Le Infezioni in Medicina, n. 4, 309-312, 2014

Caso clinico

Case reports

Unsuspected tuberculosis in COPD and use of levofloxacin: diagnostic challenges

Tubercolosi imprevedibile in corso di BPCO trattata con levofloxacina: sfide diagnostiche

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INTRODUCTION

Patients with COPD are particularly prone to frequent acute exacerbations (AECOPD), which are the main cause of morbidity and mortality of this entity, and the long-term use of oral and inhaled corticosteroids may enhance the risk of pneumonia as well as of TB [1-7]. This mycobacteriosis is one of the main pulmonary chronic infections affecting people all over the world, in special those from low-income regions, or with immunosuppression [2-4]. Fluoroquinolones are effective second-line drugs for multidrug-resistant TB, but are often used to treat other pulmonary, gastrointestinal, and genitourinary bacterial infections [8-10]. Although these drugs have been utilized to control AECOPD, their use in people with unsuspected TB can hinder the isolation of *M. tuberculosis* in the specific culture media, phenomenon which propitiates some delayed diagnosis of this ominous infection [2, 8-10]. Case studies can enhance the suspicion index of clinicians about COPD associated with TB.

CASE REPORT

A 92-year-old female with past history of smoking (50 pack-years) and GOLD III COPD, arterial hypertension and dyslipidemia, was using inhaled corticosteroid and bronchodilators. She presented with five AECOPD in the same year, and was hospitalized in three of these episodes with communitarian pneumonia in March, September and November. She underwent the protocol for AECOPD, and bacilloscopy for TB was negative. On last November, she had dyspnea on minimal efforts and cough with yellowish sputum. The chest radiography showed focal alveolar opacities and mild interstitial thickening, in addition to enlargement of the right pulmonary artery and the upper mediastinum

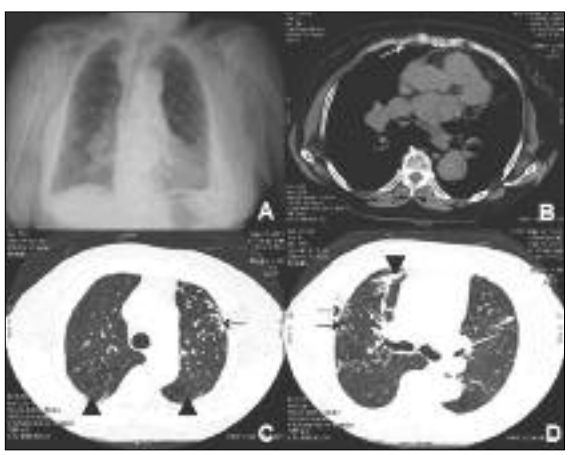

Figure 1 - (A) Chest X-ray showing scattered focal alveolar opacities, mild interstitial thickening, aortic ectasia, and enlargement of the right pulmonary artery and of the right upper mediastinum. (B) CT of thorax showing calcified granuloma in the middle lobe of the right lung (white arrow). (C) Peripheral nodules in airspaces of the left upper lobe (arrows), and multiple signs of centrilobular emphysema in the upper lobes (arrow heads). (D) Sparse centrilobular nodules like "tree-in-bud" (arrows), and alveolar opacity in the right upper lobe (arrow head).

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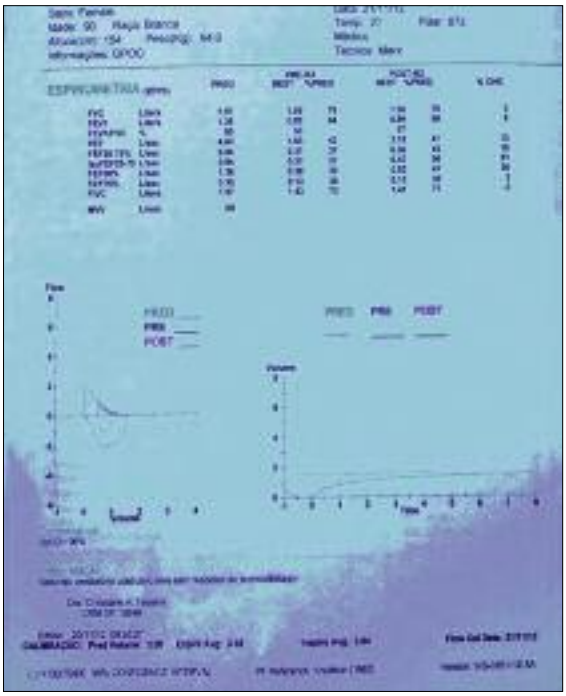

Figure 2 - Spirometry result: mild obstructive lung disease unresponsive to bronchodilators.

