

# Tuberculosis - two unusual forms of presentation

Sofia Granito\*, Margarida Jardim\*, José Luís Andrade\*, António Chaves\*, Ana Paula Reis\*\*, Sofia Freitas\*\*\*, Jorge Nóbrega Araújo\*

### Abstract

The World Health Organization (WHO) declared tuberculosis a global health emergency in 1993. In fact, in recent decades, tuberculosis has assumed an increasing importance as a public health problem. The authors present two cases with clinical presentations that are quite rare. The first was to a 32 year old female who came to the emergency service (ES) of the Hospital Central do Funchal (HCF) due to a sudden decrease in visual acuity on the left side, and ipsilateral cervical adenopathy. After the due study, optic disc edema and cervical lymph node tuberculosis were diagnosed, which were treated with corticosteroids and antituberculosis drugs. The second was a 41 year old patient, admitted to the Infectious Diseases Unit of the HCF for presumed bacterial meningitis. During hospitalization, there was the worsening of the clinical condition with depression of consciousness and

seizures, therefore the lumbar puncture was repeated, leading to a diagnosis of meningeal tuberculosis. Antituberculosis therapy was then initiated. The following complications are highlighted: ischemic cerebrovascular stroke and lower respiratory infection, with respiratory insufficiency, requiring invasive ventilation support. After improvement of the respiratory symptoms, the patient returned to the Infectious Diseases Unit, where he died.

The authors wish to draw attention to the fact that tuberculosis is assuming an important role today, as in 'more' developed countries, it is more than three decades since so-called "less typical" forms of presentation have been described in "immuno-competent" individuals.

Key words: Lymph node tuberculosis, meningeal tuberculosis, optic disc edema.

### INTRODUCTION

Tuberculosis is one of the oldest infectious diseases to affect mankind. Even now, 126 years after the discovery of the Koch's bacillum (BK) or *Mycobacterium tuberculosis* by Robert Koch, tuberculosis continues to be a serious public health problem, with increasing importance. Declared by the WHO as a global health emergency in 1993, tuberculosis is a notifiable disease.<sup>1,2</sup>

According to the WHO, there were more than five million cases of tuberculosis recorded in 2005. It is estimated that the actual number exceeds eight million. In that same year, around 1.6 million deaths were attributed to tuberculosis. Over 90% of active cases of tuberculosis and deaths occur in developing

countries. Co-infection by the human immunodeficiency virus (HIV) increases the risk of developing active tuberculosis, and it is important to note that in countries where there is a high prevalence of this infection, the incidence of tuberculosis is three to four times higher. The existence of multi-resistant strains is a growing concern in many countries, and is mainly due to inadequate treatment measures and/or poor compliance to a course of therapy.<sup>3</sup>

A global strategy, known as DOTS (Directly Observed Therapy - Short-course) has been implemented, promoted by the WHO since the mid-nineteen nineties in order to reduce mortality and prevent the emergence of new cases. This low-cost initiative was one of the more successful measures at a global level, in terms of achieving its proposed objectives. It is described that best means of preventing tuberculosis is the effective cure of infectious cases, in order to avoid contamination of healthy individuals. The main intervention for the control of tuberculosis used by the DOTS strategy is the use of short duration standard chemotherapy, tailored to each case, and observed intake of the drugs, at least initially. The primary goals of this strategy include diagnosing 70% of active cases of tuberculosis, and curing 85% of cases detected. Only 27% of individuals with active tuberculosis have been treated in this program. The goal

