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Case Reports

Complicated Silicosis Associated with Mycobacterium tuberculosis Infection

Case presentation and literature review of the TB diagnosis in silicosis

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Abstract

Romania is recognized as the European country with the highest tuberculosis rate in Europe. The association of tuberculosis with silicosis determines synergistic immunosuppression of the alveolar macrophages resulting in a higher grade of pulmonary parenchymal destruction and consequently respiratory failure. The case report approaches a patient with third stage of silicosis and associated active secondary pulmonary tuberculosis disease with positive smears. The impact of the Mycobacterium tuberculosis (MTB) infection's activation is known to be severe, worsening the prognosis of silicosis and reducing the patient's quality of life. Regarding the high morbidity rate of tuberculosis, an early diagnosis of tuberculosis in patients with silicosis is paramount, and sometimes cannot be achieved by usual bacteriological tests. Therefore, a better strategy is to be considered in silicotuberculosis, namely to prevent the progression of the latent tuberculosis foci by testing the positive predictive value of up-to-date tests such as IFN-γ inducible protein 10 biomarker, which may allow early detection and treatment.

Keywords: *silicosis, latent tuberculosis, IFN-γ inducible protein 10 biomarker*

Introduction

Silicosis is a disease caused by inhalation of crystalline silica [1-3]. Although its incidence has dropped with the increasingly safer work ethics, it still is an important cause of potential life cost in people under 65 years old, especially since it may be underdiagnosed [4,5]. The people at risk are mainly those who have a history of exposure to sandblasting, quarrying, mining, stone dressing, or foundry work [2]. Tuberculosis (TB) is an infectious disease spreading easily from person to person through airborne transmission of droplets contaminated with Mycobacterium tuberculosis (MTB). An immunocompetent organism manages to control the infection, causing a so-called latent TB infection (LTBI). However, when the immune system fails, MT manages to multiply causing active TB [6]. Romania is among the countries that bear most of the TB burden in Europe, with an incidence of 72 cases per 100.000 populations in 2017 [7] and silicosis is the second highest risk factors for TB disease, after HIV infection [8].

The present case report approaches a former foundry worker with complicated silicosis associated with tuberculosis. In the discussion section, we take the opportunity to review the mechanisms of this association, as well as the current methods of diagnosis for latent tuberculosis, such as reactive tuberculin skin testing (TST), in contrast with the more efficient method, positive interferon-gamma release assay (IGRA).

We want to assess whether current medical practices in Romania should require a better algorithm of LTBI investigation in order to better serve the needs of complex medical cases, such as silicotuberculosis.

Case presentation

A 53 year-old female is admitted to the Colentina Hospital, Bucharest, Romania, in the department for of Occupational Diseases, complaining of persistent productive cough with mucopurulent sputum and progressive exertional dyspnea with limitation to the mild efforts. The patient is known as a smoker with severe comorbidities as complicated silicosis (stage III silicosis), chronic bronchitis, chronic respiratory failure, blood hypertension stage III (highest values of 190/110 mmHg), ischemic heart disease, grade I of obesity. She is also a hepatitis C virus (HCV) carrier.

The occupational history showed a foundry worker for 18 years in the Romanian automobile industry, where she was exposed to several occupational hazards as free crystalline silicon dioxide, asbestos fibers, casting gases and smoke. By her current admission, the retention time of the respirable dust particles was 36 years.

The clinical exam reveals a severe ill patient, anxious, afebrile but asthenic, hemodynamic stable, with a blood pressure of 140/90 mmHg, a heart rate of 94/min, normal peripheral pulse and SaO2 = 94%. The inspection reveals slightly cyanotic skin coloration. Respiratory system examination showed dorsal kyphosis, and upon auscultation, a rough bilateral vesicular murmur and bronchial rales in both pulmonary fields. Besides accusing pain in the epigastrium upon palpation and having positive Romberg sign, the rest of the clinical exam is within normal limits. The sputum smears showed the presence of numerous acid fast stain bacilli, revealing TB disease diagnosis.

