Progressive intraparenchymal lung nodules dissemination in a heavy smoker and seropositive rheumatoid arthritis suspected of tuberculosis relapse

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Abstract

Anthony Caplan first described rheumatoid lung nodules associated with pneumoconiosis in coal-miners (Caplan, 1953). Intraparenchymal lung nodules were later described in rheumatoid arthritis (RA) patients who were never exposed to coal dust and/or without pneumoconiosis. Rheumatoid lung nodules are usually detected in unselected patients: 0.2% in chest radiography and 4% in high-resolution computed tomography (Nannini et al., 2008). Patients could be reluctant to perform surgical lung biopsy for an accurate histopathological diagnosis. We present a peculiar association between a seropositive RA and a presumptive active tuberculosis (TB) disease in a 59-year-old male patient, ex-smoker with a previously healed pulmonary TB disease. The purpose of this report is to describe an unusual case of a presumptive relapse of the nodular TB disease, which progressed to an extensive nodular bilateral dissemination under anti-tuberculosis therapy, mimicking a metastatic carcinoma. The diagnosis of rheumatoid necrobiotic lung nodules was confirmed after open biopsy left pulmonary was performed. Formalin-fixed paraffin-embedded pulmonary rheumatoid nodules were processed for histology and stained with Masson's trichrome. Central structure of the removed pulmonary nodules is typical of a rheumatoid nodule with central necrosis surrounded by a palisade of macrophages. The accumulation of anthracotic pigment was noticed inside the pulmonary nodules in a RA patient without professional exposure to coal or mineral dust. This rare entity is an appearance of the rheumatoid nodules lung syndrome and anthracosis in a heavy tobacco former smoker.

Keywords: tuberculosis, rheumatoid arthritis, anthracosis, pulmonary necrobiotic nodules, tobacco smoking.

Introduction

The pattern of multiple pulmonary nodular lesions with different sizes, small or large, homogenous or not, poorly circumscribed or often irregular in shape could be generally suggestive of malignant or infectious causes, as well [3]. Nodular opacities are a well-known reported pulmonary manifestation of the rheumatoid arthritis (RA) disease, occurring most often in men who smoked and have had high titers of the rheumatoid factor [3]. After interferon gamma (IFN-γ) releasing assays (IGRA) were discovered, necrobiotic rheumatoid nodules in RA patients not treated with tumor necrosis factor (TNF)-α inhibitors could provoke a real diagnostic dilemma in the presence of a positive IGRA test, such as Quantiferon-TB gold in-tube (GIT). The question of an association between rheumatoid arthritis and tuberculosis has been raised since 1955, when Miall suggested that a relationship between the two diseases may exist and could be the so-called “rheumatoid diathesis” [4]. The gold standard of the TB positive diagnosis is considered a positive culture for the Mycobacterium tuberculosis. In the absence of a certain bacteriological exam, the lung biopsy with histopathological exam remains the main method for the etiologic diagnosis of lung nodules.