\*Medicine Service 1

\*\*Ophthalmology Service

\*\*\*Infectious Diseases Unit

Hospital Central do Funchal

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is to effectively treat 70% of cases by 2013.<sup>2</sup> Another form of prevention involves the application of the vaccine, ideally to all newborns infants, in countries where there is high prevalence of the disease.<sup>1</sup> This vaccine was initially prepared in 1921 from attenuated *Mycobacterium bovis* (bacillus Calmette-Guerin or BCG) and has been part of our National Vaccination Plan since it was officially implemented in 1965.<sup>4</sup> In 2005, vaccination coverage reached 94.4% for infants in the first few months of life, and 97.2% in the first year. In 2006, vaccination coverage reached 97.3%.<sup>5</sup> The third most important measure for the control of tuberculosis is the treatment of latent infection in patients at risk of developing active infection.<sup>3</sup>

In our country, in recent years, we have seen a reduction in the incidence and prevalence of tuberculosis, and a reduction in cases of resistance to the drug, thanks largely to the efforts made as part of the National Plan to Fight Tuberculosis. In large urban areas such as Lisbon and Porto, this trend has not been observed, and these are the areas with the highest number of cases, and where a lower rate of decrease and therapeutic success, and a higher incidence of resistance, are registered.<sup>2</sup> According to the National Statistics Institute (INE), the incidence per 100,000 Portuguese inhabitants was 33.8 in 2005. In the Autonomous Region of Madeira, this figure was 20.8. Of the European Union Countries, Portugal is one with the greatest incidence of notified cases, and the greatest expression of the aspects that define tuberculosis as an emerging infection.<sup>2</sup>

### CLINICAL CASE 1

Female, 32 years old, a professor at the Prison of Funchal, with no relevant previous pathological history. History of BCG vaccination in infancy. The patient came to the ES of HCF on 15 March 2007 due to a sudden loss of visual acuity on the left side, with one day of evolution. She was initially served by Ophthalmology department, which noted the existence of optic disc edema, reduced visual acuity on the left side (OD-10/10 and OE-4/10 without correction) and decreased pupil light reflexes (direct and consensual) also on the left side. The assistance of Internal Medicine was requested. During further exploration of the clinical history, the patient reported a painless mass in the neck with one week of evolution, which was treated with ibuprofen by the Assistant Physician, with no improvement. The patient did not give much

importance to it, at the date of the observation. She also reported that she had lost weight in the previous month, but did not know how much. The patient denied fever, excessive sweating at night, cough or other symptoms.

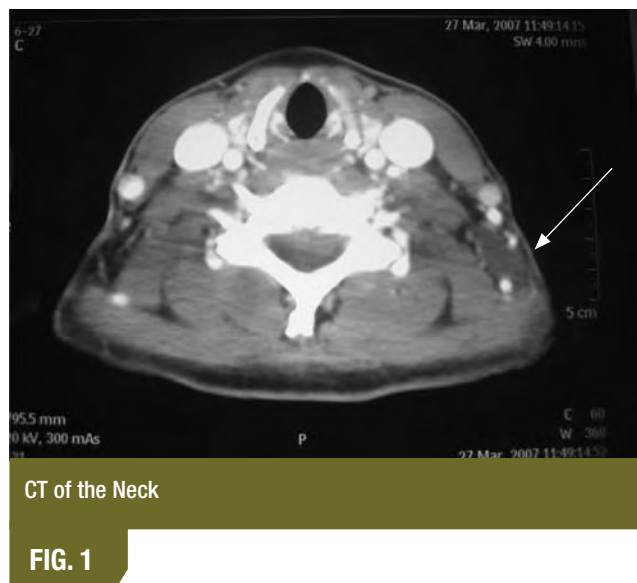
Physical examination revealed the following: funduscopy indicated the presence of exuberant edema of the left optic discs, and palpitation of the neck indicated an enlarged neck lymph node of three centimeters in diameter on the left side, mobile, of a hard elastic consistency, not adhering to the adjacent tissues, and painless. Analytically, only hypochromic and microcytic (MCHC-30 g/dl, MCV, 65.2 fL) anemia (hemoglobin-10.1 g/dL) were observed. Tests for HIV 1 and 2 were negative. CT-EC was carried out, showing no abnormalities. Treatment with corticosteroids (prednisolone, 40 mg/day) was begun immediately, on the recommendation of Ophthalmology.

