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Cavitating lung lesion as a manifestation of inflammatory tumor (pseudotumor) of the lung: A case report and literature review

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 60
Final Diagnosis: Inflammatory pseudotumor of the lung
Symptoms: Cough dry • fever
Medication: —
Clinical Procedure: —
Specialty: —

Objective: Rare disease

Background: Inflammatory pseudotumor of the lung involves a benign, non-neoplastic lung lesion of unknown etiology.

Case Report: We present a case of a 60-year-old female smoker who had been under intermittent immunosuppressive medication for discoid lupus, who was admitted to hospital with fever of 39.5°C of 10-day duration, not responding to an oral cephalosporin. Chest CT examination showed a cavitating opacity in the upper zone of the left lung. It was not feasible to establish a diagnosis based on clinical and laboratory testing nor based on CT scanning and bronchoscopy. Thus, the patient underwent left thoracotomy and sphenoid resection of the lesion, which was sent for biopsy. The histopathologic features aided by immunohistochemical staining proved the lesion to be an inflammatory pseudotumor of the lung.

Conclusions: The case is reported because of the extremely rare radiologic presentation of the development of a lung pseudotumor emerging as a cavitated lesion, which relapsed during the follow-up period while the patient was still under immunosuppressive medication.

MeSH Keywords: Plasma Cell Granuloma, Pulmonary – immunology • Plasma Cell Granuloma, Pulmonary – radiography • Plasma Cell Granuloma, Pulmonary – surgery • Plasma Cell Granuloma, Pulmonary – therapy

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Background

Cavitary lesions of the lung may be attributed to a number of infections and inflammatory illnesses of pulmonary parenchyma, causing a serious diagnostic problem in chest medicine due to their resemblance to lung tumors. These lesions are represented by a variety of alterations in imaging examinations, including pulmonary opacities, nodular shadows, and solid lesions with air inside. A wide spectrum of disease can have the latter radiological presentation [1].

Using PubMed, we reviewed the relevant literature from 1993 to date and found 8 studies reporting a total of 62 cases of pulmonary parenchyma lesions mimicking lung tumors [2–9]. A cavitary lesion with pus, in the upper lobe of the right lung, was first presented in the relevant literature in 1993 [2]. It had been suggested that this case represented a classic plasma cell granuloma disease [2]. A report of 28 cases of pulmonary inflammatory pseudotumors was also published in 2002 [3]. In this study, cavitary lesions were observed in 11.1% of participants [3] (3 patients). In 2006, 7 cases of lung inflammatory pseudotumors were further presented [4]. According to chest computed tomography (chest CT scan), a cavitary lesion was found only in 1 patient [4]. A case of a large inflammatory myofibroblastic tumor mimicking a posterior mediastinal tumor was also published in 2008 [5]. Chest X-ray (CXR) and chest CT scan revealed a soft-tissue mass, without cavitation, located in the right lung's lower lobe [5]. The tumor was surgically excised and necrosis was found in the central region [5]. In 2009, a case of a solid lung pseudotumor was reported as an initial presentation of Wegener's granulomatosis [6]. Histopathological examination established fibrosis and large necrosis accompanied with an inflammatory process [6]. Cavitary lesions can be found in 50% of all Wegener's granulomatosis cases [6]. Two cases of inflammatory pseudotumors were reported in 2011 [7]. On admission, CXR and chest CT scan showed an abnormal nodule with irregular margins for both patients [7]. No cavitation was detected and the patients were thoracoscopically treated [7]. In the same study [7] it was reported that, in the sequel of a review search of the Japanese literature, 9 more cases of inflammatory lung pseudotumors were registered from 1998 to 2011.

Three cases of inflammatory pseudotumors of the lung, caused by pulmonary actinomycosis, were published in 2012 [8]. In all 3 cases, necrotizing infections causing cavitary and tumorous lesions in lung parenchyma were surgically identified [8]. A very recent retrospective study [9] was published in 2013, reporting 13 cases of infectious lung pseudotumors, including the aforementioned 3 cases of pulmonary actinomycosis [8]. In this particular work [9], a cavitary lesion was present in 1 out of 10 remaining patients. To the best of our knowledge, cavitary lesions were detected in 9 out of the above-mentioned 62 cases mimicking lung tumors. The diagnostic priority in such a case is to differentiate among carcinomatous, infectious, or autoimmune disease.

