

Active tuberculosis in surgical patients with negative preoperative sputum smear results*

Tuberculose ativa em pacientes cirúrgicos
com baciloscopia negativa no pré-operatório

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Abstract

Objective: To determine the proportion of negative preoperative sputum smear results among patients presenting active TB, as identified through the evaluation of surgical samples. **Methods:** A retrospective study of patients undergoing surgery between 2003 and 2006 at a university hospital and receiving a histopathological diagnosis of active or latent TB. We reviewed patient histories, TB-related clinical aspects, acid-fast bacilli (AFB) test results, type of surgery performed and histopathological findings in surgical samples. **Results:** We included 43 patients, 27 of whom were male. The mean age was 44 ± 19 years. Twenty-eight patients had a history of TB (treated appropriately), and 15 reported no history of the disease. The main reason for seeking treatment was recurrent infection, followed by alterations seen in imaging studies. Of the 43 patients, 35 underwent preoperative AFB testing: 32 tested negative, and 3 tested positive. Among those 35 patients, the histopathological diagnosis was active TB in 26 and latent TB in 9. The 8 patients not submitted to preoperative AFB testing were also diagnosed with latent TB. The proportion of active TB in patients with negative sputum smear results was 72% (23/32), whereas that of negative sputum smear results in patients with active TB was 88% (23/26). Only 11.5% (3/26) of the patients had tested positive for AFB. **Conclusions:** Direct sputum smear microscopy has a very low yield. Many previously treated patients can present negative sputum smear results and yet have active TB. Active TB can be mistaken for secondary infections or for cancer.

Keywords: Tuberculosis; Diagnosis, differential; Sputum; Thoracic surgery; Thoracic surgery, video-assisted.

Resumo

Objetivo: Verificar a proporção de pacientes com baciloscopia negativa no pré-operatório e que apresentaram TB ativa na peça cirúrgica. **Métodos:** Estudo retrospectivo de pacientes com diagnóstico histopatológico de TB ativa ou sequelar e operados entre os anos de 2003 e 2006 em um hospital universitário. Foram pesquisados antecedentes e aspectos clínicos relativos à doença, pesquisa de bacilos álcool-ácido resistentes (BAAR), tipo de cirurgia realizada e exame histopatológico da peça cirúrgica. **Resultados:** Foram incluídos 43 pacientes, com média de idade de 44 ± 19 anos, sendo 27 do sexo masculino. Apresentavam história prévia de TB com tratamento adequado 28 pacientes, e 15 não referiam antecedentes para TB. O principal motivo da procura pelo serviço foi infecção de repetição, seguida por achados em exames de imagem. Dos 43 pacientes, foi pesquisado BAAR no pré-operatório em 35: 32 apresentaram resultados negativos e 3, resultados positivos. Dos 35 pacientes pesquisados, 26 apresentavam diagnóstico histopatológico de TB ativa e 9 de TB sequelar na peça cirúrgica; os outros 8 também foram diagnosticados com TB sequelar. A proporção de TB ativa em doentes com baciloscopia negativa foi de 72% (23/32), e a de baciloscopia negativa em TB ativa foi de 88% (23/26), sendo a pesquisa de BAAR positiva somente em 11,5% (3/26). **Conclusões:** A baciloscopia direta tem rendimento muito baixo, e muitos pacientes mesmo já tratados podem permanecer com TB em atividade com baciloscopia negativa. A TB ativa pode ser confundida com infecções secundárias ou com câncer.

Descritores: Tuberculose; Diagnóstico diferencial; Escarro; Cirurgia torácica; Cirurgia torácica vídeo-assistida.

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Financial support: None.

Submitted: 10 February 2009. Accepted, after review: 12 May 2009.

Introduction

For hundreds of years, TB was the major cause of death due to pandemics. However, with the adoption of the current regimen of antituberculous drugs, more adequate control of the disease has been possible. Currently, due to the rapid growth of the population, together with the poor health and nutrition conditions found in certain parts of the world, as well as sexual promiscuity, the abusive use of injection drugs and the advent of AIDS, TB is again a health problem worldwide.