The patient was transferred to the "Marius Nasta" Pneumophthysiology Institute of Bucharest, where first regimen of antiTB standard treatment was initiated.

The evolution was favorable with complete treatment and stable negative conversion of cultures.

Discussion

Silicosis

Silica respirable dust particles reach the alveoli of the lungs. Only a small quantity is cleared and the vast majority gets deposited by initiating an inefficient phagocytosis by the alveolar macrophages and a cascade of inflammatory events. The result of this inflammatory process is the formation of multiple macroscopic nodules visible on imaging techniques, the extended fibrosis and, in some cases, an autoimmune process [1-3]. The process is not a self-limited disease, but the speed of progression is variable, according to the intensity and duration of the exposure and personal risk factors (such as smoking, infections, genetic defense mechanisms or predisposing factors to fibrosis formation). The main concerns come from the complications of this chronic condition, such as airflow limitations, cor pulmonale and cardio-respiratory failure [9]. The association with mycobacterial infection has been reported for many years, but the underlying mechanism is not completely understood. The severity of our patient's evolution, marked by the activation of tuberculosis disease on a susceptible substrate, might be elucidated by considering her exposures as a foundry worker. It has been shown that freshly obtained silica produces more damage to alveolar macrophages, as compared to aged silica. An explanation for the increased toxicity of the former is a greater production of oxidants [10] with the promotion of lung fibrosis through different cytokines, of which TNF alpha is particularly important [11]. Tuberculosis onset was neglected because of her history of respiratory symptoms started in 1999 with frequent paroxystic dyspnea episodes at the workplace for which she was prescribed symptomatic treatment. In 2000, she was diagnosed with Silicosis stage I and, after occupational disease was discovered, she retired. After 8 years of follow up, in 2008, the silicosis became stage III and was associated with chronic bronchitis and cardiovascular comorbidities; however her condition was otherwise unremarkable. Since 2008, the patient has been followed up yearly and evaluated by imaging tests for the silicosis staging and by spirometry for the assessment of respiratory dysfunction progression.

Over the course of the following 10 years, chest radiological lesions staging, interpreted following the International Labour Organization guide [12], revealed a steady progression of the silicosis, complimented by the important progressive deterioration of lung function and aggravation of

of respiratory failure (Table 1). In the last 10 years, from 2008 to 2018, the large lung opacities increased in size from A to C. Functionally, the patient had a slight improvement between 2008 and 2012, only to see a steady, further aggravation afterwards, which still persists in the present. However, it is possible that the apparent initial improvement be due to a bias of the periodic yearly evaluation, as it measures the patient's status at the readmission in the Occupational Diseases Department, with first admission driven by acute symptoms and yearly controls performed in a more stable respiratory status (Figure 1).

Table 1. The evolution of the radiological signs, according to the The International Classification of Radiographs of Pneumoconioses [9] is briefly described below:

2008	2009	2010	2012	2013	2014	2015	2016	2017	2018
A, 3q, hi	A,3pq, hi	A, 3qr, hi	A, 3qr, hi	B, 3qr, hi	A, 3q, hi	B, 3qr, hi	B, 2r, hi	C, 2r, hi	C, 2r, hi