In the present study we had 2 aims: 1) to report a case of a smoker with febrile illness who presented with a cavitary lung lesion relapsing during the follow-up period, given that the patient had been on immunosuppressive medication due to discoid lupus (because a meticulous literature search failed to reveal any reported lung pseudotumors on the grounds of autoimmune disease under immunosuppressive medication) and 2) to make an overview of cavitary lesions that presented in the form of lung pseudotumors, published in the relevant literature during the last 24 years, (from 1 January 1990 to present), by simultaneously discussing aspects of their differential diagnosis and treatment.

Case Report

A 60-year-old smoking (35 p/years) housewife was admitted to our hospital, from 9 to 26 October 2009, due to fever up to 38.5°C, dry cough, and constitutional symptoms of 10-day duration prior to admission, with no response to oral cephalosporin for 7 days. She had a history of discoid lupus on intermittent immunosuppressive medication (chloroquine and azathioprine) for the past 11 years (from November 2001 until October 2012).

On admission, the patient looked unwell but had normal vital signs except for elevated temperature (38.5°C). Complete physical examination revealed no abnormality in any of the organ systems. Laboratory test values were: O_2 saturation 98% (room air), Hct: 33%, Hb: 11 g/dL, WBC: 11.0 k/μL (neutrophils: 80%, lymphocytes: 15%, monocytes: 3%, eosinophils: 2%), PLT: 278 K/μL, ESR: 103 mm/1st hour, urea: 7 mg/dL, creatinine: 0.6 mg/dL, CRP: 9.843 (<0.500 mg/dL), ALT: 38 U/L, AST: 21 U/L, γ-GT: 105 U/L, and ALP: 148 U/L. The purified protein derivative (PPD) result was negative, and urine was normal, without detection of pneumococcus and legionella antigens. Sputum acid-fast bacilli (AFB) and culture for infectious agents were also negative. Chest X-ray showed a heterogenous round opacity with irregular margins on the left upper zone (Figure 1) and chest CT scan (Figure 2) depicted a relatively large thick-walled cavitated lesion of heterogeneous density in contact with the left apical pleura. Small infiltrations were detected in the apical posterior segment of the left upper lobe and there were marginally enlarged tracheobronchial and aorto-pulmonary window lymph nodes. Moreover, tests for p-ANCA and c-ANCA antibodies were negative.

Fiberoptic bronchoscopy (FOB) showed no abnormality, while cytology of bronchial secretions and brushing smears from

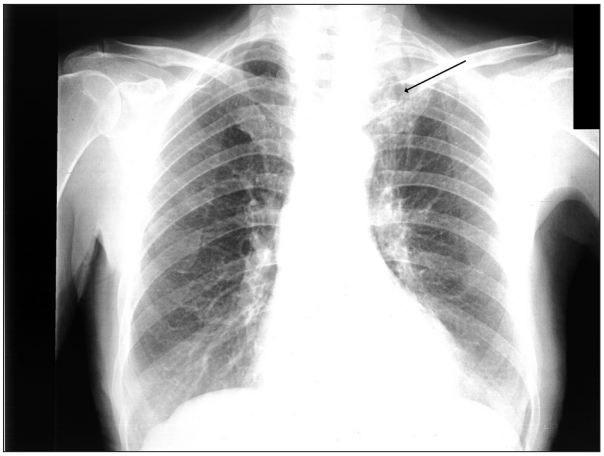

Figure 1. Heterogenous round opacity with irregular margins found on the left upper zone on patient's first admission.

the affected segment were negative. Cultures for bacteria and fungi were also negative. She was treated with tazobactam/piperacillin 4.5 g q.i.d. intravenously for 8 days (from 10 to 17 October 2009) with recession of fever and improvement of her general clinical condition. She was then discharged from hospital with prescription of oral ciprofloxacin (500 mg b.i.d.) for 2 weeks, and advised to come for re-evaluation in 30 days. She was re-admitted to our hospital on December 15 2009. On re-evaluation there was no change in CT findings, so the patient was referred to our hospital's Thoracic Surgical Department, where she underwent left thoracotomy. A wedge resection of the lesion was performed and the removed portion of lung parenchyma was sent for biopsy (specifically, a lung tissue segment of a soft structure weighing 27 g and measuring 5×4×3 cm). Frozen section was negative for malignancy. The examined specimen, measuring 3×2.5×1 cm, contained a central, defined, tough-elastic, inflammatory myofibroblastic tumor (pseudotumor) of the plasma cell granuloma variant, consisting of an intense lymphoplasmacytic infiltration with a significant number of foam histiocytes and myofibroblastic hyperplasia of its stroma in a type of a fascicular or storiform pattern. Bronchiolar branches trapped in this focus showed transmural and intraluminal histiocytic and lymphocytic infiltration. The surrounding parenchyma had foci of lipoid pneumonia (Figure 3). Histochemical staining for presence of viral or parasitic agents (*PAS*, *GIEMSA*) proved negative.

