Case Report

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Syphilitic Pulmonary Inflammatory Pseudotumor: A Diagnostic Challenge

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Abstract

A 46-year-old man presented with nonproductive cough and lower limb swelling. Chest radiograph showed a left lower lobe lung mass and multiple subpleural nodules. Other investigations revealed that he had nephrotic syndrome. Core biopsies of the left lower lobe lung mass showed features of inflammatory pseudotumor with endarteritis obliterans and a lymphoplasmacytic infiltrate. Immunohistochemical stain for *Treponema pallidum* was positive. Resolution of the lung mass and nephrotic syndrome was achieved after treatment with intramuscular benzathine benzylpenicillin. The differential diagnosis of pulmonary inflammatory pseudotumor, manifestations of pulmonary syphilis, and a literature review of secondary syphilis of the lung are discussed.

Keywords

infections, inflammatory pseudotumor, lung, pulmonary, syphilis

Introduction

Inflammatory pseudotumors (IPTs) are etiologically diverse and morphologically heterogeneous and are characterized by a varying admixture of myofibroblasts and inflammatory cells, usually lymphocytes, plasma cells, and histiocytes. Although originally regarded as a reactive inflammatory condition, with the advent of molecular genetic testing and new immunohistochemical markers, this heterogeneous entity has been stratified and true neoplastic conditions have been identified. The term "inflammatory pseudotumor" has been used generically to refer to a wide range of distinct entities and some less well-defined lesions. These include true neoplasms, such as inflammatory myofibroblastic tumor (IMT)[1,2] and follicular dendritic cell sarcoma (FDCS),[3] chronic fibroinflammatory autoimmune disorders, such as IgG4-related disease,[4] pulmonary hyalinizing granuloma (PHG),[5] and the so-called "plasma cell granuloma,"[6] and specific infections. Other associated features may be present and helpful in determining the etiology or nature of the lesion. There is a significant group of IPTs that are induced by a range of pathogenic microorganisms, including bacteria, fungi, and viruses, which we refer to as infective IPTs.

In the lungs, IPTs are well described and both neoplastic and infective types have been described.[7] In this location also, a number of different organisms have been implicated, including mycobacteria, *Coxiella*, *Histoplasma*, and *Cryptococcus*.[8-11]

Syphilis is a chronic disease caused by *Treponema pallidum* and is usually transmitted by sexual contact, from mother to child and rarely by blood-borne infection. If untreated, syphilis has a long progressive natural history consisting of primary, secondary, and tertiary stages. Pulmonary involvement in syphilis is rare and occurs in congenital syphilis as pneumonia alba, in tertiary syphilis as gummata, and in secondary syphilis there have been reports of pulmonary nodules but the morphology has not been well described since lung biopsies were not performed in all cases. We were able to find 26 cases of pulmonary syphilis reported in the English language literature since 1980 of which 9 had lung biopsies.[12-20]

In this article, we describe the clinical and pathological features of a pulmonary IPT due to secondary syphilis in an adult male patient and review the pathology of pulmonary syphilis.

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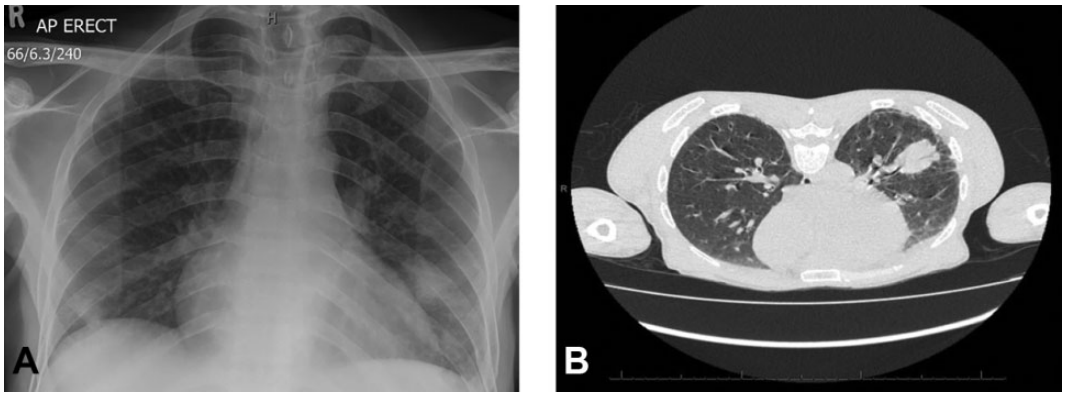

