Pseudotumoral Form of Primary Progressive Tuberculosis: A Diagnosis to be Considered

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The diversity of clinical presentations of primary progressive tuberculosis (TB) and the difficulty in establishing the diagnosis of paucibacillary forms is the subject of painstaking research, as well as a cause of delay in therapy. We report the case of a 10-year-old black child who presented with chest pain and progressive widening of the upper mediastinum. Computerized tomography of the chest revealed multiple calcifications that were not identified with X-rays. Biopsy through mediastinoscopy was compatible with a diagnosis of tuberculosis. Despite exhaustive investigation that included direct examination, culture for mycobacteria and PCR (Polymerase Chain Reaction) of tissue samples, the etiologic agent was not revealed. Tuberculin conversion was observed during the follow-up and resolution period of the lesion, after administration of isoniazid, rifampicin and pyrazinamide. The nodal pseudotumoral form of tuberculosis is rare in immunocompetent children and it may simulate neoplastic disease; therefore, it should be included in the list of differential diagnoses of masses located in the anterosuperior mediastinum.
Key Words: Lymph node tuberculosis, pseudotumoral form, diagnosis.

The diagnosis of tuberculosis in children is a major challenge, even in the third millennium. The diversity of clinical presentations of primary progressive tuberculosis and the difficulty to establish the etiology in its paucibacillary forms often leads to treatment without microbiological confirmation; instead diagnosis is based on clinical, epidemiological and radiological findings as well as on the tuberculin test [1,2]. When the lymph node involvement of the mediastinum, which is a result of lymphogenic and hematogenic dissemination of the primary infection, is not accompanied by manifest pulmonary lesions the diagnosis is more difficult because in these cases there is a larger number of possible differential diagnoses. The usual presentation in these cases is unilateral (on the right side) [3]. We report a case of primary progressive tuberculosis with isolated and extensive lymph node involvement of the mediastinum in an immunocompetent child, without evidence of disease at other sites. This demonstrates the difficulties encountered in the diagnosis of those cases that have this unusual form of presentation of the disease.

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Case Report

The patient was a 10-year-old black female child, born and raised in Salvador, Bahia, vaccinated with BCG (Bacillus Calmette-Guérin), and with no known contact with tuberculosis patients. Her only symptom was pain of moderate intensity in the right periclavicular region, unaccompanied by other manifestations. A chest X-ray made at another institution revealed a slight

widening of the upper mediastinum due to a right paratracheal expansive formation that did not receive much attention (Figure 1). The persistence of pain lead to a radiological exam 55 days later, and it showed rapid growth of the lesion, which was then 5 cm in diameter (Figure 2). The tuberculin test was initially non-reactive, but tuberculin conversion (11 mm) occurred three months later. Erythrogram: Hb = 11g/dL, Ht = 32%. Leukogram: 13,900 leukocytes (1% rods, 71% segmented cells, 2% eosinophils, 24% lymphocytes, 2% monocytes). Computerized tomography of the chest indicated a solid 5-cm diameter mass in the right anterosuperior mediastinal compartment, with bosselated contours, containing hypodense areas and punctiform calcifications. The lesion compressed and deformed the right lateral wall of the trachea (Figure 3). Other tomographic cuts also clearly revealed the presence of tiny adenopathies, some of which contained calcium deposits. The fast growth of the lesion and the calcifications suggested a benign character. However, the negative epidemiological history and the absence of tuberculin induration made diagnosis of tuberculosis questionable. A mediastinoscopy, with a biopsy, was performed and the histopathological exam revealed a ganglion bearing a granulomatous chronic inflammatory process with caseous necrosis, along with Langhans type giant multinucleated cells and lymphohistiocytic inflammatory cells, compatible with an etiology of tuberculosis (Figure 4). The direct search for acid- and alcohol-fast bacilli (AAFB) and fungi, as well as attempts to culture mycobacteria from these samples, yielded negative results. The cellular immunity evaluation revealed: candidine = 13 mm; thrichophytin was non-reactive. HIV serology was negative. The PCR exam and the nested PCR from the biopsy fragment were negative for Mycobacterium sp. and for the M. tuberculosis complex. This technique extracts the DNA from the tissue, submits it to amplification through the polymerase enzyme and performs the analysis of the gene sequences. In this case, the gene sequence examined for M. tuberculosis was IS6110.