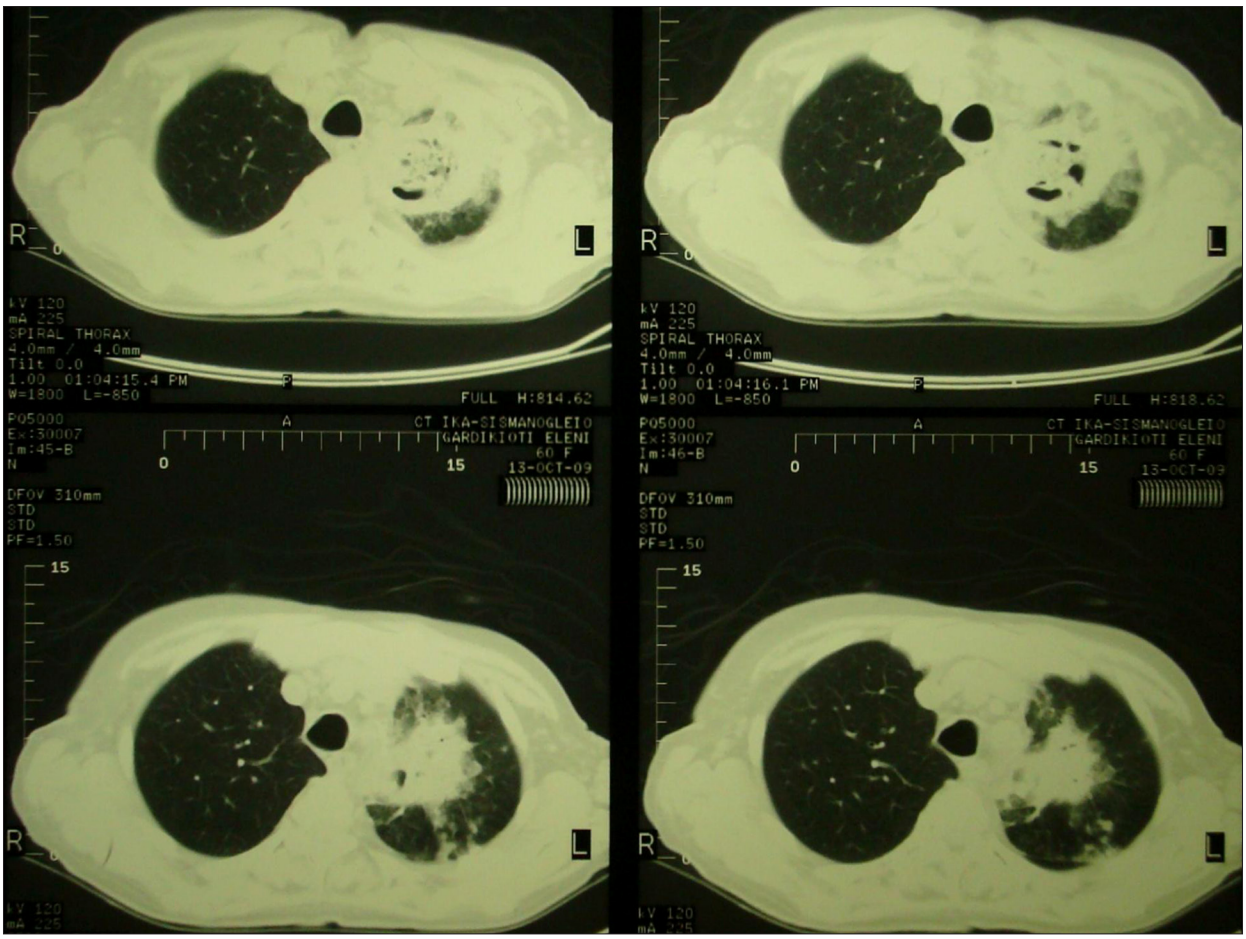

Figure 2. Chest CT scan showing a cavitating lesion in the left upper lobe.