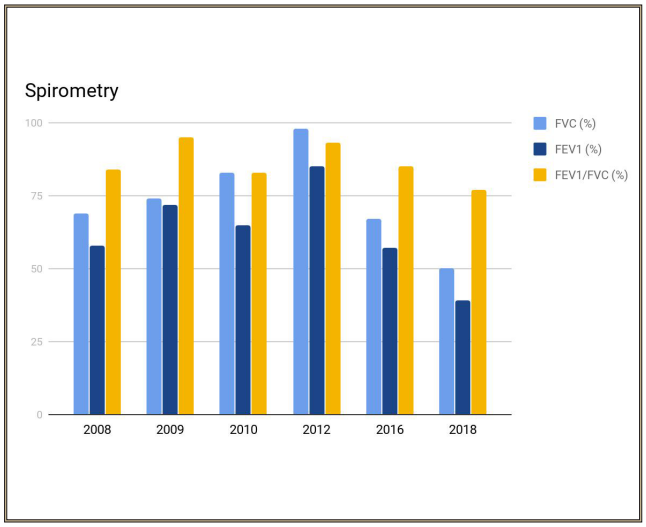

Figure 1. Spirometry tests throughout the years

Silicosis associated with pulmonary tuberculosis

There is plenty of literature on the increased risk of TB in silicosis and even only after silica exposure without manifest silicosis [13,14]. This association is strongly based on epidemiological studies but has also physiopathological explanations such as: 1. silica particles role in the ineffective microbicidal activity of alveolar macrophages, 2. incorporation of infected macrophages as silicotic nodules grow more and more becoming a potential source of TB disease reactivation 3. altered local immunity [15]. The TB mycobacteria that reach the alveoli are phagocytized by the resident alveolar macrophages and start a slow intracellular multiplication process [16]. The macrophages as well as the resident dendritic cells initiate a cellular immune response, which results in the formation of granulomas that either succeed or fail at containing and preventing the progression of the infection, based on the lymphocyte activity and cytokine profile [16,17]. Treated TB patients are known contributors to the rising incidence of the chronic obstructive lung disease by 2.5-fold independent of other factors, including smoking [18]. Obstructive lung disease results from inflammation and airway narrowing, distortion of airways due to cavitation and fibrosis, caseous TB lesions with endobronhial disease propagation, destruction of the elastic and muscular components of the airways forming bronchiectasis [19]. The restrictive airways defect arises from the excessive parenchymal fibrosis of the lung, mediated by TNF-alfa, TGF-beta and IL1-beta, with stiffening of lung parenchyma and pleural thickening. Fibrosis, distortion of lung airways and inflammation are also explanations for the mixed respiratory dysfunction in silicosis. Therefore, it is not surprising that a 5 year outcome of a follow up study in a retrospective silicotuberculosis cohort found a higher excess of FEV1 and FVC decrease (40.3 ml/year and 42.7 ml/year, respectively), compared to silicosis patients [20].

Current control of the Silicosis associated TB focuses on periodic radiological screening, sputum staining if the patient shows specific symptoms and anti-tuberculosis preventive treatment [13, 14].

Current diagnosis guidelines in Romania for active tuberculosis:

TB diagnosis is made following 3 steps, and while clinical and chest radiological examination usually raise suspicion of TB, the specificity is not high enough, particularly in patients with silicosis, in which disseminated lung opacities are already present. The majority of patients have one or two respiratory

symptoms, of which the most common is cough which persists for at least 3 weeks (95%), also associated with dyspnea, hemoptysis, mucopurulent sputum, thoracodynia, night sweats, weight loss, fever, fatigue. The standard radiological examination of the chest is highly sensitive but has low specificity and, sometimes, it is inconclusive because some peculiar radiological pattern of silicosis can mimic miliary TB, confusing the diagnosis [21]. Statistic reports of silicotuberculosis are unavailable in Romania. TST remains the only test recommended in patients with silicosis by Romanian TB Guide [22].

The certain diagnosis of TB disease is made by a sputum bacteriological exam which can take up to 3-8 weeks for solid culture media and 1-2 weeks for liquid culture media of BACTEC MGIT 960 to be validated [23]. In our reported patient's case, the first therapeutic approach to the presenting symptoms was to initiate anti-inflammatory and empirical antibiotic therapy and a complete sputum exam. Amoxicillin/ clavulanic acid and Fenspiride were prescribed but the patient's condition altered. The Ziehl Nielsen exam of sputum revealed the presence of acid-fast bacilli. Appropriate 8 months antiTB treatment was initiated, although it can last longer in severe cases (8-12 months) than the standardized therapy of 6 months [22].