The patient's family was investigated; the tuberculin test was 19 mm in one of the brothers, even though he did not show any signs of this disease. Based on these findings, we opted for a regimen composed of isoniazid, rifampicin and pyrazinamide. Two months later, the radiological exam evidenced a substantial reduction of the lesion, which remained unaltered until the 4th month of treatment (Figure 5). The patient had satisfactory clinical improvement, becoming asymptomatic, and concluded the treatment after six months.

Discussion

Lymphatic tuberculosis has a higher incidence in young black individuals, in whom it is usually more serious [1-3]. The cervical lymph node chains are the most affected, and in general there is tuberculin hyperergia, accompanied by phlyctenae [1,3-5]. Tuberculosis located exclusively in deep lymph nodes was not easily diagnosed in the past due to difficulties in identification and access. More recently, with the advent of more refined methods of imaging diagnosis, such as ultrasound, computerized tomography and magnetic resonance, these lesions have been identified with greater accuracy [6]. Mediastinal adenopathies are frequent in primary tuberculosis during childhood, and when associated with pulmonary foci of infection they present the typical bipolarity of the primary progressive form [5]. More rarely, mediastinal masses can be dissociated from the pulmonary lesions and this characterizes the pseudotumoral form. In our patient, the diagnosis of tuberculosis was suggested by the histopathological aspects, along with the tuberculin conversion and the fast response to the treatment regimen. Given the paucibacillary character of the primary forms of this disease, it is often difficult to obtain a microbiological confirmation. In Newcombe's series, cited by Pico et al. [3], out of 45 patients with nodal tuberculosis AAFB was identified in just 22% of the cases; the culture was positive in 56%, while diagnosis was established by lymph node biopsy in 91% of the cases. We tried to avoid impairing cellular immunity (which might occasionally be responsible for the initial tuberculin anergy) and therefore performed specific skin tests, with normal results, and we also used a serological test for HIV, which was negative. The initial

Figure 1. Chest X-ray (frontal view): slight widening of the upper mediastinum caused by an expansive right paratracheal lesion. There are no signs of pleural or pulmonary parenchyma involvement.

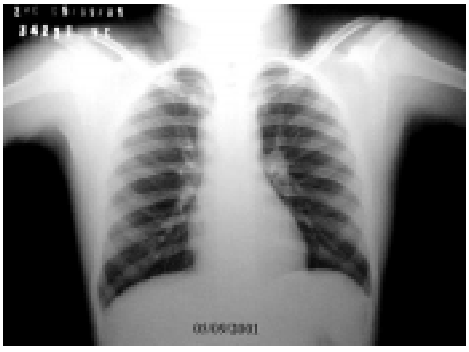


Figure 2. Chest X-ray (frontal view): large mass in the upper right mediastinum, measuring 5 cm in its largest diameter.

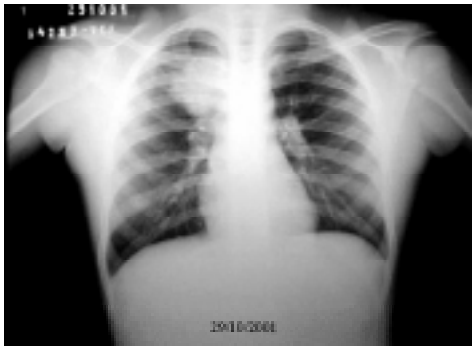


Figure 3. Computerized tomography of the chest: a 5-cm mass in its largest diameter localized in the right anterosuperior mediastinum, with bosselated margins, punctiform calcifications and hypodense areas in between that compresses and deforms the right lateral wall of the trachea. In other tomographic cuts not illustrated here there were tiny adenopathies and some had calcium deposits in other mediastinal chains.

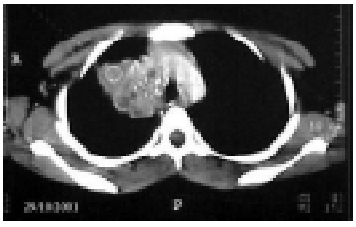


Figure 4. Sections of lymph node: showing the architecture of the organ disorganized by the presence of aggregates of lymphohistiocytic inflammatory cells as well as Langhans type multinucleated giant cells and extensive central caseous necrosis (HE, 100x).