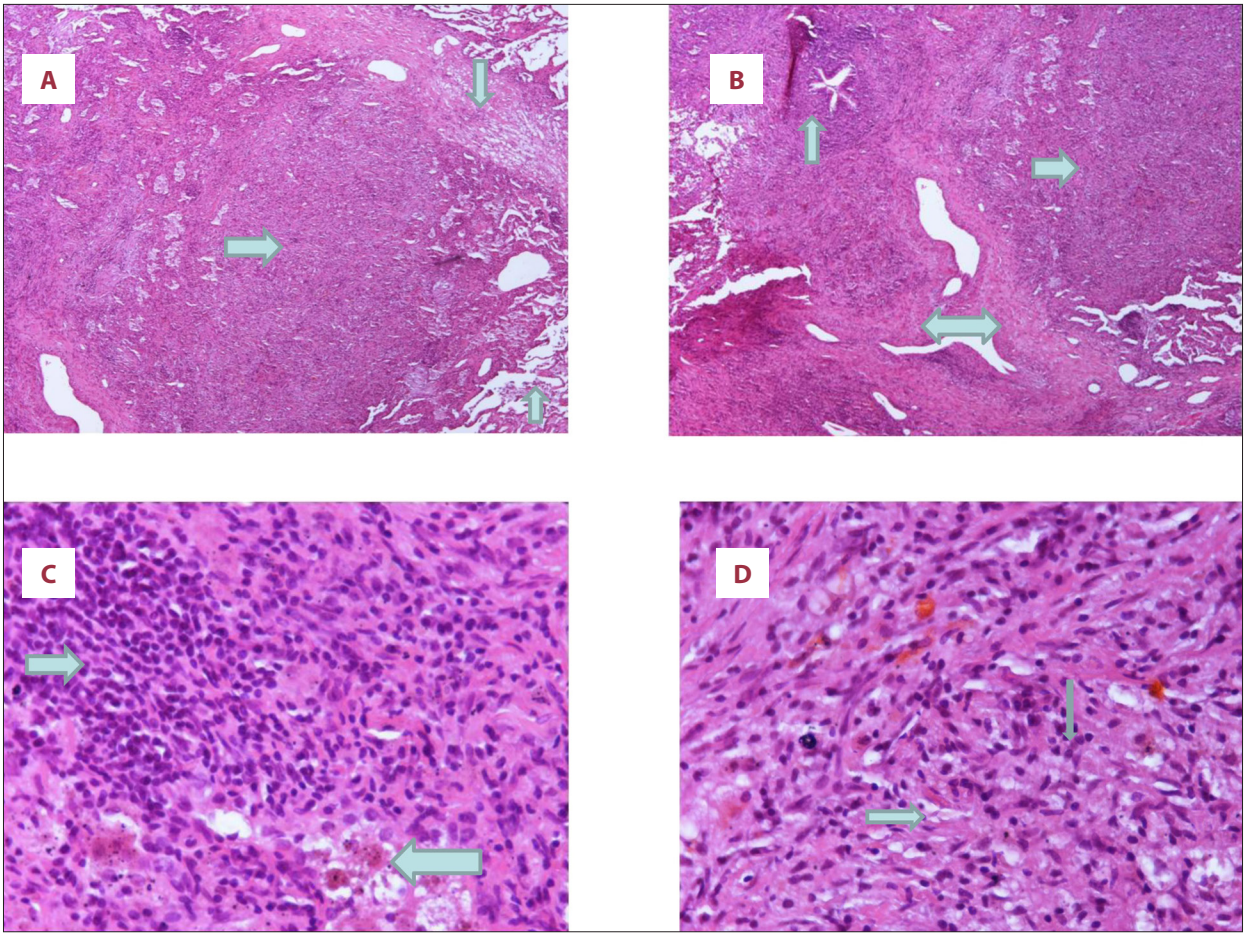

Figure 3. H-E. (**A**) Inflammatory nodule (right arrow), fibroblastic area (down arrow), normal parenchyma ×40 (upper arrow). (**B**) Inflammatory nodule (right arrow), inflammation of a bronchial wall (upper arrow), fibrotic areas included vascular spaces ×100 (double arrow). (**C**) Lymphocytes and plasmacytes (right arrow), foamy histiocytes down field ×400 (left arrow). (**D**) Admixed inflammatory cells (lympho-plasmacytes-right arrow and foamy histiocytes-down arrow) ×400.

Formalin-fixed, paraffin-embedded archival tissue was stained immuno-histochemically for: CD45R0, CD20, SMA, κ (Kapa), λ (Lambda), CD68, ALK-1, Herpes virus-8 (HHV-8), and Epstein-Barr virus (EBV). Lymphocytes and plasma cells were polyclonal (CD45R0+, CD20+, κ-light chains+ and λ-light chains+). Smooth-muscle actin (SMA) was expressed in stromal myofibroblasts and CD68 in histiocytes. No immunohistochemical reactions were observed for ALK-1, HHV-8, and EBV antibodies.

