PLEUROPULMONARY MANIFESTATIONS OF ANKYLOSING SPONDYLITIS: A LITERATURE REVIEW

Eugerta Dilka[1,2], Valbona Duraj[3], Klara Ziu[1], Luljeta Hoxha[4]

[1]University Hospital "Shefqet Ndroqi", Tirana, Albania

[2] Faculty of Medicine, University of Medicine, Tirana, Albania

[3]Rheumatologist, University Hospital Center "Mother Teresa", Tirana, Albania

[4]University of Florida Hospital, Jacksonville, Florida, USA

Correspodent E-mail: eugerta@yahoo.com

ABSTRACT

Ankylosing spondylitis is a chronic seronegative spondyloarthropathy, which results in ankylosis of the spine and sacroiliac joints, although involvement is also seen in large and small joints. AS is a chronic, multisystem inflammatory disease of unknown etiology. *HLA-B27* is the gene with the strongest association. Although classically thought of as a spinal disease, it can also involve other organs, such as the eyes, lungs, and heart. Pleuroparenchymal involvement is uncommon and is seen in the later stages of the disease. Pulmonary involvement in AS is usually in the form of upper lobe fibrocavitary disease

Keywords: Ankylosing spondylitis, pleuropulmonary, HRCT

MANIFESTIMET PLEUROPULMONARE TË SPONDILITIT ANKILOZANT: RISHIKIM LITERATURE.

ABSTRAKT

Spondiliti ankilozant është një spondiloartropati kronike seronegative, e cila rezulton në ankilozë të shtyllës kurrizore dhe nyjeve sakroiliake, megjithëse përfshirja vërehet edhe në nyje të mëdha dhe të vogla. AS është një sëmundje inflamatore kronike multisistemike me një etiologji të panjohur. HLA-B27 është geni me lidhjen më të fortë. Edhe pse klasikisht mendohet si një sëmundje e shtyllës kurrizore, ajo mund të përfshijë organe të tjera si sytë, mushkëritë dhe zemra. Përfshirja pleuroparenkimale është e pazakontë dhe shihet në fazat e mëvonshme të sëmundjes. Përfshirja pulmonare në AS zakonisht është në formën e sëmundjes fibrokavitare të lobit të sipërm.

Fjalë kyçe. Spondiliti ankilozant, pleuropulmonare, HRCT

I. Ankylosing spondylitis.

Ankylosing spondylitis (AS) (less commonly known as Bechterew disease or Marie-Strümpell disease) is a chronic seronegative spondyloarthropathy, which results in fusion (ankylosis) of the spine and sacroiliac (SI) joints, although involvement is also seen in large and small joints (1), with the major histocompatibility antigen HLA B27 (2). Traditionally, it was thought there was a male predilection of 3:1 or more. The disease usually manifests in young adults, with the first symptoms becoming evident in the third decade, although up to 18% of cases manifest in the second decade (1). AS is a chronic, multisystem inflammatory disease of unknown etiology (3). Patients are rheumatoid factor (RF) negative, hence seronegative. *HLA-B27* is the gene with the strongest association. Other possibly contributing genes include *ERAP-1*, *IL23R*, and TNF-associated genes (4). Diagnosis requires showing sacroiliitis on imaging or spine inflammation using MRI. Treatment is with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or tumor necrosis factor inhibitors or interleukin-17 (IL-17) inhibitors and physical measures that maintain joint flexibility (5).

Although classically thought of as a spinal disease, it can involve other organs such as the eyes, lungs, and heart (6). Systemic manifestations of ankylosing spondylitis occur in approximately 25% of patients (7).

II. Pleuropulmonary manifestations of ankylosing spondylitis

Ankylosing spondylitis, a chronic multisystem inflammatory disorder, can present with articular and extra-articular features. It can affect the tracheobronchial tree and the lung parenchyma (8).

Pleuroparenchymal involvement is uncommon and is seen in the later stages of the disease or may follow an asymptomatic clinical course (9,10), and the rate of abnormal findings increases with increased duration of AS (3). The lung parenchymal involvement generally occurs many years after the onset of arthritic changes (11).

