Africa. Because of the enzymatic induc- tion effect of rifampin on cyclosporine, the levels of cyclosporine in serum were monitored as the dose of the drug was increased (from 150 to 225 mg BID). At 1 month after initiation of therapy, there was a reduction in the swelling of the hand but only a very slight alleviation of pain.

Antibiograms performed by using a \emph{M. tuberculosis} suscep-

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Fig1.pdf}
\caption{Paraffin-embedded biopsy section, stained with hematoxylin-cosin-safran, showing inflammatory lesions with caseous necrosis, large granulomas of epithelioid cells and giant cells. Magnification, £200.}
\end{figure}

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\section*{FIG. 1. Paraffin-embedded biopsy section, stained with hematoxylin-cosin-safran, showing inflammatory lesions with caseous necrosis, large granulomas of epithelioid cells and giant cells. Magnification, £200.}
Tubercular tenosynovitis is fairly rare and essentially affects the upper limb (hand and wrist). Infection appears to start in the synovium and then gradually spreads to the tendons and even the bones. Prior to the advent of effective antituberculous chemotherapy, tuberculosis was one of the most common causes of chronic infections of the tendon sheath of the hand (2) as a secondary infection from pulmonary (50% of cases) or abdominal tubercular lesions (1). Mycobacteria are believed to be introduced hematogenously. An examination should thus be conducted to locate other foci. Nontuberculous mycobacterial tenosynovitis has also been reported (4, 15, 17) and appears to be the result of previous trauma, surgical procedures, corticosteroid injections, or nonapparent inoculation. Common risk factors include age (>60 years), low socioeconomic status, malnutrition, alcoholism, immunosuppression, and prior local injection of corticosteroids (11, 13).

The main problem remains the difficulty in diagnosing the disease because of nonspecific clinical signs that point to a number of other possibilities, such as carpal tunnel syndrome as a result of carpal canal involvement, rheumatoid arthritis, and nonspecific synovitis mimicking De Quervain’s disease (5) or granulomatous tophaceous gout (9). In rheumatoid arthritis patients, when tenosynovitis is extensive and adherent, a diagnosis of tuberculosis should be considered.

The most effective treatment involves surgical debridement with excision of the necrotic synovium, early postoperative mobilization, and the use of antituberculous drugs, with three or four drugs followed by bitherapy for at least 6 months. The incidence of *M. tuberculosis* infections in organ transplant recipients ranges from 0.35 to 15%. A vast meta-analysis of cases of tuberculosis among transplant recipients revealed three additional specific risk factors: nonrenal transplantation, rejection within 6 months prior to the onset of tuberculosis, and the use of OKT3 or anti-T cell antibody immunosuppressors (14). A targeted evaluation of all heart transplant recipients at a Madrid hospital found an incidence of tuberculosis of 1.35/100 patient-years of transplantation over a 5-year period, a value 20 times greater than among nontransplant patients (10). A similar study involving 727 heart transplant patients in Westphalia over a 7-year period revealed an incidence of tuberculosis of 1.3/100 patient-years, or 74 times greater than in the general population of Germany (8).

The most striking feature is the delay between the onset of symptoms and the final diagnosis, especially when pulmonary symptoms are lacking (16). Diagnosis is often established after culture of mycobacteria from biopsies or tenosynovectomies because direct microscopic examinations are often negative and isolation of the strain is required for more precise identification and susceptibility testing. Mycobacteria are acid-fast bacilli that can be stained by using specific procedures (e.g., by using auramine and Ziehl-Neelsen stains). On solid media, colonies appear after 10 to 21 days and occasionally later, depending on the inoculum. Traditional identification is based on colony morphology and conventional biochemical tests: catalase, thermosensitivity, niacin production, nitrate reduction, and resistance to thiophene-2-carboxylic acid hydrazide (12). Gas chromatographic analysis of cell wall fatty acid composition is also a useful tool. After extraction and esterification, the fatty acid profile is compared to a library of well-characterized mycobacteria. Pattern recognition software matches unknown profiles with those in the database (6).

The major problem is to perform a prompt specific diagnosis in order to start the suitable antimicrobial treatment. Traditionally, the precise identification of mycobacteria requires the use of selective media and specific biochemical tests. Molecular biology techniques allows a much faster diagnosis directly from biopsies. Direct detection and identification (InnoLipa Mycobacteria v2) requires nucleic acid extraction, amplification of 16S-23S RNA, and hybridization. This technique makes it possible to detect and quickly identify (<6 h) 16 species of mycobacteria at the same time.

Multidrug-resistant *M. tuberculosis* strains, which are defined as being resistant to at least isoniazid and rifampin, have been emerging in recent years. The annual prevalence of these strains in France is estimated to be <0.5% and has remained stable since 1992 (7). Poor treatment compliance and the use of first-line antituberculous drugs to which the strain has already developed primary resistance could explain the multidrug resistance. Multidrug-resistant strains are more difficult to treat, especially when they are resistant to isoniazid. In cases reported in the literature, the prognosis is generally good without sequelae when the proper treatment regimen is instituted (3).

Tubercular tenosynovitis should be considered as possible in any patient with chronic or recurrent tenosynovitis. Although this etiology is now very uncommon, it should not be discounted or ignored. The presumptive diagnosis can be made with a positive direct examination. Confirmation by culture takes 10 to 15 days. Molecular biology techniques can be used to detect and identify the main species of mycobacteria involved in human pathologies much more quickly, making it possible to start the appropriate therapy much sooner. The development of molecular techniques allowing simultaneous detection and susceptibility testing of mycobacteria will be, in a near future, a very useful tool for quickly managing mycobacterial infections.

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**REFERENCES**