(Figure 1A). Computed tomography (CT) images showed a calcified granuloma in the right middle lobe, peripheral nodules in the left upper lobe, emphysema in both upper lobes, sparse centrilobular nodules like "tree-in-bud", and an alveolar opacity in the right upper lobe (Figure 1B, 1C and 1D). A spirometry evaluation revealed mild obstructive lung disease unresponsive to bronchodilators (Figure 2), and administration of levofloxacin resulted in good clinical improvement of breathlessness. The repeated search for AAFB in bronchopulmonary secretions was negative.

However, concomitant with this admission the result of cultures in Lowenstein-Jensen medium, seeded in the last week of September with sputum for the isolation of *M. tuberculosis*, was positive. Worthy of note is that during her previous hospitalizations because of pneumonia she was treated with levofloxacin, which is effective against *M. tuberculosis* and can hinder its growth in the culture medium. However, in September she utilized piperacillin-tazobactam, which allowed obtaining the growth of *M. tuberculosis* in the respective cultures of sputum. Thereafter, the standard therapy for TB with isoniazid along with rifampin, pyrazinamide and ethambutol was administered. Nowadays, the patient is asymptomatic, on routine follow-up.

DISCUSSION

Elderly individuals with COPD and presenting a worsened dyspnea may pose diagnostic challenges in primary care setting, involving various possibilities, including systemic entities, HIV-related infections, pulmonary thromboembolism, atypical acute coronary insufficiency, pulmonary hypertension, heart failure, and pulmonary lymphangitic carcinomatosis [11]. Although the origin of this patient was from a region highly endemic, the diagnosis of active TB coexistent with COPD remained unsuspected for a very long period because of the bacteriological tests repeatedly negative, due to the use of quinolones to treat pneumonias [9]. Tedesco et al. recently described late diagnosis of TB in a young Romanian patient who utilized fluoroquinolones in empiric therapy for communitarian pneumonia. They emphasized the development of *M. tuberculosis* resistance to these drugs and the increase in the mortality rate among people with active tuberculosis and previously exposed to fluoroquinolones [9]. Laurenti et al. highlighted the importance of TB as a leading infectious cause of death overall the world and the increasing rates of this chronic disease in low-endemic regions as well [12]. They called attention for the relative insufficient knowledge of young doctors about TB, which at least in part, may explain the increased tuberculosis rates in low-endemic areas [12]. TB is the major infectious cause of death in the whole world, with prevalence between 1.8% and 9.2%, mainly in low income areas, and can have a mortality rate of 50% if untreated [2]. This chronic disease, as well as tobacco smoking, is associated with development of COPD, and nearly 30% of the patients treated for TB may have pulmonary obstructive disorders [2]. Delay in diagnosis and the late onset of treatment for TB play a major role in this setting [2]. The risk of communitarian pneumonia in patients with COPD is increased with age, low BMI and pulmonary alterations, which propitiate the repetition of the episodes of AECOPD [6, 8]. The frequent use of oral and inhaled corticosteroids, a very common occurrence in patients with COPD, can cause decrease in immunity and increase the risk of developing TB [3, 5, 7]. In medium- and low-income countries effective measures should be implemented for early detection of TB as well as of HIV infection and other immunosuppressive conditions [2-4]. Quinolones with good activity in respiratory