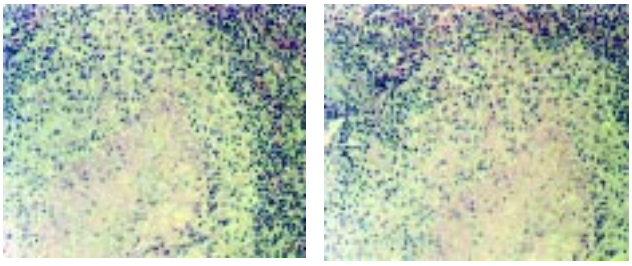
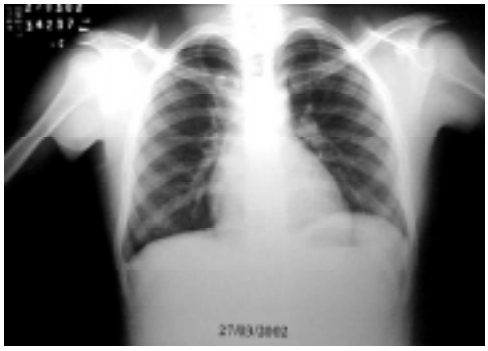


Figure 5. Chest X-ray (frontal view): Substantial regression in the dimensions of the mass located in the right paratracheal area after four months of treatment with Regimen I for tuberculosis.



anergy served as a confounding element, due to the usual hyperergic and sometimes phlyctenar character of these forms of disease presentation. This was probably a consequence of the anergic phase of tuberculosis that is observed during the first couple of weeks of this disease, until a delayed hypersensitivity response to PPD is fully established [4,7]. Even the attempt to confirm the presence of M. tuberculosis in the lymph node fragment by means of PCR and nested PCR techniques (tests still rarely available for clinical use because of their high costs and the complex laboratory technology required) yielded negative results. This is due to the technical limitations of diagnosis by PCR, which can generate false-negative results in samples fixed in formaldehyde and included in paraffin or when the genome analysis of M. tuberculosis involves a gene sequence that is different from that of the mycobacterium affecting the patient [8,9]. Limitations inherent to the characteristics of the sample may also lead to false-negative PCR results, as in our patient, who had an extensive area of caseous necrosis with scanty intact DNA. This necrosis also could explain why the bacillus was not found in direct tests or in tissue cultures. Tuberculosis in children may not follow the basic requirements for the diagnosis of infectious diseases, where the identification of the etiologic agent by microbiological or immunological methods is necessary; consequently the physician may decide to treat suspected cases even without a clear diagnosis [2,7]. An isolated mass in the anterosuperior mediastinum of children allows a number of possible alternative diagnoses, among which we can cite thymoma, teratoma, aneurysm and lymphoma. In this patient, calcifications were also seen in a teratoma. The rapid growth of the lesion suggested an infectious nature and made malignancy unlikely, with little possibility of a diagnosis of lymphoma or malignant thymoma. Congenital aneurysm of the aorta is very rare, but when it is dissected, it can grow very rapidly. However, its evolution is usually acute and serious [10], which was not the situation in our patient. Sarcoidosis is another granulomatous disease that is rare in children; it does not usually present caseous necrosis and tuberculin conversion is not one of its characteristics. Deep mycoses are granulomatous diseases, but they normally do not respond to treatment for tuberculosis and no fungus was found in the samples from our patient. In general, the histology of atypical mycobacteria does not present well-formed granulomas and/or caseous necrosis, they do not respond to the therapeutic regimen employed in our study and they usually do not produce a strongly reactive tuberculin test.

Conclusions

Due to the high prevalence of tuberculosis in Brazil, a possible diagnosis of this disease must always be considered in children who have isolated masses in the anterosuperior mediastinum, even with a negative tuberculin test and without a history of exposure to adults infected with tuberculosis. Rapid evolution of lesions in radiological exams and remission with specific therapeutics are useful clues for diagnosis. Computerized tomography is extremely useful because of its accuracy in defining the characteristics of the lesion, especially calcifications. In the paucibacillary forms, which are common in pediatric patients, a precise diagnosis may be impossible, even after exhaustive investigation. Given these difficulties, treatment is justifiable on the basis of signs and symptoms, especially the classical histopathological changes provoked by tuberculosis.

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