Mechanisms of Pleural Involvement in Orphan Diseases

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Abstract
Over the past 10 years, the widespread clinical applicability of semi-invasive and noninvasive diagnostic tools including medical thoracoscopy and ultrasonography has expanded the occurrence of pleural effusions to include several rare diseases such as granulomatous, connective tissue and autoimmune disorders including sarcoidosis, granulomatosis with polyangiitis (Wegener’s), systemic sclerosis, lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, amyloidosis, Langerhans cell histiocytosis, and others. The purpose of this review is to summarize the current state of the knowledge regarding pathogenetic mechanisms of pleural involvement in rare disease entities and to highlight the need for more efforts to understand the underlying mechanisms for a more effective therapy.

Introduction
In the normal pleural space, there is a steady state in which there is a roughly equal rate of formation (entry) and absorption (exit) of liquid. This balance must be disturbed in order to produce a pleural effusion (PE). Thus, there must be an increase in the entry rate and/or a reduction in the exit rate. It is likely that both mechanisms contribute to effusion formation. No single mechanism is likely to explain the development of a PE. It is likely that, for many effusions, multiple factors contribute to effusion formation. In addition, alteration of one mechanism can lower the threshold for effusion formation later by another mechanism [1]. Direct involvement of pleural membranes by disease can lead to a PE by increasing the formation of liquid and interfering with parietal pleural lymphatic function. Hydrostatic pressure elevations can also increase filtration from the pleural membrane microvessels [2]. Most of the PEs accompanying systemic autoimmune disorders are exudative and lymphocytic [3]. However, many patients could have concomitant diseases, making the discrimination of an exudative or transudative disease difficult [4].

In this review we will focus mostly on the rare autoimmune diseases involving the respiratory system, avoid-
ing an exhaustive presentation of all rare pulmonary diseases. We emphasize that the underlying pathogenetic mechanisms are poorly understood since there is a significant lack of knowledge regarding systematic and basic studies (table 1) [5].

Sarcoidosis

Pleural involvement in sarcoidosis with the development of PE has been regarded as a rare complication. The incidence of PE ranges from 0.7 to 10% among patients with sarcoidosis [6–9]; however, the origin of this controversial percentage is the absence of an exhaustive workup to confirm pleural involvement. Until recently there have been only rare cases [10] of massive effusions that could occur with any radiographic stage of sarcoidosis, although the majority of sarcoidosis patients have been reported to develop PE at stages I–III [11].

Nevertheless in all series the detection of pleural fluid relied on chest radiographs, which lack sensitivity in detecting minimal amounts of pleural fluid. To this end Huggins et al. [12] performed the only prospective study so far to estimate the exact incidence of PEs in a large cohort of 181 outpatients with sarcoidosis by applying ultrasoundographic analysis and demonstrated a relatively rare occurrence of PEs in 5 patients (2.8%). Pleural fluid analysis corroborated earlier findings showing lymphocyte-predominant exudate in 4 out of 5 patients, while the fifth patient developed a transudate.

Sarcoidosis-related PEs occur slightly more commonly in the right lung (45%) than in the left lung (33%) [11]. The reason for the right-sided predominance is unclear and is not related to organ involvement. Bilateral effusions have been reported in 22% of cases [11].

The mechanism of PE formation in patients with sarcoidosis is presumably similar to that of other infiltrative diseases. Involvement of the pleura may lead to increased capillary permeability with minimal pleural space inflammation. Superior vena cava obstruction [13], endobronchial sarcoidosis leading to bronchial stenosis and lobar atelectasis [14], trapped lung [15, 16], and lymphatic disruption with the development of chylothorax have been reported as causes of sarcoid-related PEs [13].