Potential ways of identifying LTBI

Once the host is exposed to MTB, the primary infection is established and latent tuberculosis infection can be diagnosed based on immunological evidence. Host parameters influence the outcome of LTBI - most significantly, host age, immune status, pneumoconiosis and nature of exposure [23]. A current challenge is the ability to identify the presence of LTBI as well as its risk of progression to active TB in order to further provide an effective preventive therapy.

The current diagnosis of LTBI uses two tests: reactive tuberculin skin testing (TST) and positive interferon-gamma release assay (IGRA). TST remains the standard method due to its greater reliability and lower cost [23]. TST consists of an intradermal inoculation of tuberculin purified protein derivative (PPD) and the measurement of the subsequent inflammatory response. IGRA uses the MTB antigens ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein-10) to elicit interferon-gamma (IFN-γ) production. If TST and IGRA results do not overlap, subjects are considered MT infected. This is not the case if BCG-vaccination is provided, because of a higher chance of false positive of the PPD test [23].

IGRAs and TST are weak predictors of LTBI risk of progression. Therefore, it was mandatory to develop new tools for diagnosis of LTBI in order to lower the TB incidence. Interferon-γ inducible protein 10 (IP-10) has been proposed as a tuberculosis biomarker. IP 10 is a chemokine expressed by the antigen presenting cells in response to IFN-γ, determining the CD4+ T cell migration to the inflammation site. IP 10 is a very sensitive biomarker which rises in blood in day-1 after tuberculosis infection and its value decreases after treatment in active tuberculosis infection. Another advantage is that it can also be measured in urine [24,25].

Nowadays, the level of industrial silica exposure is better controlled; therefore, most patients are older than 30 years, the threshold considered in Romania for the latent TB infection. As consequence, in a TB burden country, most patients with silicosis have been exposed to reinfection with Mycobacterium tuberculosis, being at risk of re-activation of the disease. The interferon inducible IP10 sensitivity and specificity has not been yet tested in silicosis patients, but as these patients represent a high risk population, in order to achieve an early diagnosis of TB, there is a need to investigate the predictive value of this test.

The biomarkers of both silicosis and tuberculosis continue to evolve. Research focused on circulating miRNA, the small nucleotides acting as posttranscriptional regulators, had offered interesting results in both diseases. For example, the gene expression in peripheral leucocyte found miRNA-19 significantly lower in the early stage of silicosis. The proposed pathogenic pathway involves the lack of inhibition of the tissue factor by the miRNA-19, with higher expression of this inflammation inducer [26]. In experimental silicosis, miR-1224-5p expression is increased, resulting in the impairment of the mitochondria and the activation of the mitophagy [27]. While the miRNA research in silicosis was focused on the pathogenic pathways, TB researchers were also interested in the discrimination between latent TB infection and active TB disease. For example, distinctive serum panels of miRNAs were found in LTBI, active TB disease, including TB HIV related, extra-pulmonary TB, other pulmonary infectious diseases and, even, in healthy subjects [28]. These findings open the perspective of new diagnostic tools eventually capable to detect TB in an early stage of the transition from LTBI to active TB disease. There are also expectations that innovative therapeutic solutions such as vesicle-mediated gene therapy will

develop based on a better understanding of the circulating miRNAs.

Conclusions

Given the potential severity of the association of silicosis and TB disease, both the current screening algorithm and the medical attitude towards tuberculosis among patients with silicosis are in a great need of improvement. Moreover, the insidious nature of the onset and the clinical ambiguity of respiratory symptoms and signs of active TB disease, mimicking bronchitis, bronchiectasis, chronic obstructive lung diseases make TB diagnosis more difficult and hard to be suspected, causing delayed adequate treatment. Thus, it is clear that a better awareness of the association between pneumoconiosis and tuberculosis is essential, as well as faster and more reliable methods of diagnosis. This would help improve patient's outcomes diminishing tuberculosis infections reservoir in the community.

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