

# Multiple pulmonary nodules presenting a difficult diagnostic challenge

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## Abstract

We describe the case of a 56 years-old man with a subacute onset of symptoms mimicking a granulomatosis with polyangiitis. He was admitted to our hospital with acute respiratory failure requiring oxygen therapy, fever and crusted rhinitis. Despite initial improvement in radiological and clinical features with a steroids therapy, his condition worsened rapidly and he was re admitted to our department with ARDS. Despite antibiotic, antiviral and anti-

fungal therapy, an endotracheal intubation was necessary and ultimately the patient passed away. Only a histological examination on autopsy had shown the presence of a diffuse Anaplastic Large Cell Lymphoma (ALCL), a rare type of non-Hodgkin lymphoma (NHL) originated from mature post-thymic T cells. It represents 1–3% of NHL. Different subtypes have been described: Kinase (ALK)-negative ALCL, ALK-positive ALCL and breast implant-associated ALCL. ALK-negative ALCL affects mainly old males and has the worst prognosis.

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## Introduction

The presentation of this case emphasizes the difficult diagnostic challenge of a patient presenting with symptomatic multiple pulmonary nodules even when a well-structured diagnostic approach is available.

## Case Report

A 56 years-old male carpenter presented at the local hospital complaining of progressive dyspnoea on exertion for 4 months and a one-month history of chest pain and high fever, especially at night. He was a 23 pack-years smoker and he suffered from celiac disease. The laboratory data showed normal haemoglobin and white cells count and a C-reactive protein of 64.53 mg/dl (normal range 0-6 mg/dl).

A chest and abdomen computed tomography (CT) with medium contrast was performed revealed multiple irregular necrotic bilateral nodulations, left hilar lymphadenopathy and left pleural effusion in the chest CT. Instead no abdominal lesions were evident. An electrocardiogram revealed atrial fibrillation. Bronchoscopy was not diagnostic and microbiologic and cytologic analyses of bronchial aspirate were negative for fungus and bacteria. Colonoscopy and gastroscopy were within normal limits. The patient was discharged from the suburban hospital with a diagnosis of suspected pneumonia and a pain-relieving therapy was prescribed.

Because of persistent chest pain, the patient two months later presented to our institution and was hospitalized for further evaluation. At admission he appeared distressed, febrile (38°C), and dyspnoeic. Physical examination revealed dullness to percussion in the basal part of left hemithorax and bilateral reduction of vesicular murmur. Percutaneous oxygen saturation (spO<sub>2</sub>) was 92% with 6 l/min supplemental oxygen. Blood gas analysis showed a respiratory alkalosis with a pH of 7.50, pCO<sub>2</sub> 31.5, pO<sub>2</sub> 65 mmHg and bicarbonate of 25 mmol/L, and alveolar-arte-

rial oxygen gradient of 45 mmhg. Laboratory data indicated a normal haemoglobin and a white cells count of  $3.75 \text{ cell} \cdot 10^9/\text{l}$  (normal 4,40-11,00), a dimer-D of 919 ug/L (normal 0-300 ug/L), C-reactive protein (CRP) of 116 mg/dl (normal 0-6 mg/dl), lactic dehydrogenase of 883 U/L and normal liver enzymes. Chest X-ray showed hilar adenopathy and bilateral irregular nodules (Figure 1). Pulmonary function test revealed a moderate restriction (total lung capacity 57% predicted) and a CO diffusion capacity of 44% predicted.