Consequently, based on the above suggested mechanisms, the observation that pleural sarcoidosis is more frequent in the presence of active widespread parenchymal disease and following disease progression the incidence of PEs declines, while pleural thickening and pneumothorax increase, seems conceivable and rational. Finally, we should always bear in mind that not every PE in patients with sarcoidosis is related to disease itself. Therefore, sarcoidosis patients that present with PE should be carefully evaluated for other coexisting conditions including tuberculosis, congestive heart failure and malignancy. A definitive diagnosis of sarcoid PE relies on pleural biopsy revealing noncaseating granulomas and a negative acid-fast-bacilli stain [10].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with multisystem complications leading to chronic inflammation and immune complex deposits in several tissues and organs including the lungs and pleural space. PE is common in SLE patients and is included as a diagnostic criterion for SLE. Clinically apparent PEs have been reported in 30–50% of patients with SLE during the course of their illness [17, 18]. They are invariably exudative, with higher glucose and lower lactate dehydrogenase levels than those found in rheumatoid arthritis (RA) [17]. Antinuclear antibody (ANA), anti-DNA antibodies, and lupus cells have been found in pleural fluid [17]. Lupus cells appear to be relatively specific [19].

Suggested pathogenetic mechanisms of pleural fluid accumulation in SLE patients include the following: (1) autoimmune reaction, as indicated by deposits of immunoglobulin on the visceral pleura [20], or (2) secondary cardiopulmonary complications of SLE such as heart failure, infection, pulmonary emboli, and rarely lupus nephritis [17]. Regarding the first mechanism, data support the premise of a lymphocytic and plasma cell infiltration that can lead to increased pleural fluid production due to increased capillary permeability and impaired pleural fluid absorption on the inflamed pleura. Consequently, it has been demonstrated that pleural thickening and lung restriction (shrinking lung) due to fibrotic changes and fibrinous pleuritis is characteristic in untreated chronic conditions [21].

Unfortunately, there is a significant lack of evidence regarding the histologic changes of pleural disease in SLE which could provide pivotal information toward the understanding of the pathogenetic cascade driving pleural fluid accumulation. The latter represents a consequence of the original inadequacy of autopsy studies to provide such evidence since they represent the end result of multiple episodes, leading to fibrotic changes that mask the preceding lesions [17, 22]. In particular, an autopsy study...
of 54 SLE patients clearly demonstrated that in 40% of patients acute fibrinous pleuritis was present. Furthermore, pleural thickening and fibrosis reflected the presence of previous inflammation in almost one third of the studied population. Thoracoscopy has revealed nodules on visceral pleura, and immunofluorescence of biopsy samples of these nodules revealed immunoglobulin deposits [17, 22]. Further studies utilizing the beneficial diagnostic advantages of medical thoracoscopy in serial time points through the disease course in SLE patients presenting with PEs are required to delineate etiopathogenic mechanisms and provide data of high scientific rigidity.

**Systemic Sclerosis**

Scleroderma is a connective tissue disease causing fibrosis of the skin and visceral organs such as the lungs, gastrointestinal tract, and heart [23]. Based on current data...
reports in the literature, PEs only rarely occur in the context of systemic sclerosis (less than 10%) both in limited and diffuse form. Scleroderma patients are more likely to present with pericardial effusion rather than pleural involvement. Nevertheless, a retrospective analysis of the archives of 37 scleroderma patients revealed a frequency of PEs equal to 7% of the studied population. PEs were predominantly lymphocytic; however, there have been reports in the literature of eosinophilic infiltration [10, 17, 23].

Etiologic factors leading to pleural fluid accumulation are largely unknown and in the absence of histopathologic studies only suggestions can be made regarding this issue. Based on scleroderma pathogenetic data it is conceivable to speculate that circulating immune complexes, complement elements, lymphocytes, and proinflammatory cytokines encompassing the profile of autoimmune serositis may lead to activation of mesothelial cells resulting in excessive pleural fluid production. Additionally, it has been suggested that CA-125 levels might reflect the activity of serositis since they are usually within the normal range in the absence of pleural involvement [10, 17, 23]. Finally, based on histopathologic data from systemic sclerosis patients with interstitial lung involvement, where evidence of active or anecdotical septal capillary injury driven by antibodies against endothelial cells was present, one can easily suggest that microvascular injury resulting in increased capillary permeability could provide a possible explanation [24].