The annual incidence worldwide, which in 1990 was 125 cases per 100,000 population, was on the rise until 2004, when it surpassed 140/100,000 population. However, it has since decreased, gradually, to 139/100,000 population, approximately 9 million new cases being reported in 2007. An even more encouraging result is related to the prevalence of TB, which was approaching 300 cases per 100,000 population in 1990 and dropped precipitously to 206/100,000 population by 2007, when there were 13.7 million cases. Mortality, which was nearly 29 cases per 100,000 population in 1990, increased until the year 2000, when it reached 31/100,000 population, after which it began to decline, reaching less than 27/100,000 population in 2007, when the number of TB-related deaths was approximately 1.8 million.⁽¹⁾

Prior to 2004, the incidence in Brazil, as estimated by the World Health Organization (WHO), was approximately 110,000 cases/year, although only approximately 80,000 cases/year were reported. However, with the changes in the case registry database made by the Brazilian National Ministry of Health in 2004, the number of estimated cases and the number of reported cases both decreased, and the estimated incidence for the year of 2007 was 92,000 cases. In that same year, slightly more than 70,000 cases were reported, more than the goal set in the accord between the WHO and the Brazilian government, which is to identify 70% of the estimated cases.^(1,2) It is very difficult, not only for Brazil, but also for other countries, to identify a number of cases approaching the estimated number. This difference in Brazil was 20-30%. In a publication of the Brazilian Unified Health Care System in the year of 2001, it was stated that the goal of the government was to increase detection by 20%.⁽³⁾ However, the years passed

and the number of reports remained the same, showing that it is a difficult task to carry out.

Given that the number of estimated cases cannot be detected and that many of our patients who were sputum smear-negative despite multiple smears presented active TB in the surgical sample, we decided to quantify the frequency of such cases (those undetected in the preoperative period) within the total cases at our clinic submitted to surgery due to TB.

Smear-negative patients can be submitted to surgery because they have symptomatic anatomic sequelae (bronchiectasis, cavitations, fibrosis/atelectasis, empyema or tracheobronchial tree stenosis) or because they have a TB pseudotumor that has been categorized as bronchogenic carcinoma. When these patients undergo surgery for the treatment of those sequelae, or in order to rule out neoplasia, the diagnosis of active TB in the histopathological examination of the surgical sample frequently surprises the surgeon. The objective of this study was to evaluate the proportion of smear-negative patients who underwent thoracic surgery and were diagnosed with active TB based on the analysis of the surgical sample.

Methods

After approval by the Research Ethics Committee of the São Paulo State University Botucatu School of Medicine *Hospital das Clínicas*, a retrospective descriptive study was initiated by analyzing the data obtained from the medical charts of the patients who underwent surgery in the Department of Thoracic Surgery of this Institution between 2003 and 2006. All patients with a histopathological diagnosis of latent or active TB in the surgical sample were included. The following factors were analyzed: gender; history of TB; previous treatment; respiratory signs and symptoms, acid-fast bacilli (AFB) test of the sputum, bronchial lavage or bronchial brush; surgery performed; and physician reason for recommending surgery. Sputum collection and sputum-smear microscopy (AFB testing) were carried out in accordance with the guidelines of the Brazilian National Ministry of Health.

Results

In the period between March of 2003 and November of 2006, 43 patients who met the

Table 1 - Anatomopathological test results in the 43 TB cases and the frequency of TB.

Anatomopathological test result	n
Fibrotic process suggestive of latent TB	17
Chronic granulomatous inflammation and productive caseous necrosis	15
Productive caseous active TB	6
Chronic granulomatous pleuritis and Mt+ in pleural fluid	2
Tuberculous cavitation with Mt+	1
Biopsy of thoracic spine with Mt+ culture	1
Tracheitis with granulomatous inflammatory process	1
Total	43

Mt+: positive result for *Mycobacterium tuberculosis*.

inclusion criteria were selected, as shown in Table 1.

Mean age was 44 ± 19 years, and 27 patients (63%) were male. Twenty-eight patients (65%) had a history of TB and received appropriate TB treatment. Fifteen patients (35%) reported no history of TB.

The principal reason given for seeking specialized treatment was recurrent infection (42%), followed by findings on imaging studies (35%), hemoptysis (28%), dyspnea (14%), chest pain (14%) and evening fever (2%).

Thirty-five patients (81.4%) were submitted to AFB testing in the preoperative period, and 32 patients (74%) were submitted to bronchoscopy with bronchial lavage and bronchial brush. In 32 patients, AFB test results were negative, and only 3 cases presented positive test results (multidrug-resistant TB). Eight patients (18.6%) were not submitted to AFB testing.

The anatomopathological examination confirmed the diagnosis of active TB in 26 of the 35 patients studied and latent TB in the other 9 patients. For the 8 patients not tested, the diagnosis was latent TB. The surgical procedures performed as well as the reasons for recommending the surgery are presented in Table 2.

The proportion of active TB in patients with negative sputum smear results was 72% (23/32). The proportion of negative sputum smear results in patients with active TB was 88% (23/26). Positive AFB test results were only observed in 11.5% (3/26).

Discussion

Our case series is not distinct from a Brazilian population sample of TB patients regarding sex and age, since male patients in their fifties predominated.