Fibroblasts of the stroma expressed smooth-muscle autoantibody (SMA) positivity (Figure 4), suggesting the diagnosis of an inflammatory pseudotumor. The patient was discharged from hospital on 23 December 2009 in good clinical condition (Figure 5).

During the follow-up period, lasting for about 2 years, the patient appeared to be well. Nevertheless, on 1 November 2011 she was again admitted to our hospital with a fever of 2 weeks duration, up to 39.5°C, not responding to clarithromycin intake, administered per os at a dosage of 500 mg ×2 daily. Chest X-ray film on admission showed a new, inhomogeneous opacity located in the upper zone of the right lung (Figure 6). Laboratory tests showed that CRP, Hct, WBC, and PLT values were 11.1(<0.500 mg/dl), 27%, 8.44 k/μL (neutrophils: 77%), and 411k/μL, respectively. Urine culture was positive for *Pneumococcus* antigen, while sputum culture was positive for *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* ssp.

FOB was negative for abnormal findings. The new chest CT scan verified the presence of a new cavitary lesion in the right upper lobe. The patient refused to undergo any other surgical intervention. Tazobactam/piperacillin 4.5 g q.i.d. were also intravenously administered for a week. Her fever resolved and she was discharged on 11 November 2011 in an improved clinical condition.

A new evaluation of the patient after 2 years (in January 2014) showed a normal CXR (Figure 7) although the patient had received no immunosuppressive treatment for more than 1 year.