Patient and Methods

A 59-year-old white man (D.R.), a 30 pack-year ex-smoker, without professional exposure to coal, diagnosed in 2000 with a seropositive form of rheumatoid arthritis, has been concomitantly treated with Methotrexate (20 mg weekly since 2000), Arava (20 mg daily since 2006) and corticosteroids cure (Medrol followed by Prednisone) alternatively with non-steroidal anti-inflammatory agents (as Ketoprofen). In 2005, a pulmonary secondary nodular tuberculosis disease was diagnosed and, after eight months of anti-tuberculosis first regimen of therapy (2 HREZ 7/7 + 6 HR 3/7), a small nodular lesion of 0.8 mm remained in the apical segment of the right upper lobe. Three years later, the patient was suspected of a tuberculosis relapse based on a history of moderate productive cough with whitish sputum, associated sweats, an 8 kg loss of weight during the summer of 2008, a mild exertional dyspnea occurred since November 27, 2008. On November 28, 2008, Quantiferon-TB gold in-tube (GIT) test was performed and the result was a positive one, correlated with a positive tuberculin skin testing. The conventional X-ray done on December 8, 2008 revealed four nodular lesions in the lower lobes of the lung. The patient was admitted to Hospital of Clinical Pneumology...
of Constanta on December 8, 2008, for initiating the anti-tuberculosis second regimen of treatment. The therapy with Methotrexate and Arava was stopped and the arthritis was controlled with a daily therapy with 2 cp of Aspirin. Physical examination of the patient revealed a temperature of 37.2°C, blood pressure of 145/85 mmHg, heart rate 72 beats/min., a normal oxygen saturation of arterial blood (SaO₂=96%), bilateral thickened wrist, metacarpophalangeal and proximal interphalangeal joints with limited motion, pain and swelling, clear breathing sounds without crackles superimposed. A 12-lead electrocardiography (ECG) identified normal sinus rhythm (80 rate), normal QRS axis (+60). Lung function testing revealed normal spiographic parameters (FEV₁=3.44 L; 106%). The patient has been known since youth with an essential tremor of the head and arms with a mild difficulty in performing some of the routine activities of daily living. Laboratory studies disclosed normal values for chemical and hematological constituents of the serum (Hb 13 g/dL, white blood cell count 9000/mm³, neutrophils 6700/mm³, erythrocytes 4.61 millions/mm³), an inflammatory syndrome with high erythrocyte sedimentation rate 72 mm in the first hour, CRP 87.22 mg/L (normal <5 mg/L), a very elevated titer of rheumatoid factor 317.8 (normal <14). The bacteriological exam of sputum revealed negative smears for acid-fast bacilli and negative cultures for bacterial and fungal germs. Relapse of active pulmonary TB disease was strongly suspected based on symptomatic nodular lung lesions seen on a chest X-ray performed in December 8, 2008, and a positive result of an IGRA Test (GIT). The patient refused bronchoscopy and lung biopsy by invoking the essential tremor of the head. After two months of chemotherapy with anti-tuberculosis drugs, repeated chest X-ray revealed the emergence of many additional cavitating bilateral nodules, mimicking a metastatic dissemination and a consecutive high-resolution computerized tomography (HRCT) of the chest was performed on February 2, 2009. A possible lung cancer etiology was considered and the surgical method for a lung biopsy was recommended. Open limited left thoracotomy was performed in March 2009, in the “Marius Nasta” Pneumology Institute, Bucharest, and three nodular lesions of the lingula and Fowler segment were removed. The macroscopic and microscopic assessments of the lung tissue were performed by using standard procedures in the Department of Clinical Anatomopathology of the “Marius Nasta” Pneumology Institute. After fixation in 10% buffered formalin, specimens from the lingula and Fowler segments were cut into slices and paraffin embedded. Step sections of 5 μm thick were stained with routine morphologic methods of Hematoxylin and Eosin, Masson’s trichrome, Grocott.

Results

A RA patient with a high-risk of TB sustained by the prolonged immunosuppressive therapy was admitted for hospitalization on December 8, 2008. Relapse of active pulmonary TB disease was strongly suspected based on symptomatic nodular lung lesions and a positive result of an IGRA Test (GIT). The chest radiography performed on December 8, 2008, showed flattening of the left hemidiaphragm and four nodular opacities in both lower lobes, one placed in the right lower lobe, homogenous, 3.5/4.3 cm, three placed on the left, two homogenous and one containing a 1.5/2.5 cm cavity. In addition, in the right upper lobe, there was one stable 8 mm round homogenous lesion, well-defined, placed in the apical segment of the upper right lobe (known as a TB sequel; noticed since 2005) (Figure 1).

Persistent respiratory symptoms since the summer of 2008 included persistent dry cough and shortness of breath. Chemotherapy with anti-tuberculosis drugs was considered the most appropriate specific therapy but the evolution was not the expected one. Repeated chest X-ray, after two months of treatment, on January 29, 2009, revealed a rapid nodular growing and the emergence of many additional cavitating bilateral nodules, ranging in size from 2 to 3.5 cm, and some showed cavitation areas inside the nodules with a diameter between 5 to 25 mm. These multiple nodules varied in size and were similar in appearance to opacities caused by a metastatic disease. A HRCT scan of the chest performed on February 2, 2009, showed numerous coin-like nodules disseminated throughout the lung fields, mostly near pleural spaces, well defined, with sizes ranging from a minimum of 6 mm to a maximum of 38 mm, each net shape, homogenous and non homogenous, bilateral bronchiectasis, emphysema bubbles, bilateral pleural thickening (Figure 2).

