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CLINICAL STUDY

PARADOXICAL REACTIONS DURING ANTITUBERCULOSIS THERAPY A SINGLE-CENTER PROSPECTIVE ANALYSIS

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ABSTRACT

Background: Paradoxical reactions during anti-TB treatment represent a real challenge to pneumo-phthisiologists and require high index of suspicion. It has been suggested that this reaction during appropriate treatment is common and severe in HIV-negative individuals.

Our objective was to determine the frequency of paradoxical reactions and their associated features.

Method : A prospective study was undertaken in a population of HIV-TB+ patients to determine the frequency of paradoxical reactions and their associated features.

Results: Paradoxical reactions occurred in 1.5% of all our hospital's TB patients.

Conclusion : Paradoxical reactions during anti-TB treatment is common in HIV-uninfected individuals and must be considered after careful exclusion of medication non-adherence, other infections, development of resistance, and other similar conditions.

KEY WORDS: Paradoxical reaction, Antituberculosis therapy, SHIV-negative.

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INTRODUCTION

Paradoxical reactions during anti-TB treatment represent a real diagnostic and therapeutic challenge to pneumo-phthisiologists, and were defined as the worsening of preexisting tuberculous lesions on the basis of clinical or radiological findings or the development of new TB lesions in patients who had received anti-TB treatment for at least 10 days and whose conditions were reported to be improving (1).

This phenomenon received renewed interest because of the immune reconstitution inflammatory syndrome that can occur in HIV-infected patients with TB when they start receiving HAART (2).

The objective of our work is to report our experience through a prospective study which was 2 years long and concerned HIV-uninfected patients.

PATIENTS AND METHODS

This is a prospective study conducted in our pneumophtisiology department during a period from January 2014 to December 2015. Included in this study were patients not infected with HIV and patients whose paradoxical reaction diagnosis during anti-TB treatment was made. In all of our patients, TB diagnosis was made after histological and/or bacteriological confirmation. All of our patients showed initial clinical and radiological improvement after antibacillary treatment administration, followed by clinical and/or radiological aggravation.

A detailed medical history and a comprehensive assessment including a new intradermal reaction were performed in all our patients in order to eliminate non-compliance to treatment or differential diagnoses such as; secondary infection with nosocomial or mundane germs, inadequate or insufficient treatment, resistance, or side

effects of antibacillaries. Basic lab tests included complete blood count, basic metabolic panel, liver function tests, coagulation profile, thyroid-stimulating hormone, and urinalysis.

For statistical analysis, a chi-squared test was used for categorical variables. A P-value of <0.05 was considered significant.

RESULTS

Our study collected 30 cases, 11 of which were men. The sex ratio was 1/3 and the average age was 37.3 years. Extreme ages ranged from 10 to 60 years. One patient had a history of viral hepatitis B and another was diabetic. 3 patients were already treated for TB and 3 were smokers. The initial site of tuberculosis was in lymph node in 9 cases, pleural in 7 cases, pulmonary in 7 cases including one military TB and pleuropulmonary TB in 4 cases, peritoneal in 3 cases, pleuropericardial TB in 2 cases, genital and multifocal respectively in a single case respectively (table 1). The median time to the occurrence of paradoxical reaction was 4.08 months. Three of our cases were diagnosed after antibacillary treatment was stopped and 10 cases in the first two months of treatment. The symptoms were pleurisy in 13 cases, the appearance of new adenopathies in 7 cases with fistula in 3 cases, parenchymal involvement in 3 cases, a pleuropericarditis in 2 cases, hydropneumothorax in 2 cases, tuberculomas in 2 cases, cold abscess in a single case and ascites in three cases.

Sites of TB	No. of cases
Lymph node	9
Pleural	7
Pulmonary	7
Peritoneal	3
Pleuropericardial	2
Genital	1
Multifocal	1

Table 1: Number of cases in the initial sites of TB

The clinical symptoms and signs of paradoxical deterioration manifested in the initial site of infection in 22 of the 30 (73%) episodes, of which 20 in the respiratory system. A paradoxical reaction occurred in an anatomical site other than that of the initial presentation in 8 (27%) episodes, 2 of which were initially manifest in the central nervous system.

Four episodes of paradoxical reaction (13.3%) led to the prescription of Prednisolone in various doses (average dose, 60 mg/day; range 20–60 mg/day) and for various durations (median duration, 46 days; range 21–90 days). These patients had pericardial and cerebral lesions.

TB treatment was extended for 3 to 6 months for 6 patients. Pleurisies were evacuated. The evolution of paradoxical reaction was favorable in all patients.

DISCUSSION

Paradoxical reaction is not a rare phenomenon and requires significant medical attention. It is identified in 6--30% of patients receiving anti-TB treatment (3-6).

Since the advent of the first TB treatment, clinicians have faced worsening epithelioid granulomas and especially giant cell granulomas with clinical TB symptoms in patients successfully treated with anti-TB treatment with negativity of cultures confirming microbiological cure of infection (7).

The mecha¬nism of paradoxical reaction is not well-understood, but it has been attributed to hosting immunologic reactions, with possible mechanisms in¬cluding delayed hypersensitivity response, decrease in immune suppression and response to mycobacterial antigens (Campbell 1977).

Involvement of lymph nodes during paradoxical deterioration (30%) in our series was significantly less common than that in HIV-positive patients (41%) (3, 8).