The patient was referred to Internal Medicine for etiological study. From the auxiliary diagnostic tests performed in this context, we obtained the following results: Positive Mantoux test (20 mm). CT of the neck revealed "necrotic adenopathy in the left posterior triangle of the neck, with a diameter of about 25 mm at the widest point" (Fig. 1). Excision biopsy was performed, and the anatomical and pathological examination showed "granulomatous lymphadenitis with necrosis, compatible with tuberculosis. The search for acid-fast bacilli (AFB) by the Ziehl-Neelsen method was negative" (Fig. 2).

Anti-TNF therapy was started, with intake under direct observation (DOT), on 22 March 2007: Isoniazid 300 mg/day p.o., Rifampicin 600 mg/day p.o., Pyrazinamide 1500 mg/day p.o., Ethambutol 1200 mg/day p.o., Pyridoxine 40 mg/day p.o., with duration of two months, followed by four months of therapy with Isoniazid and Rifampicin, at the above-mentioned doses. The patient was monitored in follow-up visits to Internal Medicine and Ophthalmology. After one month of treatment, the patient showed almost complete recovery of visual acuity (Right Eye - 10/10; Left Eye-7/10 without correction) and a significant reduction in the optic disc edema. The patient was gradually weaned from the corticosteroid therapy. The patient continues to have no or alterations in vision, and no palpable enlarged lymph nodes.

### CLINICAL CASE 2

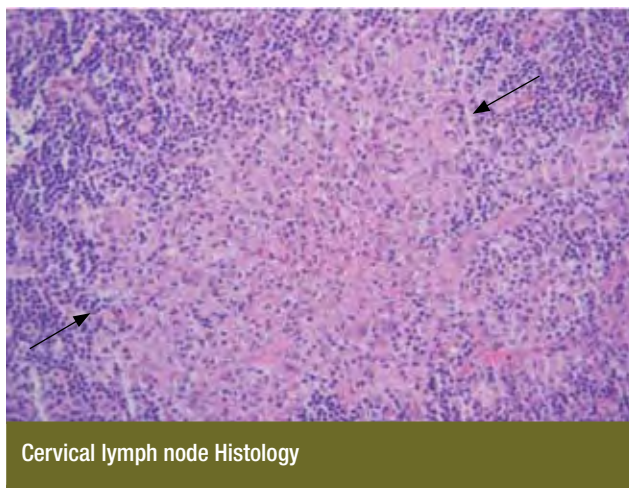
Female, 41 years old, a housemaid. With no relevant



previous pathological history. Unknown vaccination history. Family history without relevance.

The patient came to the ES of HCF on 16 March 2007 due to fever, hemicranial headaches on the left side, and photophobia, with one week of evolution. Patient showed mental confusion since the day before. She had been medicated with Paracetamol and “antibiotic” (sic) by the Assistant Physician, without improvement. Physical examination revealed the following: periods of mental confusion, neck stiffness and tympanic temperature of 38.2 °C. Analytically: Leucocytes-20900/ $\mu$ L;-92 neutrophils, 92,7% and CPR-16, 9 mg/L. Cranioencephalic CT scan (CE-CT) was performed, showing no abnormalities. Lumbar puncture (LP) was performed, revealing the presence of 336 cells/ $\text{mm}^3$  in the cerebrospinal fluid (CSF), with polymorph nuclear cells and lymphocytes, total proteins-177,6 mg/dL, glucose 34 mg/dL and positive Pandy reaction. Cytological examination revealed a “hyper cellular CSF with neutrophils and lymphocytes, consistent with inflammatory process.” Microbiological tests (direct and culture) were negative.