Associated fatigability, persistent dry cough and progressive loss in weight (an additional loss of 5 kg in the last two months) raised the suspicion of a metastatic lung cancer and surgical intervention was recommended and finally accepted by the patient. Open limited thoracotomy, performed in the Department of Thoracic Surgery, “Marius Nasta” Pneumology Institute, removed four lung nodules with different sizes (2.5/2.2 cm, 1/0.6/0.6 cm, 0.8/0.8 cm, 0.5/0.5 cm) of the lingula and left Fowler segment. The morphological exam revealed three cavitating pulmonary gray nodules from 0.8 cm to 2.8 cm and moderate fibrotic thickening of the interstitium. The microscopic examination of the Masson’s stained samples revealed pulmonary nodules with a central zone of fibrinoid degeneration and collagen necrosis,
surrounded by an immediate zone of proliferating cellular elements (patchy palisade of histiocytes, palisading mononuclear cells, proliferating fibroblasts, eosinophils and siderophages) and a peripheral area of inflammation consisting in a minimal lymphocytic infiltration (Figure 3).

Figure 2 – (a–d) HRCT scan of the chest performed on February 2, 2009, showed numerous round shaped nodules coin-like disseminated throughout the lung fields, mostly near pleural spaces, well-defined, with regular margins, sizes ranging from a minimum of 6 mm to a maximum of 38 mm, each net shape, homogenous and non homogenous, one of them with a small eccentric calcification (a).

Figure 3 – Slides 1 to 4, Masson stain, ×100. Slides 1 and 2: The specimens show pulmonary nodule with a clear center which reveals central necrobiosis, a middle zone of palisading well defined macrophages, and lymphocytes, an outer layer of fibrotic capsule and anthracotic inclusions suggestive for anthracosis; Slide 3: One lymphoid node surrounded by a palisade of alveolar macrophages, coniofages and siderophages; Slide 4: Subpleural lung tissue with a minimal lymphocytic infiltration, a deposit of anthracotic pigmentation, surrounded by a fibrous capsule- possible etiology of anthracotic arthritis.

This chronic inflammatory infiltrate including necrobiotic debris, was surrounded by fibrous tissue. The histological findings are very consistent with the diagnosis of rheumatoid pulmonary necrobiotic nodules. The boundary between the necrotic centre and the outer area of the fibrous shell represents one of the characteristics of the rheumatoid nodule, which is known as a cellular palisade. The palisade consists in a densely packed layer
of cells as macrophages and fibroblasts, which are arranged radially. Chemotherapy against TB was no longer useful and it was stopped. Surgical removal and biological treatment with Adalimumab started for the rheumatoid arthritis lung nodular syndrome were successful. All the so-called previous “metastatic” bilateral pulmonary lesions disappeared in the next three months and did not appear again since July 2012. Smears and cultures of the sputum for *Mycobacterium tuberculosis* were constantly negative after one year.

**Discussion**

The pulmonary nodule is radiologically defined as an intraparenchymal lung lesion with a diameter less than 3 cm, which is not associated with atelectasis or adenopathy [3]. Lung lesions greater than 3 cm in size are defined as lung masses and frequently suggest lung cancer. The differential diagnosis of pulmonary nodules is usually made between malignancy, benign tumor and infection. Metastatic malignancy is considered the most common cause of multiple nodular lesions spreading in the lungs [3]. The incidence of malignancy in pulmonary nodules ranges from 50% to 75% [4–8] and it is recommended that all pulmonary nodules should be considered malignant by clinicians until proven otherwise [9]. Non-infectious benign etiologies for pulmonary nodules include rheumatoid nodules, hamartoma, plasma cell granuloma, silicotic nodule and sarcoidosis [10]. Rare causes include parasitic infections, intrapulmonary Castleman’s disease and inflammatory pseudotumor [11]. In the presence of RA, pulmonary nodules may mimic any malignant neoplasm or tuberculosis. Caplan described, in 1953, a syndrome of nodular lung fibrosis and rheumatoid arthritis in more than 50% of coal miners [1]. Later, it was demonstrated that nodular involvement in this variety tended to be more discrete than the usual variety of pulmonary fibrosis with frequent coalescence and cavitation of the nodule [6]. Initially, RA was considered to be three times more common in women than in men [12] but the nodular rheumatoid pulmonary disease occurs more commonly in smokers (which may explain the male preponderance). A positive smoking history is not always helpful in differentiating between carcinoma and rheumatoid lesion [4]. In fact, the radiographic characteristics of rheumatoid nodules are nonspecific: they tend to occur near pleural surfaces, are usually bilateral, often produce minimal pulmonary symptoms, with excavation in one-third of the cases, and, occasionally, can rupture into the pleural space producing spontaneous pneumothorax [5, 6, 10, 12]. Rheumatoid nodules are rarely seen as a solitary lesion in the lung. They are multiple and variable in appearance and most times may resolve spontaneously, without relation to the course of the arthritis. If pulmonary nodular lesions are clinically asymptomatic, they require no treatment unless they become quite large, infected or cavitated with bronchopleural fistula [10–12].