Figure 1. Pretreatment imaging. (A) Chest radiograph showing a mass in the left lower lobe and smaller nodules in both lower lobes. (B) Computed tomography scan showing an irregular mass in the left lower lobe measuring 37 × 28 × 26 mm. There are also multiple subpleural nodules.

Case Report

A 46-year-old man presented with a 3-month history of nonproductive cough and lower limb swelling. Findings on initial examination included normal temperature, significant pedal edema, no skin rash, and normal cardiovascular, neurological, and respiratory examination. Urine dipstick showed significant proteinuria, and the patient was investigated for nephrotic syndrome. Initial laboratory investigations revealed the following: urine protein: creatinine ratio (U-PCR) 0.317 g/mmol, creatinine 58 μmol/L (normal), calcium 3.12 mmol/L (raised), negative HIV and hepatitis B serology. Liver function tests revealed a cholestatic profile. Chest X-ray on admission showed a lower lobe mass with multiple smaller nodules in the lower zones (Figure 1A). Contrasted computed tomography (CT) scan of chest revealed an irregular lower lobe mass (37 × 28 × 26 mm) with multiple posterior lower lobe subpleural nodules, no significant mediastinal lymphadenopathy, and no pleural effusions (Figure 1B).

The initial clinical impression was that of lung cancer with metastases complicated by nephrotic syndrome. Subsequent CT-guided core needle biopsies of the left lower lobe lung mass were taken. The lung biopsies showed areas of varying cellularity composed of spindle-shaped cells arranged focally in a vague storiform pattern (Figure 2A). There were admixed inflammatory cells of varying density composed of lymphocytes, plasma cells, and focal neutrophils (Figure 2B). The less cellular areas contained focal hyalinization. There was also obliterative endarteritis (Figure 2C) with surrounding lymphoplasmacytic infiltrates but no features of an obliterative phlebitis. Small areas of fibrin deposition were present. There were no lymphoid follicles, granulomas, or areas of necrosis. Immunohistochemistry did not show an increase in IgG4 plasma cells. The following histochemical stains for pathogenic microorganisms were negative: Ziehl-Neelsen, Fite, periodic acid-Schiff, Grocott, and Brown and Brenn. The *T pallidum* immunohistochemistry test revealed numerous spirochetes (Figure 2D). The subsequent renal biopsy showed a mesangioproliferative glomerulonephritis.

The *T pallidum* antibody was positive and a subsequent rapid plasma reagin (RPR) test was positive with a titer of 1:256.

The patient received intramuscular benzathine benzylpenicillin (2.4 mU), which was repeated after 2 weeks. He responded well to treatment, and his symptoms resolved within a few days. Subsequent laboratory investigations at 6-week follow-up showed a U-PCR of 0.049 g/mmol, RPR titer of 1:64, normal serum calcium and liver functions, and chest X-ray showed resolution of the lung lesions (Figure 3).

Discussion

As described, the term "inflammatory pseudotumor" has been widely used to refer to various entities with distinct etiologies and pathogenesis. It is noteworthy that in view of the great etiological diversity, the term "inflammatory pseudotumor" without qualification may not convey correct and adequate information for appropriate management of the patient. Hence, the use of the term "inflammatory pseudotumor" should be discouraged or used with qualification, for instance, in the setting of a specific infection.