Nevertheless, biopsy studies coupled with detailed histopathologic analyses are needed to shed further light on the disease pathogenesis.

Rheumatoid Arthritis

RA is a chronic, systemic autoimmune inflammatory disorder with multisystem complications that may produce diffuse inflammation in several organs and tissues including the lungs and pleura. Pleural involvement is reported to be the most frequent intrathoracic manifestation of RA [25]. However, one of the largest retrospective analyses so far of 516 patients with RA revealed a relatively rare occurrence of PEs (3.3% or 17 patients) [17, 26]. These results were further corroborated by another study encompassing 289 RA patients where only 11 patients (3.8%) who underwent CT of the chest wall were reported to have PE [27]. PEs were in most cases small, asymptomatic, and of no clinical significance [28]. In addition, among 2,346 patients evaluated for the etiology of exudative PE, only 14 patients (0.6%) were identified as suffering from RA-associated PE [29–32]. Very rarely, PE is the first presentation of RA. Pleural fluid associated with RA is characterized by being aseptic and exudative, with a low glucose content and reduced pH [10, 17, 25].

Pivotal evidence regarding potential pathogenetic mechanisms driving pleural fluid infiltration has been derived from detailed histological studies in 9 patients who underwent thoracoscopic biopsies [33]. The PE in RA is thought to be caused by rheumatoid nodules on the parietal pleural surface which increase the permeability of the pleural capillaries [33]. Mesothelial cells are replaced by a pseudo-stratified epithelioid cell layer that may be multinucleated and of macrophage origin. This layer is easily detached and leaves a denuded inflamed pleural surface, a pattern described as ‘an opened out rheumatoid nodule with palisading epithelioid cells’, and multinucleated giant cells and characteristic elongated ‘tadpole’-shaped cells on a background of granular necrotic material of decaying leukocytes; the ‘tadpole’ cells have been shown by staining to be of macrophage origin [46, 50]. These histopathological findings in the pleura are considered by Naylor [19] to be pathognomonic for RA-associated PE and similar to the findings seen in RA synovitis [19, 34, 35]. Classic rheumatoid nodules on the pleura are seen occasionally in thoracoscopic biopsies; however, they are rarely detected in small pleural samples obtained by closed pleural biopsy [33].

The high cellular content seen in RA-associated PE has been reported to be due to exfoliation of inflammatory cells from the rheumatoid nodules [19, 34, 35].

Sjögren’s Syndrome

Sjögren’s syndrome (SS) is a chronic inflammatory disease characterized by dryness of the mouth (xerostomia), the eyes (keratoconjunctivitis sicca), and other mucous membranes. Pleuritis with or without PE is exceedingly rare in primary SS; however, sometimes it is present in secondary SS associated with RA or SLE. Retrospective analyses comprising 507 overall patients with SS reported only 5 cases of PE (1%) complicating the disease course [36–38]. So far only 9 cases of primary SS complicated by PEs have been reported in the English literature. Pleural fluid accumulation is often bilateral and pleural fluid analysis reveals a lymphocytic exudative pattern.
with normal glucose levels. The exact mechanism leading to serositis is still unclear as the pathogenetic features and the course of the disease are heterogeneous in different patients. Responsiveness to corticosteroids may suggest the presence of inflammation in the context of autoimmunity and circulating autoantibodies characterizing the immunologic profile of the underlying disease [10, 17].

**Amyloidosis**

Amyloidosis (AL) is a family of diseases derived from the overexpression and excessive deposition of fibrillar aggregates of several proteins in various tissues resulting in disruption and ultimately failure of the involved organs. In patients with primary systemic AL, clonal plasma cells secrete monoclonal immunoglobulin light chains that deposit in the kidney, heart, nerves, and other tissues [39, 40]. Biopsy of an involved organ typically confirms the diagnosis. Although parenchymal lung involvement occurs in almost a third of AL patients and does not affect survival, the prevalence of PEs is generally uncommon and when present can significantly alter the disease’s clinical course with major detrimental effects [40].