The paradoxical reaction does not correspond to a relapse of the opportunistic infection but to restoration of a pathological immune response. Reported in 30 to 35% of HIV-infected patients through immune restoration syndrome during antiretroviral treatment, these paradoxical reactions have also been described in HIV-uninfected patients (9). This diagnosis should not be made at first hand, and should primarily eliminate TB treatment inefficiency, for poor adherence, absorption problem, potentially due to drug interactions, or because of resistant mycobacterium strain. Another inter-current opportunistic infection should also be eliminated (10). Despite many hopes, today we do not have immunoassays that are used routinely to assist this diagnosis of exclusion (2). The paradoxical reaction manifested clinically by a worsening of preexisting symptoms in 74.6% of cases, or the occurrence of new clinical signs in 25.4% of cases (3). Some authors set the occurrence time to an average of four weeks (11, 12). The slow action of anti-TB drugs could explain the latency. The time of occurrence of other lesions or worsening of pre-existing symptoms may correspond to the time required for the action of anti-TB drugs (13).

The pathogenesis of paradoxical reactions is not fully elucidated. The hypothesis of a restoration of the specific immune response was proposed. It is considered that the pathophysiology of paradoxical reactions is quite similar to the pathophysiology described in HIV-infected patients. Immunity is initially altered by TB itself due to its immunosuppressive effect. However, it is gradually corrected through TB treatment. The immunosuppressive effects of M. tuberculosis in tuberculosis disease were found at several levels: apoptosis, dysfunction of antigen-presenting cells, T cell lymphopenia and reduced production of IFN by T cells. The main risk factors of paradoxical reactions are extrapulmonary or disseminate tuberculosis sites, initial lymphopenia and increased lymphocytes (2). The paradoxical reaction is encountered in 6 to 30% of patients undergoing treatment for all forms of tuberculosis (13). Extrapulmonary tuberculosis is found in 80% of cases of paradoxical reaction (3, 14). Tuberculosis meningitis and miliary tuberculosis come at the top of the list (15). The central nervous system, pleura and lungs are the most commonly affected sites. [6] The frequency of lymph node site is variable according to the authors. Tuberculous lymphadenitis is complicated by paradoxical reaction in 4 to 23% of cases (3, 16). with an increase in the size of lymph nodes (12%), a fluctuation (11%), erythema and spontaneous discharge (7 %). New lymphadenopathy may occur in 27 to 36% of cases (17).

The site is cervical in 68% of cases (1). Sample taken at the time of paradoxical reaction usually shows no results (1, 9, 14). PCR can remain positive for a long period (18). The finding of concomitant increase in ALC and conversion of the tuberculin skin test in our patients during paradoxical deterioration concurred with the observation in a previous reports who demonstrated a conversion of the tuberculin skin test in five HIV-negative patients during paradoxical deterioration (3, 19-21).

In rare cases, M. tuberculosis could be isolated and its sensitivity to the used anti-TB drugs is not changed (22). The changing of anti-TB molecules is not necessary in a paradoxical reaction. Nevertheless, some authors have extended the quadruple tuberculosis therapy during three months then relaying by triple therapy instead of a double therapy for the rest of treatment. The use of corticosteroids is recommended in meningitis, cerebral tuberculoma, pericarditis or hypoxic miliary (1). Corticosteroid therapy has been widely used (40% of cases) in all forms to limit the exaggerated inflammatory reaction of the body (3). Faced with a tuberculous lymphadenitis in an English study, corticosteroid therapy is recommended if there was a risk of compression of adjacent organs (9). In neuromeningeal forms, corticosteroid therapy remains subject to discussion; however, it appears in some recommendations of experts (23). If a mortality reduction was reported in a series including a small number of patients, the advantage in terms of morbidity seems more modest. In pericarditis, the advantage of corticosteroid therapy on mortality reduction and prevention of occurrence of constrictive pericarditis is controversial. Important abscesses should probably be drained but it is not known how often it should be done (18). The duration of treatment is an average of two to four weeks (22). The prognosis is favorable in most cases. Most ganglion forms show spontaneous resolution in about 2.5 months and 7 to 11% had residual lymphadenopathy at the end of treatment (18). Concerning the damage to the central nervous system, deaths were reported especially in patients co-infected with HIV with 13 to 30% of mortality, despite treatment with corticosteroids, and in pregnant women with 38% of mortality (2).

The use of corticosteroids in the adjunctive management of paradoxical reactions is common. Some case reports have described rapid recovery after initiation of corticosteroid therapy (1, 24-26). The advantage of corticosteroid therapy in reducing edema around enlarging intracranial tuberculomas is apparent, but the advantage associated with the use of such therapy for lymph node TB is less clear.

CONCLUSION

Paradoxical reaction during anti-TB treatment can take many aspects. Paradoxical reaction requires the implementation of a comprehensive test before making the diagnosis: a diagnosis of exclusion. There is no consensus on the therapeutic management of this possibility but some authors suggest an extension of TB treatment and/or corticosteroids. Although evolution is usually spontaneously favorable, complications are possible.

Further studies are also needed to better understand the pathogenesis and risk factors in immunocompetent patients, which would help identify patients at risk of developing paradoxical reaction during TB treatment and better control its clinical manifestation. We believe that the role of corticosteroid therapy can only be defined by a randomized placebo-controlled trial.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

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COMPETING INTERESTS

The authors declare no competing interests.

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