The following microorganisms have been reported to cause an IPT reaction: mycobacteria, *Coxiella*, *Histoplasma*, *Cryptococcus*, Epstein-Barr virus, and *Cytomegalovirus*. The causative agents in infective IPTs are identified in most cases by demonstrating the infective organism using special histochemical stains (Ziehl-Neelsen, Warthin-Starry, periodic acid-Schiff, and Grocott),

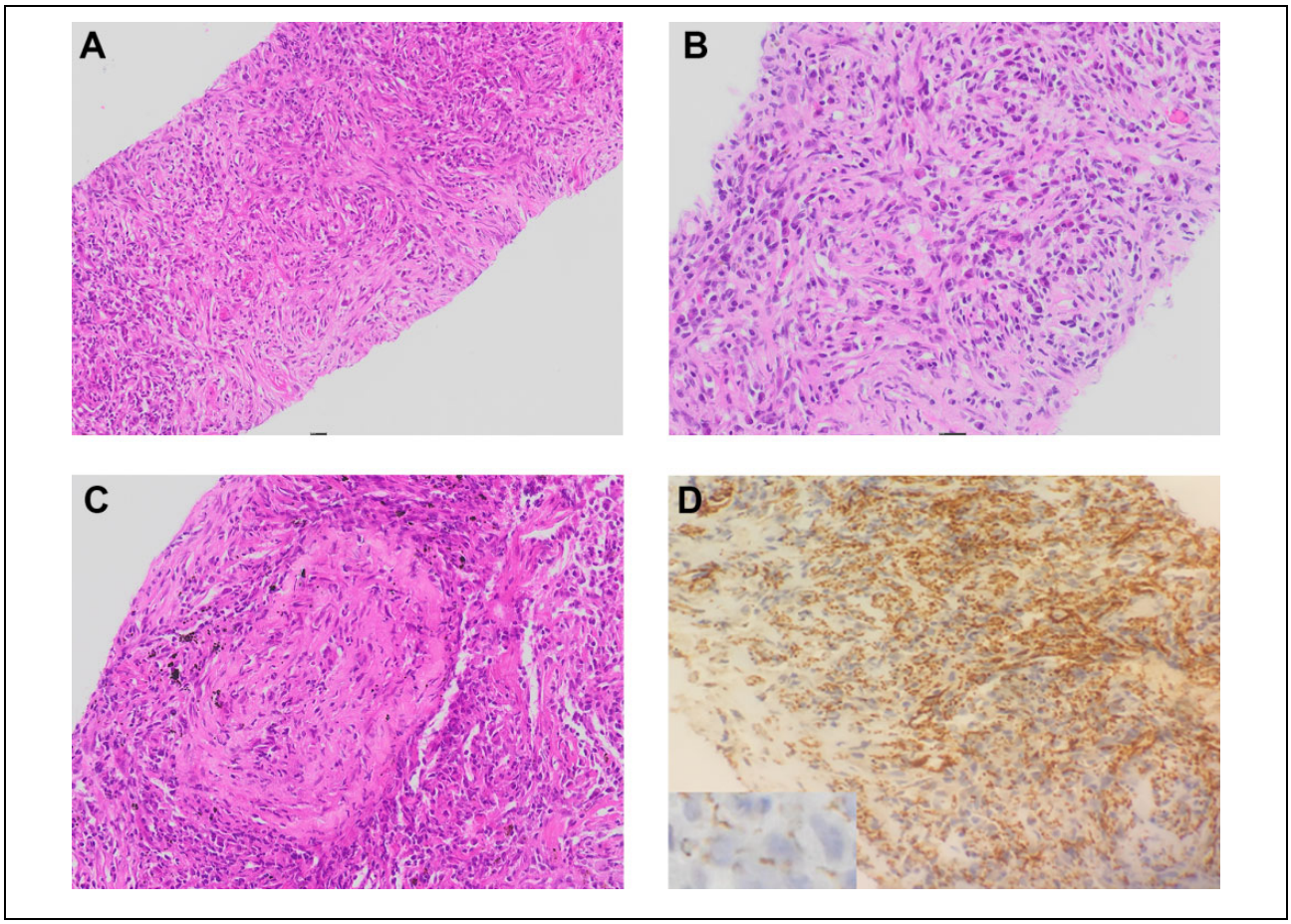

Figure 2. Histomorphology of the left lower lobe lung mass. (A) Proliferating spindle cells arranged in a vague storiform pattern with admixed lymphocytes, plasma cells, and focal neutrophils (hematoxylin and eosin, original magnification ×200). (B) Bland spindle-shaped cells with intervening collagen and admixed plasma cells with focal Russell bodies and lymphocytes (hematoxylin and eosin, original magnification ×400). (C) Obliterative endarteritis with perivascular lymphoplasmacytic infiltrate (hematoxylin and eosin, original magnification ×200). (D) Numerous spirochetes present on immunohistochemical stain (*Treponema pallidum*, original magnification ×200, inset magnification ×800).