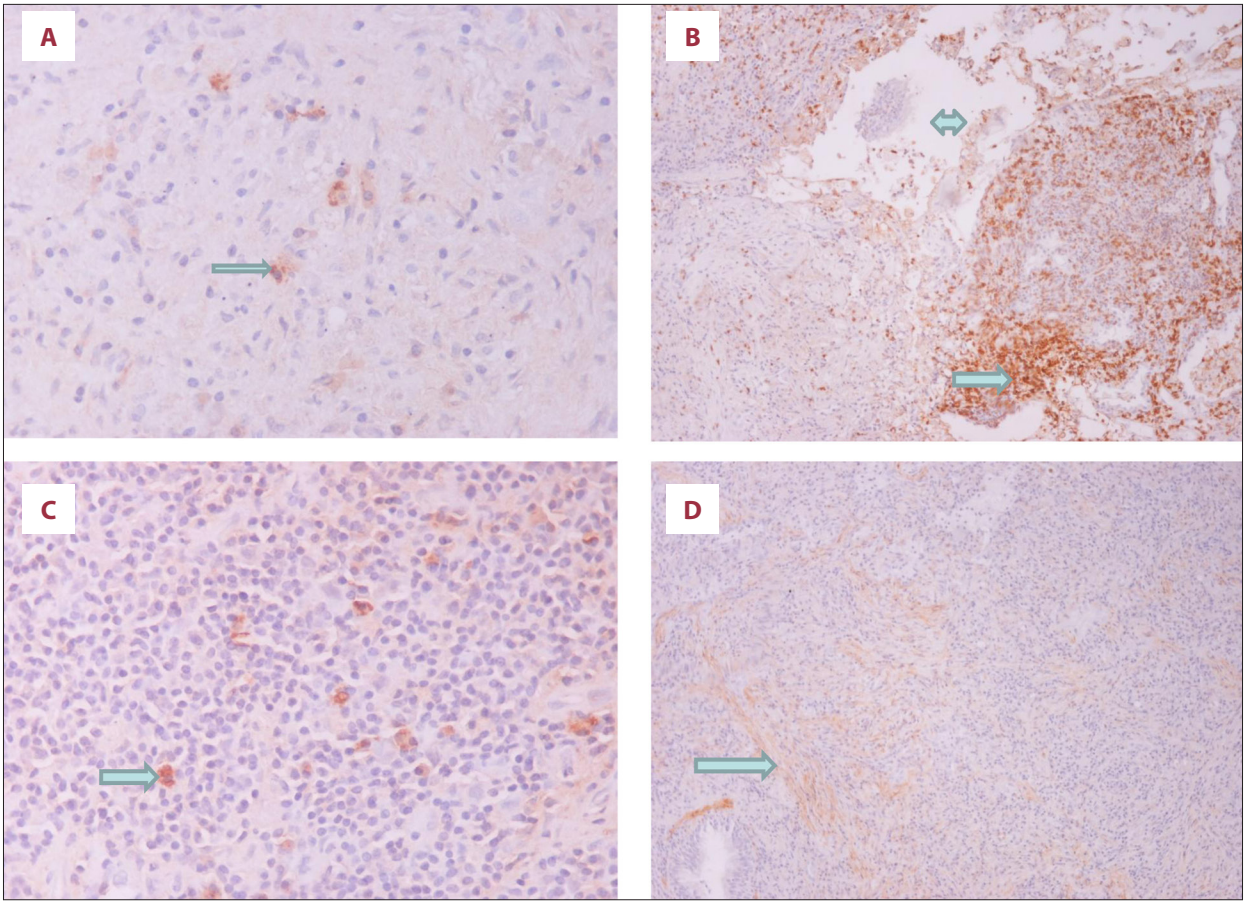

Figure 4. Immunohistochemistry. (**A**) Scattered κ-chain positive plasma cells ×400 (arrow). (**B**) Cavity area in the middle field of picture ×100 (double arrow), foamy histiocytes (right arrow). (**C**) Scattered λ chain positive plasma cells ×100 (arrow). (**D**) SMA positive myofibroblasts in a fibrotic area ×100 (arrow).

Discussion

Inflammatory pseudotumor is a benign lesion of the lung of unknown origin, first described in 1973 [10]. Other synonymous terms include post-inflammatory tumor, histiocytoma, xanthoma, fibroxanthoma, xanthogranuloma, and plasma cell granuloma [11]. These tumors are of low malignant potential and are considered to be myofibroblast or reticular neoplasms of 2 main types: 1) fibrohistiocytic type and 2) plasma cell or lymphoplasmacytic inflammatory type [12]. Fibrohistiocytic inflammatory pseudotumors are characterized by xanthogranulomatous inflammation, giant cells, and neutrophilic infiltration, all developed in a substrate of spindle cells with a storiform pattern [12]. Lymphoplasmacytic inflammatory pseudotumors are histopathologically characterized by either a diffuse lymphoplasmacytic or prominent eosinophilic infiltration containing fibroblastic areas with inflammatory cells of plasma origin [12]. Cellular or collagenous tissue presenting dense lymphoplasmacytic infiltration associated with foam histiocytes at various ratios can also being detected in the above-mentioned pathologic types of inflammatory pseudotumors [13]. Fibrohistiocytic and plasma cell type are reported to constitute 0.7–1% of lung neoplasms [13], although according to a study [14] the percentage of inflammatory pseudotumors seems to be smaller, calculated to 0.04% of all lung tumors. Although inflammatory pseudotumors are more common in children and teenagers [10], they can also appear in patients who are approximately 40 years old [10,14]. The occurrence of the above tumors, including the ones presented in lungs, is associated with a past medical history of viral infections such as HHV8 and EBV infections, or other inflammatory pathologic entities, including autoimmune diseases [15]. The latter is in accordance with our case presenting a cavitating lung lesion formation in a patient being under immunosuppressive medication for discoid lupus. Moreover, according to Kim et al. [3], males more commonly experienced the emergence of inflammatory pseudotumors, which are usually associated with respiratory symptoms such as cough (44.4%), chest pain (29.6%), hemoptysis (15%), sputum (15%), and dyspnea (11.1%). Fever was present in 22.2% of the participants [3]. Results reported by Kim et al. [3] agree with a report [15] that the clinical symptoms emerging in the sequel of inflammatory pseudotumor of the lung were cough,

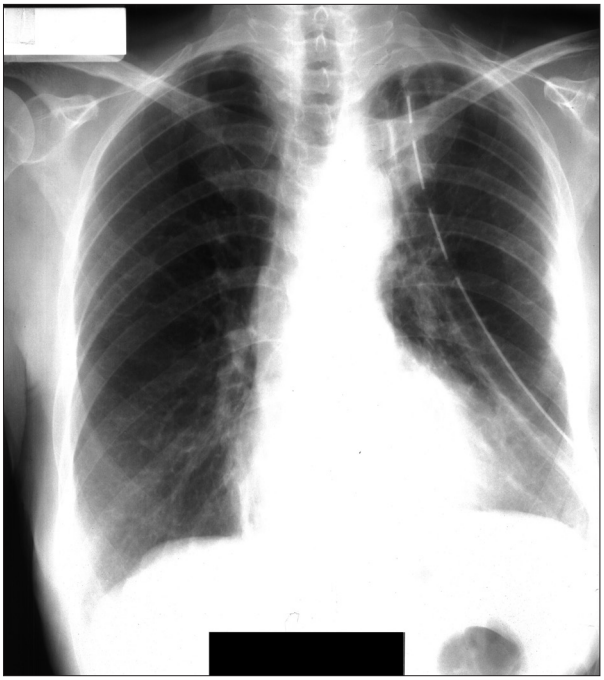

Figure 5. Normal chest-X-ray taken 3 days before discharge from hospital after re-evaluation and wedge resection of lung pseudotumor.