The principal cause for seeking medical treatment was recurrent infection. We can easily associate the recurrent infections with the sequelae; however, the masking of the active disease can be attributed to the use of antibiotic therapy for the treatment of pneumonia, with temporary improvement of the infection and subsequent resurgence of the disease.⁽⁴⁾ Therefore, we still can not state whether the cases treated were sequelae of the disease appropriately treated or were sequelae related to the lack of appropriate treatment. The chance of the latter will perhaps decrease over time, since the WHO and the United Nations have commended Brazil on its supervised treatment program,⁽²⁾ the irregular use of the medication having proven to

Table 2 - Surgical procedures performed and reason for recommendation in the 43 patients studied.

Procedure performed	Reason for recommendation	n
Lobectomy	Sequelae: pulmonary destruction and 1 case of multidrug-resistant TB	15
Thoracoscopy + wedge resection	Indeterminate pulmonary nodule	8
Thoracotomy + wedge resection	Indeterminate pulmonary mass	5
Mediastinoscopy	Mediastinal mass suspected of lymphoma	3
Decortication	Lung entrapment following empyema	2
Pneumonectomy	Sequelae pulmonary destruction	2
Tracheal dilatation with biopsy	Tracheal stenosis	2
Bilobectomy	Sequela: pulmonary destruction	1
Bilobectomy	Multidrug-resistant pulmonary TB	1
Pneumonectomy	Multidrug-resistant pulmonary TB	1
Thoracomyoplasty	Cavitation throughout the left hemithorax	1
Spinal fusion	Pott's disease	1
Tracheobronchoplasty	Sequelae bronchial stenosis	1
Total		43

be independently associated with recurrence in multivariate analyses.^(5,6) The strategy of supervised treatment has significantly reduced the rate of treatment abandonment.⁽⁷⁾ Educational sessions conducted in waiting rooms have also proven useful in decreasing the rate of treatment abandonment.⁽⁸⁾ However, the decentralization of the treatment, which has been shifted to Family Health Care Clinics, has not proven useful in some locations, resulting in lower cure rates and higher rates of treatment abandonment.⁽⁹⁾

The findings in imaging studies, which represent the second reason for seeking the hospital, were all suggestive of neoplasia, and, in some cases, even tomography with contrast enhancement indicated a high probability of malignancy. However, those were cases of caseous nodules with intense inflammatory process and high bacterial activity, without specific symptoms of TB. This is in accordance with the literature: in developed countries, tuberculomas account for 14–24% of the cases of resection of suspicious nodules.^(10–12) In practice, high-risk patients and patients with pulmonary nodules presenting enhancement greater than 15 UH are submitted to biopsy or surgical excision of the nodules.⁽¹³⁾

Imaging studies showed involvement of all types and in all thoracic compartments, from the airways, with tracheal and bronchial stenosis, to the spinal column, with collapse of the thoracic vertebra, to the lung parenchyma, with nodules and cavitations, and to the pleural cavity, with pleural effusion and thickening.

Positive sputum smear results occurred only in the 3 cases of multidrug resistant TB; however, not all patients were submitted to the test, due to the lack of symptoms and because the initial diagnostic hypothesis was not TB. However, 74% of the patients were submitted to bronchoscopy prior to the surgery, and 26 negative lavage/brush results were obtained, as well as 6 indeterminate results. This might be due to the presence of AFB located only in the infectious focus (active nodule), since the yield of bronchoscopy varies from 11% to 96%.^(14,15) In cases of minimal lesion, accuracy is low and increases with the performance of transbronchial biopsy in the affected segment.^(15,16) Bronchial lavage and bronchoalveolar lavage are the diagnostic procedures with the greatest yield, whereas bronchial brush has the lowest yield, and their accuracy is increased when they are used in conjunction.^(14,15)

However, even when these procedures were used in combination, the results were negative in our sample. Bronchial lavage presents a yield equal to that of induced sputum. However, before any of these procedures are performed, sputum smear microscopy should be carried out. In our sample, the sputum smear microscopy results were also negative.

A positive result in direct sputum smear microscopy is defined as at least 5,000 bacilli/mL; the test has a yield of 50% to 80%,⁽¹⁷⁾ although this varies widely depending on the prevalence in the locale and on the methodological precautions taken in the handling of the samples.^(18–20) We should therefore consider that a negative test result, although potentially indicative of a lack of bacilli in the sputum, might indicate either inappropriate sample collection (which is carried out by the patient at home) or inappropriate storage of the material after collection.