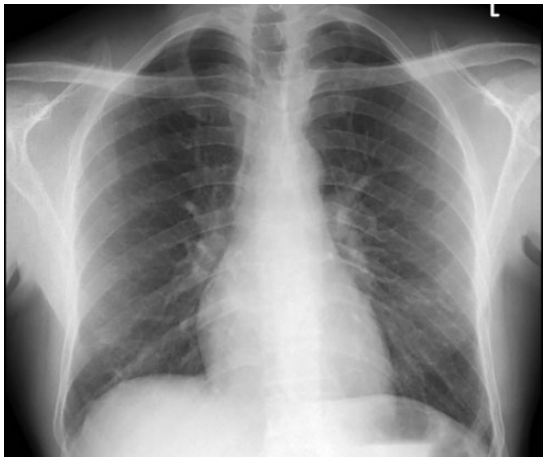

Figure 3. Posttreatment radiograph showing resolution of the left lower lobe mass and smaller nodules.

immunohistochemical stains (using specific antibodies), in situ hybridization (for Epstein-Barr virus), or polymerase chain reaction. In addition, *Cryptococcus* has a mucin capsule that is easily demonstrated with a mucicarmine stain. In some cases, serological tests may be required for confirmation.

In 2012, it was estimated that there were 18 million prevalent cases of syphilis globally and that approximately 6 million new cases of syphilis are diagnosed globally in individuals aged 15 to 49 years.[21] Classically, acquired syphilis has 3 stages, primary, secondary, and tertiary. The primary lesion is characterized by a painless ulcer, a chancre, usually located at the site of entry of the spirochetes. The secondary stage often has multisystem involvement due to the presence of a spirochetemia. The classical lesions of secondary syphilis include a skin rash, condyloma lata, oral mucosal lesions described as "snail track" ulcers, and generalized lymphadenopathy.[22]

Other less common findings in secondary syphilis include hepatitis (often subclinical), periostitis, uveitis, iritis, glomerulonephritis, arthritis, alopecia, and pulmonary involvement.[22,23] A proportion of patients who remain untreated will, after a latent period, progress to tertiary syphilis, which is characterized by cardiovascular and neurological involvement and gummata. In HIV-infected individuals, there are often multiple chancres, ocular and nervous system involvement are more common and progression to gummatous disease is rapid.[23]

Syphilis with pulmonary involvement is rare and can occur in congenital, secondary, and tertiary stage syphilis. The diagnosis of pulmonary lesions of secondary syphilis has been a challenge, and Coleman and colleagues[24] proposed the following diagnostic criteria: physical and historical findings typical of syphilis, positive serology for syphilis, radiographic pulmonary abnormalities, other forms of pulmonary disease excluded, and radiological response to antisyphilitic treatment. Recent reports show that multiple subpleural nodules, often situated in the lower lobes, are a prominent feature of secondary syphilis with pulmonary involvement.[12,16,19,25-28] Although there are many reports of secondary syphilis with pulmonary involvement, the histological features of the lung lesions are not well described. In fact, in many cases, a lung biopsy was either not performed or not included, and treatment was based on serological confirmation and associated clinical features.[24,25,27-41] Although not specifically stated, some descriptions suggest the morphology of an IPT[12,19] while others showed varied morphology (Table 1). Granulomas, seen in 5 cases, and lymphoplasmacytic infiltrates were the most common findings. Other reported findings were necrosis and abscess formation, mixed inflammatory infiltrates including neutrophils, organizing pneumonia, perivascular plasma cells, and fibrosis. Interestingly, the Warthin-Starry stain was not positive in all cases, and confirmation of syphilis depended on serology, immunohistochemistry, or polymerase chain reaction for *T pallidum*. In all cases, the pulmonary lesions showed regression after appropriate antibiotic treatment.