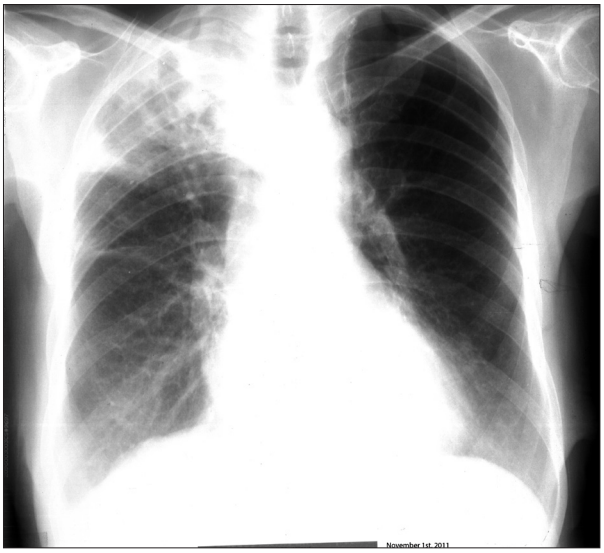

Figure 6. Heterogenous round opacity on the right upper zone on patient's admission on November 1st 2011.

hemoptysis, chest pain, and dyspnea. Focusing on cough, this was mainly attributed to the central endobronchial location of the lung pseudotumor, causing a compression [5] or obstruction [16] effect.

Radiologic findings vary, including a solitary nodule that can mimic primary or metastatic neoplasm, non-homogenous opacity, pleural effusion, atelectasis, and opacities with calcifications,

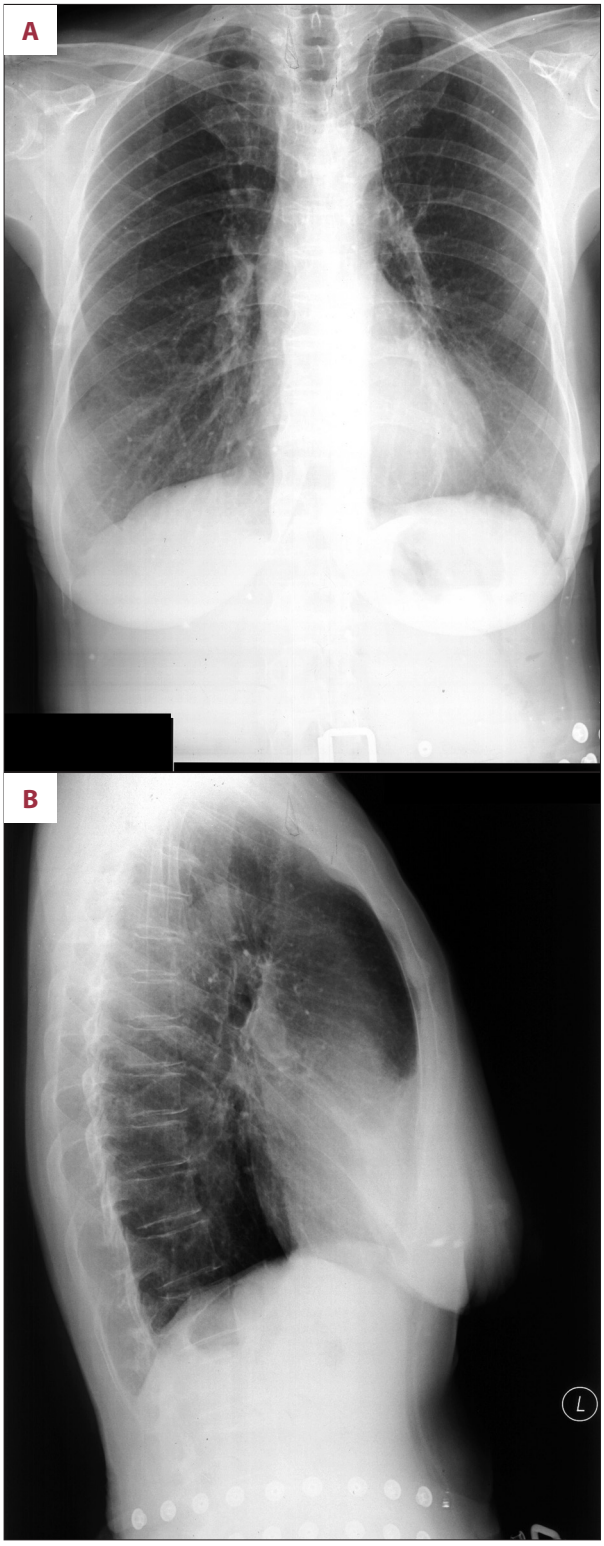

Figure 7. (**A, B**) Chest-X-ray without abnormal findings one year and three months after discontinuation of immunosuppressive medication.