The English literature, between the years 1977 and 2010, includes 25 case reports of PEs associated with AL, 21 of which document pleural amyloid infiltration [10, 41–46]. Pleural fluid analysis revealed that 10 out of 17 patients (60%) presented with an exudate, while the rest of the patients (40%), all with congestive heart failure associated with AL, had a transudate. Nonetheless, thoracentesis is insufficient to establish a rigid diagnosis of pleural AL. To this end, a histopathological analysis with special stains (Congo red) performed by transparietal biopsy or thoracoscopy is sorely needed. When performed, thoracoscopy reveals edema and hyperemia of the pleural surface, inflammation with nodular lesions, or brown nodules of the parietal surface [47].

Given the systemic manifestations of AL, involving heart, pleural, renal, and thyroid function and based on the above observations, four major pathogenetic mechanisms through which systemic AL involves the pleura have been suggested: (1) direct amyloid infiltration of pleural surfaces, (2) nephrotic-range proteinuria, (3) hypothyroidism, and (4) cardiomyopathy associated with AL resulting in systolic and diastolic dysfunction.

The only retrospective study so far estimating the prevalence of pleural involvement in a large cohort of patients with systemic AL was published 8 years ago by Berk et al. [42] The latter constitutes the basis of disease etiopathogenesis and prognosis. Among 636 patients with AL, the authors evaluated, with repeated thoracenteses, echocardiography, and assessment of renal and thyroid function, 6% of patients presenting with large persistent PEs. Based on the significant frequency of exudative PE (37%), the resistance to aggressive diuresis, the inconsistent role of left ventricle dysfunction, and the absence of a causal-effect relationship between hypothyroidism and low oncotic pressure associated with nephrotic-range proteinuria and hypalbuminaemia with PE, the authors supported the noncardiogenic mechanism of the disease. In particular, it has been hypothesized that amyloid infiltration of the parietal pleura appears to be the driving force behind pleural fluid formation and recurrence resulting in both increased pleural fluid production through increased permeability of the pleural capillaries caused by severe inflammation as well as decreased fluid resorption by blocking lymphatic drainage and, therefore, disrupting pleura mechanics [42, 43]. The above observations led chest physicians to apply alternative therapeutic regimens including antivascular endothelial growth factor agents (bevacizumab) [48–50] to massive PEs resistant to so far conventional treatments, such as repeated thoracenteses, aggressive diuresis, and surgical procedures, including video-assisted thoracoscopic surgery. Results from the above case reports seem promising and tantalizing.

Despite extensive analysis data arising from case reports and retrospective studies regarding the disease’s clinical course, prognosis and treatment responsiveness seem controversial and it is rather difficult to delineate potential pathogenetic mechanisms based on the above observations. Larger multicenter prospective randomized studies are definitely required.

**Adamantiadis-Behcet’s Disease**

Adamantiadis-Behcet’s disease is a rare immune-mediated systemic vasculitis that often presents with mucous membrane ulceration and ocular involvements. Adamantiadis disease was named in 1931 after the Greek dermatologist Benediktos Adamantiadis firstly described the triple-symptom complex of recurrent aphthous ulcers, genital ulcers, and uveitis. As a systemic disease, it can also involve visceral organs such as the gastrointestinal...
tinal tract and pulmonary, musculoskeletal, and neurological systems [51]. PE with or without associated chest pain is common; usually it is attributed to pulmonary infarction or an infectious process. Vasculitis of the pleura has been demonstrated by pleural biopsy. PE may result from vasculitis of the pleura or thrombosis of the superior vena cava or subclavian vein leading to obstruction of the thoracic duct [52–54].