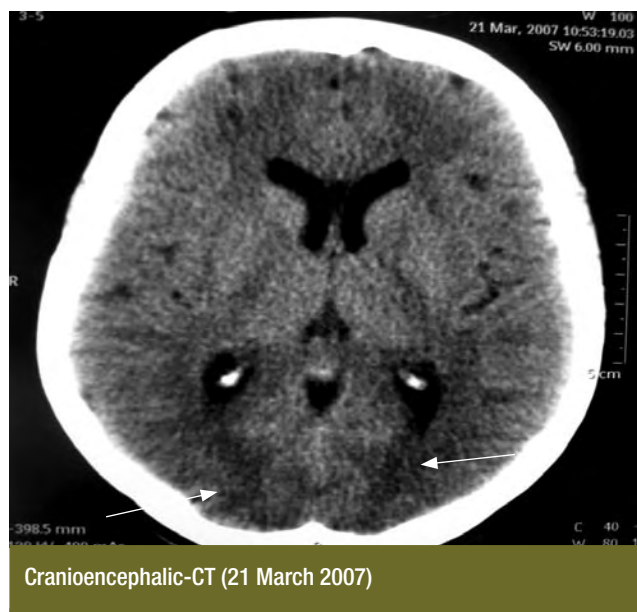
Chest X-ray, electrocardiogram and the arterial blood gas revealed no changes. The patient was admitted to the Infectious Diseases Unit (IDU) with a diagnosis of meningitis, medicated empirically with Ceftriaxone 2g e.v. every 12h, Dexamethasone 5 mg e.v. every 6h and Paracetamol 1g e.v. when in need. Serologies were requested for the CMV, EBV, HSV, and HIV 1 and 2 viruses, which were negative. Three blood



cultures were carried out, also negative.

On day five of hospitalization (21 March), the patient had a seizure, which was not witnessed by medical staff. CE-CT was repeated (Fig. 3) which showed “small periventricular hypodensities in the occipital regions, possibly corresponding to recent ischemic lesions. A new LP was performed, showing a slightly turbid CSF with 400 cells/ $\text{mm}^3$ , and a predominance of mononuclear and ADA-37 U/L cells. One AFB per field was isolated. The patient was treated with intravenous phenytoin infusion and subsequently at a dose of 100 mg p.o. three times a day, at the recommendation of Neurology, and platelet anti-aggregation of 250 mg of acetylsalicylic acid per day was initiated. The empiric antibiotic therapy was suspended, and antituberculous therapy initiated, precisely as described in clinical case 1, maintaining the corticosteroid therapy. Between days six and nine of hospitalization, the patient was more reactive and remained clinically stable.

One day ten (26 March), due to cough with phlegm and mucous and signs of difficulty breathing, a chest x-ray was performed, showing opacity of the lower third of the left lung field, suggestive of pulmonary condensation. Arterial blood gasometry (FiO<sub>2</sub> 50%) showed metabolic alkalosis and hypoxemic respiratory failure (pH 7.52, pO<sub>2</sub> -54 mmHg, pCO<sub>2</sub> -38 mmHg, O<sub>2</sub> saturation-91%, HCO<sub>3</sub><sup>-</sup> 30.7 mmol/L; Lact-1, 7 mmol/L), which remained refractory to oxygen therapy. Due to the patient’s general clinical status and the need for invasive ventilator



Cranioencephalic-CT (21 March 2007)

FIG. 3



Cranioencephalic-CT (02 April 2007).

FIG. 4

support, she was transferred to the Intensive Care Service (ICU), where she was medicated, in addition to the aforementioned therapy, with ciprofloxacin 400 mg e.v. every 8h, for thirteen days, and where she remained for sixteen days. At 24h the patient showed the following severity scores: APACHE II-26 and SAPS II- 57.