which are more common in children [5]. In some cases, patients are found to have enlarged hilar or mediastinal lymph nodes or a posterior mediastinal mass [5].

Differential diagnosis includes Wegener's granulomatosis (WG), primary or metastatic lung neoplasm, hamartoma, mycetoma, pneumonia, lung abscess, or tuberculosis. In imaging examinations, WG disease is frequently accompanied by cavitations, frequently associated with pulmonary infiltration or nodules [6,17]. Particular attention should be paid in differential diagnosis of inflammatory pseudotumors from lung cancer, as, according to the relevant literature, the endobronchial inflammatory pseudotumor can mimic a carcinoid tumor [18]. As CXR films and chest CT cannot both ensure a differential diagnosis between lung inflammatory pseudotumors and other lung diseases of neoplasmatic, infectious, or inflammatory origin, technical means such as tomographic-guided percutaneous biopsy [6] and thoracic surgical intervention [7–9] (including video-assisted thoracic surgery/VATS) were used, followed by histopathologic examination of the specimen received. Similarly, in our described case, the work-up with the aid of FOB, chest CT, abdomen CT, sputum cultures, and cytology was not diagnostic, being in accordance with the majority of cases of patients presenting inflammatory pseudotumors [19]. Our decision to perform a surgical biopsy was made due to the possibility of missing a bronchogenic carcinoma [7]. Moreover, the surgical approach, except for diagnosis establishment, also constitutes the safest curative treatment resulting in avoidance of either local recurrence or spreading of lung pseudotumor [7,14], including lung inflammatory pseudotumors attributed to pulmonary infections [8,9]. The possibility of recurrence or spreading is proportional to local invasion of the vessels and lung parenchyma found in the anatomical site of inflammatory pseudotumor development [7,14]. Complete surgical resection of a lung pseudotumor can inhibit the expansion of the disease by avoiding increased morbidity, which is particularly attributed to metastases and mediastinal or chest wall infiltration [7,14]. In our case, the re-appearance of an inflammatory pseudotumor in the other lung at this time might be attributed to continuation of immunosuppressive treatment. We suggest that discontinuation of immunosuppressive therapy for such a long time (1 year) seems to why our patient had no new relapse of this condition. Choice of surgical procedure depends on the pseudotumor type: wedge resection for non-invasive type and segmentectomy or lobectomy for invasive type [7]. The surgical technique of VATS, except for lung biopsy [20], is a curative treatment of non-invasive inflammatory pseudotumor [7], which is useful for patients with deranged lung function. In case of pulmonary infectious diseases mimicking lung cancer, surgical curative methods such as classical thoracotomy or VATS technique are also used [8,9]. According to the relevant literature [9,21,22], pulmonary infections, specifically pulmonary actinomycosis, enhance immunodeficiency and contribute to cavitary lesion occurrence. Meticulous surgical removal of lung pseudotumors of infectious origin protects lung tissue from further contamination and loss of function. In all inflammatory lung pseudotumors, 60% of patients undergoing incomplete resection have a recurrence [5,14].

Conclusions

In our extensive review of the relevant literature of the last 24 years, we found 10 cases of inflammatory pseudotumors mimicking lung cancer, including our case. Our patient's case is reported because of the extremely rare combination of an autoimmune disease while receiving immunosuppressive medication, presenting with a cavitary lesion on chest CT. The other 9 cases were of unknown or infectious origin. To exclude lung cancer, differential diagnosis should be performed using interventional procedures followed by histopathologic examination of the specimen. Surgery is the curative treatment of choice and seems to be required to prevent regression of the inflammatory pseudotumor. Thoracoscopic techniques, when appropriate, are preferable, due to less invasiveness compared to classic thoracic surgical methods.

In cases being treated with immunosuppressive medication, the emergence of a solid cavitary lesion in lung should alert to the possibility it is an inflammatory pseudotumor and should be included in the differential diagnosis list.

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