In Brazil, 30% of the adults with TB are smear-negative. In a study carried out in a prison hospital in the state of Bahia, Brazil, it was found that, although 2.5% of the prison population had TB, only one third of those prisoners were smear-positive. The other two thirds of the population were diagnosed based on culture or on the clinical and radiological profile.⁽²¹⁾ Those patients present difficult diagnoses due to the variety of clinical and radiological presentations, and, therefore, a clinical-radiological score has been recently proposed for individuals with suspected TB.⁽²²⁾ However, our group of patients presented differently from that sample, due to the fact that not only the sputum smear was studied, but also specimen from the bronchoscopy, which shows that, in patients with negative sputum smear results, one isolated test never presents enough accuracy for the diagnosis.⁽²³⁾

We would certainly have a more successful diagnosis if culture were requested more frequently, since positivity could be determined with a much smaller number of bacilli than is necessary for direct sputum smear microscopy. The II Brazilian Guidelines for TB⁽¹⁷⁾ refer to six priority recommendations for the performance of the mycobacterial culture and, among those, are the “suspected pulmonary cases with negative sputum smear results”. Culture was not conducted in those cases due to the fact that active TB was not the main diagnostic hypothesis. Many of those patients were investigated

with highly suspected neoplasia and presented more than one negative sputum smear result. Since the culture takes several weeks, the surgeon does not want to risk waiting for the results, since, in most cases, the diagnosis of cancer is confirmed.

Some authors recommend the collection for the culture of AFB in the bronchial lavage even when TB is not the principal diagnostic hypothesis; however, this routine would only present satisfactory yield in areas where the prevalence of TB is high.⁽²⁴⁾ Therefore, the routine culture in places with low prevalence, as is our region, would only lead to an unnecessary increase in the hospital operational cost,⁽²⁵⁾ and, which is worse, to a delay in the surgical recommendation of those patients who truly have cancer. Other authors defend the unconditional request of the culture of bronchial lavage, since it is possible that indeterminate pulmonary lesions can represent active TB, even in non-endemic zones.⁽²⁶⁾

It is of note that the medical literature is not unanimous regarding culture, in addition to there being no direct data on the accuracy of the bronchial lavage in cases of tuberculoma.⁽²⁷⁾ However, it is certain that, in the absence of positive AFB culture, other invasive procedures, such as needle biopsy or video-assisted thoracic surgery, should be performed.⁽²⁷⁾ It must be borne in mind that our study assessed a sample of patients treated in a surgical ward, the operated cases being those in which less invasive tests had not provided a diagnosis, and is therefore not representative of all diagnosed cases.

The principal indication for surgery was recurrent infection with bacteria colonizing the residual cavities, which, in addition to being responsible for bleeding, are not eliminated by means of systemic treatment, making surgical intervention necessary.

The second most common reason for surgery was a radiological finding consistent with bronchial carcinoma, including nodules, with pronounced enhancement after contrast injection, which occurs principally in neoplasia but can also occur in active TB. In one study, it was demonstrated that CT with contrast enhancement presents a sensitivity of 77.1% and a specificity of 96.4% in the diagnosis of active tuberculoma.⁽²⁸⁾ However, the results obtained were from patients whose principal diagnostic

hypothesis was TB, differing from our sample, in which the principal suspicion was bronchogenic carcinoma. The II Brazilian Guidelines for TB⁽¹⁷⁾ recommend that CT be used especially in cases with negative sputum smear results, which demand a better differential diagnosis with other diseases. The principal diagnosis for most patients in our sample was cancer.

The surgical procedures performed were minimally invasive when possible (47% of the cases). However the same percentage of patients was submitted to major resection, principally due to the sequelae caused by the infection. Surgical biopsy of suspicious nodules and masses was the biopsy of choice, even when the lesions were atypical and located in lower pulmonary segments, and was justified by the limitation of transparietal thoracic puncture, which presents many false-negative results.⁽²⁹⁾ Video-assisted thoracoscopy is the best initial approach.⁽³⁰⁾ Anatomopathological testing of the samples collected in the mediastinoscopies performed due to suspected lymphoma in young adults with mediastinal lymph node enlargement revealed intrathoracic TB, the incidence of which is 10-43% in adults.^(10,11) The two decortications performed were recommended due to entrapment after pleural empyema, which was later diagnosed as resulting from secondary contamination in tuberculous effusion.

Prior to surgery, most patients in our sample accounted for part of the difference between the estimated number and the reported number of cases in Brazil.^(1,2) Had they not undergone surgery, they probably would not have been treated.

Therefore, we conclude that, in the studied group, direct sputum smear microscopy presented an extremely low yield and that many patients, even those already treated, can present active TB despite negative sputum smear results. We also conclude that many patients with TB still undergo surgery, having cancer as the principal diagnosis.

Acknowledgments

We wish to thank Professor Luana Carandina, of the Epidemiology Sector of the São Paulo State University Department of Public Health, for the epidemiological and clinical review of the article.

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