tract are indicated for treatment of AECOPD, and their use in regions with high prevalence of TB has been questioned because of the perception that it contribute to delay in diagnosis of TB and induce drug resistance [1, 2, 8, 10]. Important is to emphasize the increased risk of tuberculosis in individuals with COPD, and the need of repeated search for *M. tuberculosis*, which may be the origin of exacerbations. Moreover, if AECOPD is treated with fluoroquinolones in patients with unsuspected TB, the identification of *M. tuberculosis* can be hindered because this germ is usually sensitive [2, 10]. Studies for latent TB before start using steroid and levofloxacin were negative in this patient. Interferon-gamma release assays for detection of latent TB infection, can found up to 70-85% of positive results in elder people with COPD and silicosis [13]. Therefore, these tests might show the risk of progression of latent TB infections, and propitiate preventive treatments [13]. Clinicians and primary care workers could contribute to early diagnosis and prompt anti-tuberculous treatment if they have enhanced suspicion index about COPD associated with TB.

Competing interests: The authors declare that they have no competing interests
Source of support: Nil

Keywords: COPD, inhaled corticosteroids, levofloxacin, *Mycobacterium tuberculosis*.

SUMMARY

A 92-year-old female ex-smoker with chronic obstructive pulmonary disease (COPD) GOLD III, was admitted because of communitarian pneumonia in November 2013. She had been using inhaled corticosteroids and bronchodilators and presented five exacerbations of COPD due to pneumonia in the same year, with hospitalizations in March and September. The patient underwent the routine protocol for exacerbated COPD, and bacilloscopy for tuberculosis (TB) was negative. On admission, she had intense dyspnea and a productive cough that improved by administration of levofloxacin. Tests with Ziehl-Neelsen staining in bronchopulmonary secretions resulted negative. Notwithstanding, during actual admission, the culture in Lowenstein-Jensen medium seeded in September was found positive for *M. tuberculosis* susceptible to isoniazid, rifampin, streptomycin, and ethambutol. Therefore, the patient underwent the standard regimen for tuberculosis. Except in September, when she used piperacillin-tazobactam, all previous exacerbations of COPD were treated with levofloxacin. This effective drug against *M. tuberculosis* can hinder its growth in culture. The use of levofloxacin in unsuspected TB may constitute an additional diagnostic challenge, and risk of late diagnosis is increased in patients with COPD in use of inhaled corticosteroids. Case studies may contribute to increase the suspicion index about TB associated with COPD.

RIASSUNTO

Una donna di 92 anni, ex-fumatrice e affetta da broncopneumopatia cronica ostruttiva (BPCO) GOLD III, è stata ricoverata in ospedale a causa di una polmonite comunitaria nel mese di novembre del 2013. Nel corso dello stesso anno, aveva fatto ricorso a corticosteroidi e broncodilatatori per via inalatoria; in seguito a polmonite, aveva sviluppato cinque riacutizzazioni di BPCO, con ricoveri in marzo e settembre. La paziente è stata sottoposta al protocollo di routine per riacutizzazione di BPCO; gli esami batterioscopici dell'espettorato per la ricerca di bacilli tubercolari sono risultati negativi. Al momento del ricovero, erano presenti intensa dispnea e tosse produttiva, migliorate in seguito a somministrazione di levofloxacina. La colorazione di Ziehl-Neelsen eseguita sulle secrezioni broncopolmonari ha dato esito negativo. Tuttavia, nel corso di questo ricovero, l'esame colturale condotto a settembre, in terreno Lowenstein-Jensen, ha dato esito positivo per Mycobacterium tuberculosis, *con profilo di sensibilità a isoniazide, rifampicina, streptomicina e etambutolo. Pertanto, la paziente è stata sottoposta al regime di trattamento standardizzato per la tubercolosi. Tranne che a settembre, quando la paziente aveva ricevuto piperacillina-tazobactam, tutte le precedenti riacutizzazioni di BPCO erano state trattate con levofloxacina. Questo antibiotico, efficace contro* M. tuberculosis, *può ostacolarne la crescita in coltura e può quindi creare la premessa per una ulteriore sfida nella diagnosi di tubercolosi. Inoltre, il rischio di una diagnosi tardiva è maggiore nei pazienti con BPCO che fanno uso di corticosteroidi per via inalatoria. La pubblicazione di casi clinici può contribuire ad aumentare l'indice di sospetto di TB associata a BPCO.*

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