The tissue diagnosis of syphilis is based on the morphology, histochemical and immunohistochemical stains, and polymerase chain reaction using histopathology samples for testing. In many instances, there is a strong clinical suspicion of syphilis, and appropriate tests are requested in the initial workup. However, those cases where there is no clinical suspicion of syphilis pose a diagnostic dilemma.

As noted, syphilis can induce different inflammatory responses in the lung. Syphilitic IPT, although reported in the liver, has not been described in the lung.[42-44] IPTs of the lung, however, are well recognized.[7]

IPTs are composed of proliferating myofibroblasts and accompanying inflammatory cell infiltrate consisting of variable numbers of lymphocytes, plasma cells, neutrophils, macrophages, and sometimes eosinophils. There are no specific histomorphological features that are diagnostic of syphilitic pseudotumor. Interestingly, David et al[13] reported that the typical obliterative endarteritis with perivascular plasma cells has never been reported in small nonsurgical lung biopsies in secondary syphilis. Since we have seen obliterative endarteritis in our case, we suggest that the presence of perivascular and/or perineural lymphoplasmacytic infiltrates, obliterative endarteritis, and a predominant plasma cell infiltrate should warrant investigation for *T pallidum*.

Although pulmonary syphilis is seen more often in HIV-infected individuals, it has also been reported in HIV-negative individuals. The following radiographic features have been suggested as indicative of pulmonary involvement by secondary syphilis, pulmonary nodules (often subpleural), usually smaller than in HIV-positive patients, and absence of hilar lymphadenopathy.[12]

The diagnosis of IgG4-related disease is based on the histomorphology, increased $IgG4^+$ plasma cells, and/or a raised IgG4: IgG ratio. The major histopathological features are a dense lymphoplasmacytic infiltrate, fibrosis with a storiform pattern, and obliterative phlebitis. Other associated histopathological features include increase in eosinophils and phlebitis without luminal obliteration.[4] A significant IgG4 count per high-power field for a lung biopsy is >20, and the recommended IgG4: IgG ratio is >40%.[4]

Although PHG shares a similar lymphoplasmacytic infiltrate with IPT, it is a well-circumscribed lesion with a distinctive component of hyalinizing bands of collagen arranged in an irregular, parallel, or concentric arrangement. The etiology is unknown, but an immunologic pathogenesis has been suggested.[45-47] The term "plasma cell granuloma" has been used as a synonym for IPT.[6,48,49]

Inflammatory pseudotumor-like follicular dendritic cell tumor is regarded as a variant of FDCS.[3] In addition to the typical IPT morphology, there are foci with definite nuclear atypia, including in some cases Reed-Sternberg–like cells, immunoreactivity for CD21, CD35, CD23, and CNA.42, and there may be areas of conventional FDCS. Furthermore, this tumor has a female predilection and so far has only been described in intraabdominal locations.

Inflammatory myofibroblastic tumor has 3 basic histological patterns as described by Coffin et al,[1] often occurring within the same tumor. These are a myxoid/vascular pattern, a compact spindle cell pattern, and fibromatosis-like pattern. The compact spindle cell pattern usually contains numerous plasma cells and lymphocytes admixed with the spindle cells. The myxoid/vascular pattern has more neutrophils and eosinophils, and the fibromatosis-like pattern has scattered lymphocytes, plasma cells, and eosinophils. Approximately 50% to 70% of IMT will show immunoreactivity for ALK and *ALK* rearrangement by

Table 1. Clinical and pathological features of secondary syphilis with lung involvement.