During her time in the ICU the patient had another seizure. The patient was reviewed by Neurology, and an electroencephalogram was performed, revealing a “generally slowed record, with slow waves of highest amplitude in the frontal regions (1-2 Hz). These changes are consistent with diffuse encephalopathy”. A new LP was performed (31 March), revealing: xanthochromia in the CSF, for which the cytochemical test was consistent with previous ones. The CE-CT was repeated (Fig. 4) showing a significant increase in relation to previous ones: “prominence of the ventricular system”. Images of ischemic stroke in the right parietal and left thalamic and lenticular-capsular regions. Patient remained in a superficial coma (Glasgow: 8-9), with decerebrate posturing in response to pain stimuli, and daily peaks of fever. Patient remained hemodynamically stable, without the need for vasopressin support. From the last analytical control on leaving the ICU, the following are highlighted: leucocytes-16900/ $\mu$ L, neutrophils-87.3%, CPR-385.6 mg/L. After extubation, the patient was transferred

to the Special Care Unit and tracheotomized, where she remained for three days. After closing of the tracheostomy the patient returned to the infirmary of the IDU. Patient remained in a superficial coma, in subfebrile condition. Patient died the next day (14 April 2007). No autopsy was performed.

#### DISCUSSION

Tuberculosis is transmitted when a healthy individual inhales particles containing the KB. However, not all exposed persons develop an active infection. The elderly, children and people weakened by other diseases have an increased risk. Moreover, only patients with active pulmonary tuberculosis are smear positive and can infect new healthy subjects.<sup>1,3</sup>

The clinical presentation of tuberculosis can be variable, depending on the target organ. It normally attacks the lungs, however, it can reach other organs in about a third of cases. Extrapulmonary tuberculosis occurs more often among children and individuals with HIV infection, and results from the haematogenous spread of bacilli during the initial multiplication phase. The sites most commonly affected, in descending order of frequency, are the lymph nodes, the pleura and the genitourinary and osteoarticular systems. There are some specific symptoms that are



common to different forms of presentation, such as a general malaise, anorexia, asthenia, weight loss, fever and excessive sweating at night. The remaining clinical symptoms vary according to the organ affected by the disease.<sup>2,3</sup> Therefore, the diagnosis of forms of extrapulmonary tuberculosis is more difficult, often involving the use of more invasive techniques for sampling organic products.<sup>2</sup> Given that the pulmonary involvement is common, we generally expect to find cough (whether productive or not) in these patients, as well as chest pain and hemoptysis.<sup>3</sup> However, we must not forget other less typical clinical symptoms, sometimes with rare presentations, which may also be of tubercular etiology. In the first case presented, the form of presentation of tuberculosis was the presence of cervical adenopathy and unilateral edema of the optic discs. There are some reports in the literature of optic disc edema of tuberculosis etiology, with complete resolution of the edema and recovery of sight with antituberculous therapy alone.<sup>7,8</sup> This association appears to be more frequent in meningeal tuberculosis, but can also occur in other forms of tuberculosis.<sup>9</sup> In our case, it was associated with lymph node tuberculosis. Because corticosteroid therapy was also used, we cannot conclude that the regression of the optic disc edema and recovery visual acuity were due solely to the antituberculous therapy. However, given the clinical context, this seems to us to be the most likely etiology. Given the importance of proper diagnosis in these situations, the authors draw attention to the need to consider tuberculosis as a possible cause of swelling of the optic discs. Although a rare situation, optic disc edema may sometimes be a form of presentation of mycobacterial infection.<sup>6,7</sup> Other causes of optic disc edema include infection, immune-mediated aggression and drug toxicity.<sup>10</sup>

The diagnosis of tuberculosis is supported by imaging evidence of pulmonary disease (if there is lung involvement), cutaneous reactivity 48 to 72 h after intradermal injection of mycobacterial antigens (Mantoux test), detection of AFB by the Ziehl-Neelsen method or isolation of mycobacteria in culture (results obtained after three weeks, since the mycobacteria are slow growing) and evidence of a granulomatous reaction in tissue that we suspect to be infected.<sup>3</sup> The amplification of mycobacterial nucleic acids may enable diagnosis within a few hours. It is estimated that the isolation of AFB in the CSF is only possible in about 20% of cases, so the diagnosis