Pulmonary involvement can be both direct and indirect: Direct involvement is via the development of interstitial lung disease. Indirect involvement occurs when joints of the thoracic cage, such as the costovertebral joints, become fused; thus, movement is limited, and chest wall compliance is reduced (12).

The most frequently seen symptoms are upper lobe fibrobullous disease, interstitial lung disease, pleural thickening, pleural effusion, and the formation of mycetoma (9,13). Less often, emphysema, pneumothorax, and cor pulmonale have been reported (13). Upper lobe cavitary lesions are late complications secondary to fungal and mycobacterial infections (14, 15).

These changes seen in AS were observed using X-rays, respiratory function tests, bronchoalveolar lavage, and transbronchial biopsy in previous studies (9). HRCT changes have been described in more recent studies; however, these studies have involved only a

small number of patients. The highest number of patients included in these studies was 55 (16). In addition, fewer HRCT findings were evaluated (3).
Respiratory complications also include obstructive sleep apnea (8).

II.1. The most frequently seen pleuropulmonary manifestations are:

a. *Apical fibrobullous disease*. Ankylosing spondylitis is a common cause of pulmonary apical fibrocystic disease; early involvement may be unilateral or asymmetrical, but most cases eventually consist of bilateral apical fibrobullous lesions, many of which are progressive with coalescence of the nodules, formation of cysts and cavities, fibrosis, and bronchiectasis (8).
Upper lobe fibrobullous disease is the most common lung manifestation described in 1.3% to 30% of patients with ankylosing spondylitis (17,18).
Bilateral apical scarring is believed to be the earliest pulmonary manifestation (18). Apical/upper lobe predominant interstitial lung disease with small cystic spaces (in ~1% of patients) (19).
Pulmonary fibrosis is a rare manifestation of ankylosing spondylitis, which may be complicated by infection and haemorrhage, and determines the dismal prognosis of these patients (20).
b. *Mycobacterial or fungal superinfections* of the upper lobe cysts and cavities occur commonly. Aspergillus fumigatus is the most common pathogen isolated, followed by various species of mycobacteria. The prognosis of patients with fibrobullous apical lesions is mainly determined by the presence, extent, and severity of superinfection (8).
c. *Chest wall restriction*. The restrictive ventilator defect may develop because of either fusion of costovertebral joints and ankylosis of the thoracic spine or anterior chest wall involvement (11). The most common thoracic finding in ankylosing spondylitis (AS) is ankylosis of the costovertebral joints with severe limitation of chest expansion, inducing a restrictive syndrome. Pleural and pulmonary fibrosis can occur during the disease (21). The lung is involved in up to 30% of patients with chest wall restriction, and upper lobe fibrosis is the commonest (13,22).
d. *Apical pleural thickening* in ankylosing spondylitis is common in association with apical fibrobullous disease (23). Pleural disease is otherwise rare (24).
e. *Pleural effusion* is extremely rare (18). Pleural effusion occurs in autoimmune connective tissue diseases as a part of the inflammatory component. It could also be due to serositis related to ankylosing spondylitis (25). Pleural effusion due to connective tissue disease (CTD) develops secondary to increased capillary permeability due to immune or non-immune inflammation (26).
Pleural effusion is often associated with apicobullous disease (27). Isolated pleural effusion may be seen in patients with AS without a simultaneous apical fibrobullous involvement of the lungs, and it responds well to corticosteroid (28).
f. A recent survey has suggested that in the absence of ankylosing spondylitis, the presence of *HLA B27* may be associated with an increased frequency of pleurisy and spontaneous pneumothorax (29). There is a higher risk of pneumothorax in patients with AK, and it may be recurrent in some (11).

II.2. Epidemiology of pleuropulmonary manifestations

Lung parenchymal involvement is reported in different studies with a small number of cases, ranging in frequency ratios (3).
The rate of pleuroparenchymal involvement has been reported in various small clinical studies to be 0%-85% in X-ray or high-resolution computed tomography (HRCT) studies