Age in years, sex	HIV test	Chest radiology	Lung histology	Special stains	Treatment	Response to treatment	Ref
46, male	Negative	Irregular left lower lobe mass with multiple subpleural nodules	Spindle cells with admixed lymphocytes and plasma cells. Obliterative endarteritis present.	*Treponema* IHC positive	Benzathine benzylpenicillin 2.4 MU IM, 2 doses	Complete resolution of lung lesions at 6 weeks	Our case
48, male	Unknown	Solitary mass in left lower zone	Granulomas and lymphocytes	N/A	Benzathine benzylpenicillin 1.2 MU/day for 4 weeks	Gradual resolution at 3 months	17
37, male	Positive	Bilateral basilar reticulonodular infiltrates	Chronic inflammation with granulomas	WS negative	Penicillin IV	Complete resolution after 1 month	14
34, male	Positive	Multiple cavitating round nodules bilaterally	Organized pneumonia with small granulomas and lymphoplasmacytic infiltrate (histology after treatment commenced)	PCR positive on bronchial washings WS and PCR negative on biopsy	Penicillin G 1.8 MU/day IV for 14 days	Resolution after 3 months	13
40, male	Negative	Right lower lobe mass and subpleural nodules in right middle and lower lobes	Fibrotic tissue, dense lymphoplasmacytic infiltrate, perivascular plasma cells, and "fibrinoid thickening" of vessels	WS negative in lung biopsy, positive in skin	Benzathine penicillin 2.4 MU weekly for 3 consecutive weeks	Near complete resolution after 4 weeks	12
51, male	Negative	Multiple variably sized nodules bilaterally	Necrosis and abscess, lymphocyte and plasma cell infiltrate and peripheral fibrosis	N/A	Benzathine penicillin 2.4 MU IM	Partial resolution at 1 month and almost complete resolution at 10 months	16
37, male	Unknown	Multiple ill-defined nodules mostly in lower lobes	Peribronchovascular infiltrate with intraalveolar plasma cells and histiocytes	N/A	Penicillin	Complete resolution after 8 weeks	20
32, male	Positive	Multiple bilateral nodular opacities with the largest excavated nodule—left upper lobe	Fibrinoid necrosis with histiocytes, lymphocytes, numerous plasma cells, and noncaseating epithelioid granulomas	WS positive, *Treponema* IHC positive	Penicillin IV (also antituberculosis treatment)	Complete resolution	18
62, male	Positive	Multiple bibasilar subpleural nodules	Mixed inflammatory infiltrate of lymphocytes, neutrophils and fibrosis	WS negative, PCR positive	Benzathine penicillin 2.4 MU/day	Partial resolution after 4 months	19
34, male	Negative	Single mass in right lower lobe (4 cm)	Abscess with necrotizing granulomas (right basal segmentectomy after 5 months, due to poor response to treatment)	PCR positive on transbronchial biopsy	Amoxycillin 1500 mg/day and probenecid 1000 mg/day for 2 weeks After 5 weeks, penicillin G 2.4 MU/day IV for 2 weeks	Complete resolution at 8 months	15

Abbreviations: IHC, immunohistochemistry; IM, intramuscular; WS, Warthin-Starry stain; IV, intravenous; PCR, polymerase chain reaction.

fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction.[2,50]

In a recent study, 30% of thoracic IMTs harbored *ROS1*, *NTRK3,* or *RET* gene fusions.[50] These can be detected by FISH or targeted RNA sequencing.

Malignant spindle cell tumors with prominent inflammatory cells is another important group of tumors that may mimic the IPT reaction. Sarcomatoid carcinoma especially spindle cell carcinoma with associated inflammatory infiltrate can be distinguished by immunohistochemical stains for cytokeratin.[51] Furthermore, malignant spindle cell tumors, carcinomas, and sarcomas may show other characteristics of malignancy, such as marked pleomorphism, necrosis, lymphovascular invasion, and high cell proliferation. Immunohistochemistry will be useful in determining differentiation in these tumors.

The reporting pathologist must consider syphilis when presented with features of an IPT irrespective of the HIV status of the patient. Immunohistochemistry for *T pallidum* is a convenient and reliable test for confirming the diagnosis. Prompt diagnosis and appropriate treatment usually leads to complete resolution.

Declaration of Conflicting Interests

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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