The systemic nature of the RA disease was first suggested by Ellman and Ball in 1948 [12] and pulmonary involvement included five categories of lesions (pleuritis with or without effusion, rheumatoid pneumoconiosis known as Caplan’s syndrome, discrete nodules with or without cavitation named necrobiotic nodules, diffuse interstitial disease and pulmonary arteritis hypertension) [13]. Necrobiotic lung nodules are usually multiple and pleural based in the middle and upper pulmonary zones, occurring most often in men who have subcutaneous nodules and other systemic manifestations of RA [11–13]. In the literature, there are a few reports of lung carcinoma coincident with RA. Blodgett RC Jr et al. [15] and Shenberger KN et al. [16] reported carcinomas directly adjacent to rheumatoid nodules. Meyer EC and Liebow AA (1965) reported 32 cases of bronchogenic carcinoma associated with pulmonary fibrosis, the chronic parenchymal inflammation and fibrosis occurring in the rheumatoid disease may be the inciting factor in malignant transformation of regenerating alveolar and bronchiolar epithelium [17]. It has been suggested that cigarette smoking may cause synergistic lung damage with rheumatoid disease [13]. In our male ex-smoker patient, with an eight-year history of RA, it was an unusual case of metastatic rheumatoid pulmonary nodular pattern preceded by two months of administration of anti-tuberculosis chemotherapy. The presumptive pulmonary TB disease diagnosis was based on a positive Quantiferon-TB Gold In-Tube test and bilateral distribution of nodular pulmonary lesions in the lower lobes. Necrobiotic nodules represent a real diagnostic dilemma for the clinicians. The majority of recorded intrapulmonary nodules have been in patients with longstanding seropositive RA, occur more frequently in men than women and the etiology is usually confirmed only after open thoracotomy [18]. Cavitation of a nodule, often indicative of malignancy, may also be present in inflammatory and infectious granulomatous disease such as tuberculosis [12]. In the absence of symptoms, cavitating represents a great problem in differential diagnosis but, when symptoms are present, they may suggest tuberculosis mainly in patients from a TB burden area. Therefore, in these exposed individuals, RA is a chronic autoimmune disease considered a risk factor in pulmonary tuberculosis disease. Differences in underlying risk factors for tuberculosis are difficult to estimate but the concomitant use of Methotrexate or corticosteroids, the severity of the rheumatic disease itself could all raise the potentially TB infection and disease risk. For the immunologic diagnosis of the *Mycobacterium tuberculosis* infection, the tuberculin skin test has many limitations. The newly available IGRA tests (Quantiferon-TB Gold In-Tube and T-SPOT. TB assay) measure the production of IFN-γ by T-cells after sensitization with *Mycobacterium tuberculosis* antigens. The advantage of GIT is the potential ability to discriminate between tuberculosis infection and previous use of Bacilli Calmette-Guérin vaccine or atypical mycobacteria reactivity [19] but any of the ELISA-IGRA tests cannot differentiate between latent or active tuberculosis. That differentiation needs to be done in the clinical and radiological context. Positive GIT test in our RA patient without administered TNF-α blocking agents is uncommon but possible in the presence of a high-TB infection risk. In our case, positive GIT is suggestive only of latent TB reinfection. The probability
of malignancy was the decisive factor in open thoracotomy. This method is more invasive than the video-assisted thoracoscopy but more effective in obtaining a histological diagnosis. Open thoracotomy and resection of Fowler and lingula allowed the pathologic examination of the removed lung nodules and revealed the etiology.

Conclusions

A RA patient with pulmonary nodules living in a TB burden area may arise a difficult diagnostic dilemma, especially when history of smoking, TB disease, and immunosuppression are involved. This is an unusual case of progressive dissemination of necrobiosis in a rheumatoid arthritis patient with a previous tuberculosis disease and a recent latent tuberculosis reinfecion based on positive GIT test. Concluding, an approach to disease management of RA using IGRA-tests is of considerable interest in patients who are highly exposed to TB and present a pulmonary nodular pattern but has no value for the positive diagnosis of TB disease. The lung biopsy and a three-color staining protocol of the yielded tissue, such as Masson’s trichrome, are strongly recommended to be used for establishing the certain etiology. The histological pattern of anthracotic inclusions inside one of the rheumatoid lung nodules is an uncommon feature but could be indicative for anthracosis because of indoor pollution and tobacco smoking exposure.

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References


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