**Lymphangioleiomyomatosis**

Lymphangioleiomyomatosis is a rare disease of unknown etiology that affects almost exclusively premenopausal women, and its pathogenesis has been closely associated with proliferation of disorderly smooth muscle growth throughout the lungs, kidneys, and lymphatics [55]. Chylous PEs occur in almost 20% of affected individuals. Infiltration of lung and pleural lymphatics by uncontrolled proliferative vascular-type smooth muscle cells causes obliteration and dilatation of the lymphatic channels leading to lymph stasis, chyloptysis, and septal lines on the chest radiograph [55]. The thoracic duct is often thickened and formed of multiple narrow channels leading to chylous PEs and ascites. The pathogenesis of the disease is largely elusive but emerging notions strengthen the role of abnormalities of proteins that participate in the synthesis of catecholamines, while at the same time underlining the contribution of downregulation of tumor suppressor genes, including tuberous sclerosis complex (TSC1, 2) [10].

**Granulomatosis with Polyangiitis (Wegener’s)**

Granulomatosis with polyangiitis (Wegener’s) is an antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis of small and medium sized vessels of unknown etiology. The nose, lungs, and kidneys are classical sites of involvement. Pleural lesions are present in only 10% of granulomatosis with polyangiitis (Wegener’s) patients with pulmonary involvement. Pleural thickening and PE are the most frequent signs. PE is often unilateral, characterized by its low volume and important pachypleuritis [30]. There are studies of small group of patients reporting the presence of PE in 8 out of 95 cases (8%) [56, 57]. Pleural thickening may result from previous effusion or represent cicatricial changes resulting from nodular inflammatory lesions extending into the pleura. Whether immune dysregulation and production of ANCA result in vascular injury and increased capillary permeability and ultimately pleural fluid infiltration needs further work to be proven.

**Langerhans Cell Histiocytosis**

Langerhans cell histiocytosis (LCH) encompasses a broad spectrum of disorders of undefined origin with diverse clinical presentations including interstitial lung and pleural involvement most commonly involving spontaneous pneumothorax as well as extrapulmonary manifestations, such as skin and bone lesions [58]. PE complicating the clinical course of LCH are exceedingly rare and have been reported to be moderate to large in size, exudative, and lymphocytic. Pleural biopsies demonstrate Langerhans cells positive to S-100 and CD1a monoclonal antibodies in order to confirm diagnosis, whereas microscopic examination may reveal numerous characteristic Birbeck granules [10, 58].

Due to the disease’s rareness, coupled with the infrequency of PEs as a complication of the disease, there is insufficient data supporting potential pathogenetic mechanisms. Based on the above histopathologic data, in combination with current knowledge regarding disease imaging and pathogenesis, we may speculate that pleural fluid accumulation may involve perforation of the parietal pleura with peripheral Langerhans cell granulomas as well as lymphoid disruption by infiltration with numerous, highly proliferative migrating Langerhans cells. Further work is needed to explore the different aspects of the Langerhans cell granuloma, leading to the development of rational treatments for this orphan disease and its complications [10, 58].

**Conclusions**

Based on the existing data we may conclude that there is a significant lack of knowledge regarding the pathogenesis of pleural fluid accumulation in the context of orphan lung diseases (table 1). The aforementioned observation mainly originates in the rareness of PEs as a complication of orphan disorders but most importantly in the absence of histopathologic data that could facilitate the identification of potential etiologic factors. The emergence and widespread clinical applicability of semi-invasive and noninvasive diagnostic tools, including medical thoracoscopy [59] and ultrasonography, respectively, may
accelerate our understanding regarding the pathogenetic mechanisms that drive pleural fluid formation and accumulation and highlight the application of novel therapeutic agents. On the other hand, we should always bear in mind that patients with orphan diseases that present with PE should be carefully evaluated for other coexisting conditions, including tuberculosis, congestive heart failure, and malignancy, given the close association of the majority of rare autoimmune diseases with these entities. Further basic research is necessary in order to clarify the pathogenetic mechanisms.

References