of meningeal tuberculosis is particularly difficult and must be based on initial clinical suspicion. In the second case study, empiric antibiotic therapy was started, to cover the agents most likely associated with meningitis (*Neisseria meningitidis* and *Streptococcus pneumoniae*), given the patient's age.<sup>3</sup> Subsequently, examination and cytochemical identification of AFB in the CSF confirmed the diagnostic suspicion of meningeal tuberculosis, already suggested by the clinical worsening and insidious progression of the clinical symptoms. A high adenosine deaminase (ADA) value is useful in the diagnosis of pleural tuberculosis. In the CSF, its role is less clear.<sup>3</sup>

The Mantoux test can differentiate infected from uninfected individuals, but is unable, in itself, to diagnose active tuberculosis. In clinical case 1, the patient presented strongly positive results (20 mm) in the test, suggesting the existence of active tuberculosis. The detection of AFB by the Ziehl-Neelsen method is extremely important for the laboratory confirmation of the existence of mycobacterial disease, but this was not possible in this case. However, the pathological examination of this palpable adenopathy, with the identification of a granulomatous reaction with caseous necrosis, supported the diagnosis of tuberculosis and ruled out the main differential diagnosis that arises in this situation - a lymphoma. In the clinical case 2, the diagnosis of meningeal tuberculosis was proposed due to clinical worsening, indicating a lack of response to empiric antibiotic therapy, and the diagnosis was confirmed by the observation of an AFB/field in the CSF. The main differential diagnoses that were possible in this situation were meningitis of other etiologies, a primary or metastatic brain tumor, or other injury occupying the intracerebral space.<sup>3</sup> These three cases were ruled out by clinical examination, cytochemical and microbiological examination of the CSF and CE-CT.

The National Plan to Fight Tuberculosis (has always enjoyed great political, social and financial support. In Portugal, the first sanatorium for the treatment of tuberculosis was built in 1862, in Funchal.<sup>1</sup> However, it was not until the nineteen-forties that the start of therapy specifically targeted at tuberculosis became possible, with the discovery of streptomycin. The successive introduction of other drugs shortened the duration of the treatment regimens, and improved their efficiency, also reducing the development of resistance.<sup>3</sup> Antituberculosis drugs have three main

properties: antibacterial, sterilizer and prevention of resistance. The four essential or first line drugs are Isoniazid and Rifampicin, Pyrazinamide, and Ethambutol. There are formulations prepared with different drugs, isolated and in fixed combinations, to reduce the number of tablets daily and thus increase compliance to the therapy.<sup>2</sup> Only in cases of tuberculosis resistant to first line drugs can we resort to second line drugs (Streptomycin, Capreomycin, Cycloserine, Fluoroquinolones, among others).<sup>3</sup>

The use of corticosteroid therapy in combination with antituberculosis drugs is controversial. It is associated with reduced mortality in cases of meningeal tuberculosis, but does not reduce the incidence of neurological sequelae.<sup>3,11</sup> There are several possible regimens, but in general, and in cases of pulmonary or non-complicated extrapulmonary tuberculosis, the main basic regime consists of associating Isoniazid, Rifampin, Pyrazinamide and Ethambutol for a period of two months. The association of Isoniazid and Rifampicin must be maintained for the subsequent four months. The dose maybe be administered daily or three times a week, but regimes being equally effective and more feasible in cases of DOT. In cases of pulmonary cavitation, positive sputum culture test after two months of treatment, relapse or resistance/intolerance to Isoniazid, Rifampicin or Pyrazinamide, the treatment should be extended to nine months. The treatment of meningeal tuberculosis should be extended to nine to twelve months.<sup>2,3</sup> The main adverse effects of these drugs are hepatotoxicity (Isoniazid, Rifampicin and Pyrazinamide), Nephrotoxicity (Streptomycin and Ethambutol), peripheral neuropathy (Isoniazid) and optic neuritis (Ethambutol).<sup>1,3</sup>

Each year, more people die of tuberculosis than any other curable infection. Our patient in the second clinical case presented, on entry to the ICU, a mortality risk of about 55%, according to the severity scores. No autopsy was performed, therefore we cannot categorically state that tuberculosis was the cause of death. The unfavourable development of the clinical symptoms, including CNS injury, which worsened during hospitalization, and the onset of a nosocomial pneumonia, led us to believe that there were a number of determining factors in the outcome of this case.