(9,10,13,16,18,30-38). The incidence of pleuropulmonary involvement shows a big variation in the literature, probably as a result of selection biases (2).
Pulmonary manifestations are rare, causing upper lobe fibro cavitary disease (18). These have a significant variation in the literature (39). Dudley-Hart et a1 (40) reported two patients with a history of pleurisy, and one of them had a pleural effusion in 1950. Zorab has reported one tuberculous and one non-tuberculous pleural effusion among 53 cases of ankylosing spondylitis in 1962 (29). Crompton et al noted bilateral pleural calcification in 255 patients with ankylosing spondylitis, unrelated to tuberculosis or asbestos exposure in 1974 (41). Kinnear and Shneerson had reported only pleural effusion without apical involvement (42). These effusions were bilateral (18) or unilateral (39,42) and recurrent (42,43). There were pleural effusions coexistent with pericardial effusion in some cases (44). Spencer et al described bilateral pleural thickening in one out of 200 patients with ankylosing spondylitis (45). The temporal relationship between activity in the spinal and pleural disease or the response to treatment was not observed (24).

II.3. Diagnosis of pleuropulmonary manifestations

Chest radiographic findings may mirror the severity of clinical involvement (8).
Computed tomography is useful in delineating the extent of pleural thickening, bullous changes, volume loss, parenchymal fibrosis, and bronchiectasis, as well as identifying or excluding intracavitary pulmonary mycetoma (22).
HRCT is useful to evaluate early lung parenchymal changes in patients with AS (3). HRCT examination of the lungs may show the presence of parenchymal micronodules, parenchymal bands, subpleural bands, interlobular and intralobular septal thickening, irregular interfaces, ground glass opacities, consolidation, mosaic pattern, bronchial wall thickening, bronchial wall dilatation, thickening, emphysema, rib cage asymmetry, honeycomb appearance, structural distortion, apical fibrosis, and other additional findings (3). Cavitation is uncommon and was reported in only 0.45 patients in one series (41).
There is no correlation between the radiological extent of the disease (spinal changes and pulmonary involvement) and any of the haematological or biochemical parameters measured (30).
Pleural effusion developed in AS patients is usually exudative with a normal pH and glucose values. Inflammatory cells, including eosinophils, have been identified in cytological examination (26, 46). Other than involvement of the pleura, pleural effusion can be secondary to the drugs (sulfasalazine therapy) used for treatment of AS (47) or bilateral transudative effusion due to involvement of the heart (48,49).
It can be diagnosed via exclusion of other etiologies such as parapneumonic effusion, tuberculosis, and malignancies. Pleural biopsies can be performed and mainly result in chronic inflammation (50).
Pulmonary function test results are nonspecific and generally parallel the severity of parenchymal involvement. Restrictive ventilatory impairment can develop in patients with ankylosing spondylitis because of either fusion of the costovertebral joints and ankylosis of the thoracic spine or anterior chest wall involvement (8).

II.4. Treatment of pleuropulmonary manifestations

No treatment has been shown to alter the clinical course of apical fibrobullous disease. Although several anti-inflammatory agents, such as infliximab, etanercept, and adalimumab, are being used to treat ankylosing spondylitis, their effects on pulmonary manifestations are unclear (8).

The treatment of AS-associated pleural effusion is not well documented (50). Pleural effusion resolves spontaneously in some cases. However, systemic or local steroids or phenylbutazone had been effective in the pleural effusion (51), as recurrence may be a prominent feature of the disease, as in our case. Systemic prednisolone (30 mg daily) (42), local administration of steroids (20 mg prednisolone locally to the pleural cavity after complete drainage of the effusion) (51), or phenylbutazone (200 mg daily) (43) had been successfully used in the treatment of pleural effusion (2).

II.5. Prognosis of pleuropulmonary manifestations

Pulmonary parenchymal disease is typically progressive, and cyst formation, cavitation, and fibrosis are seen in advanced cases (8).

CONCLUSION

Ankylosing spondylitis, beyond its skeletal involvement, may be associated with significant pleuropulmonary manifestations that usually appear in the later stages of the disease and often remain clinically silent for a long time. The most frequent pulmonary finding is apical fibrobullous disease, which may be complicated by fungal or mycobacterial superinfections and can markedly worsen prognosis. High-resolution computed tomography is the most sensitive imaging modality for the early detection of pulmonary abnormalities and should be considered in patients with long-standing disease or respiratory symptoms. Early recognition and a multidisciplinary approach are essential to optimize management and improve patient outcomes.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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