When treated appropriately, and if caused by strains sensitive to the drugs currently available, it is curable in virtually all cases. About half of patients

with untreated cases die up to five years after diagnosis. When treated appropriately and in a timely way, the majority of patients are effectively cured. However, improper use of antituberculosis drugs, mainly as a result of poor adherence to treatment by patients, while reducing mortality, contributes to a high number of cases of chronic infection and the development of multi-resistant strains.<sup>3</sup>

## CONCLUSION

The authors describe and discuss two clinical cases of tuberculosis with unusual forms of presentation". The first refers to lymph node tuberculosis and the second to meningitis tuberculosis, both in "immunocompetent" patients. Thus, the intention of the authors is to emphasize the importance of this disease today.

It is vital that we have this diagnosis in mind, not only in patients with HIV infection and not just those with respiratory complaints. We stress the importance of considering tuberculosis in the differential diagnosis of optic disc edema, although not a frequent form of presentation, and also in cases of meningitis with insidious evolution and/or when no response is obtained with first line empiric antibiotic therapy. An attitude of careful patient observation and being alert to clinical signs may facilitate suspected diagnosis, even in situations where the clinic symptoms are not very suggestive, thereby guiding the proper and early treatment strategy in order to improve the prognosis. It is also essential to raise awareness of the increasing importance of tuberculosis today, in order to promote better compliance to the preventive measures and treatment. ■

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## References

1. Antunes, M.L.; Antunes, A.I.: A situação da tuberculose em Portugal: uma perspectiva histórica até 1994. EuroSurveill. Lisboa 1996 1(3): 19-21
2. Organização Mundial de Saúde (2003). Tratamento da tuberculose: linhas orientadoras para programas nacionais. 3ª edição. Direcção-Geral de Saúde. 2006.

3. Raviglione MC, O'Brien RJ. Tuberculosis. In Kasper, Braunwald, Fauci, Hauser, Longo, Jameson, Loscalzo: Harrison's Principles of Internal Medicine, 17th edition. Mc Graw Hill 2008: 1006-1020.
4. [www.setubalpeninsuladigital.pt](http://www.setubalpeninsuladigital.pt) A Vacinação. Escola Superior de Saúde. Instituto Politécnico de Setúbal. Acedido em 28 de Agosto de 2008.
5. [www.ine.pt](http://www.ine.pt) Evolução da vacinação da tuberculose. Acedido em 27 de Março de 2007.
6. [www.ine.pt](http://www.ine.pt) Incidência de casos novos e retratamentos de tuberculose, por distribuição geográfica de residência. Acedido em 27 de Março de 2007.
7. Asensio-Sanchez VM et al: Tuberculous papillitis. Arch Soc Esp Oftalmol 2006; 81(1):37-39.
8. Mansour AM: Optic disk tubercle. J Neuroophthalmol 1998; 18(3): 201-203.
9. Lamba PA, Bhalla JS, Mullick DN: Ocular manifestations of tuberculous meningitis: a clinico-biochemical study. J Pediatr Ophthalmol Strabismus 1986; 23(3): 123-125.
10. Jacob M, Kodjikian L, Ponceau B, Grange JD: Can optic perineuritis be triggered by Mycobacterium tuberculosis? J Fr Ophtalmol 2006; 29(3):6-7.
11. Prasad K, Volmink J, Menon GR: Steroids for treating tuberculous meningitis. Cochrane Database Syst Rev 2007;(3):CD002244.