Suspecting a septic process due to the presence of hyperpyrexia with  $38^\circ\text{C}$  peak, high CRP and procalcitonin, the patient underwent antibiotic therapy (piperacillin/tazobactam and levofloxacin) and hydration with resulting febrile reduction but no benefits on dyspnoea. Chest CT with pulmonary angiography excluded an ongoing pulmonary embolism and confirmed the presence of bilateral nodules (Figure 1), which were biopsied under CT guidance (Figure 2). Pathology revealed a chronic necrotizing inflammatory process, consistent with granulomatosis, PAS and Grocott staining did not reveal any fungal infection. The investigated markers of epithelial and lymphatic neoplasia and of melanoma turned out negative as well as the PCR assay for mycobacterium species. An endobronchial ultrasound

(EBUS) bronchoscopy confirmed mediastinal adenopathy, so transbronchial needle aspiration (TBNA) on subcarinal lymphnode was performed. Cytology showed small lymphocytes, hyperplastic epithelial cells (CD45+, MNF116-, TTF1-, CD56-, synaptophysin-, 10% Ki67) compatible with reactive lymph nodes. Specifically investigating signs/symptoms of granulomatoid disease, we found out that the patient presented a form of crusted rhinitis and his wife reported a probable diagnosis of polyangiitis in 2011. A rhinoscopy confirmed the rhinitis and autoantibodies dosage revealed high title of cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA title 1:160).

Based on the past history, clinical presentation and laboratory findings, a diagnosis of granulomatosis polyangiitis was considered and the patient was started on metilprednisolone 125 mg twice a day with significant clinical and radiological improvement. Because of the still unresolved diagnosis, a Video Assisted Thoracic Surgery (VATS) was scheduled but never carried out due to the rapid deterioration of patient's symptoms. In particular fever, dyspnoea and severe hypoxemia secondary due to a mixed *pneumocystis carinii*, *staphylococcus aureus* and influenza virus infection irresponsive to treatment, respiratory failure and hemodynamic instability worsened and the patient eventually died.

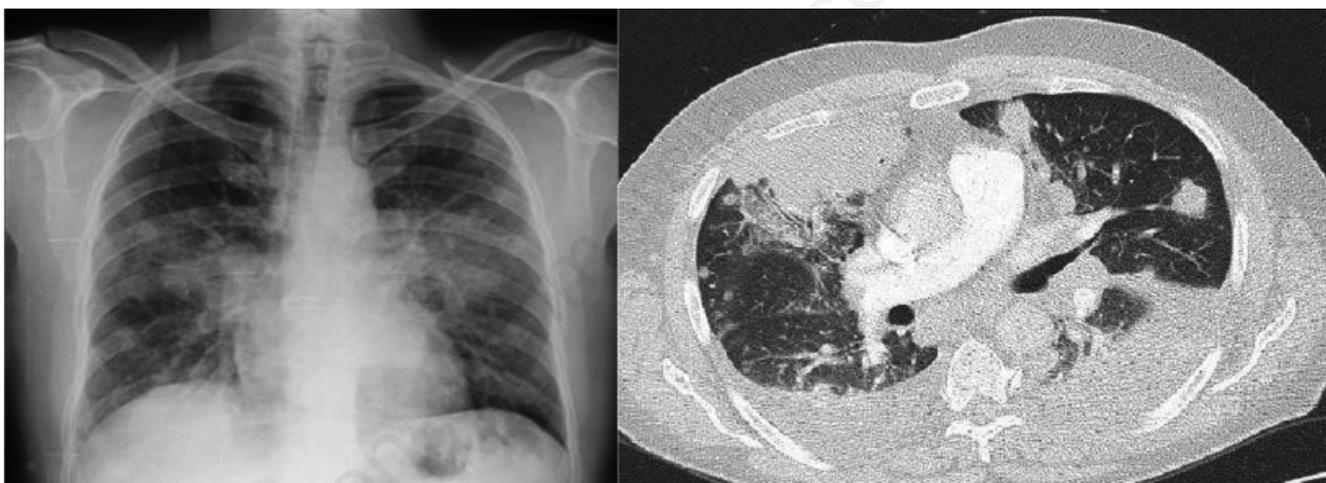


Figure 1. Diffuse lung opacities. Left: chest X-ray showing bilateral irregular nodules and hilar/mediastinal adenopathy. Right: chest CT showing an anterior right upper lobe mass, multiple nodules, aspects of consolidation and bilateral pleural effusion, more represented on the left side.

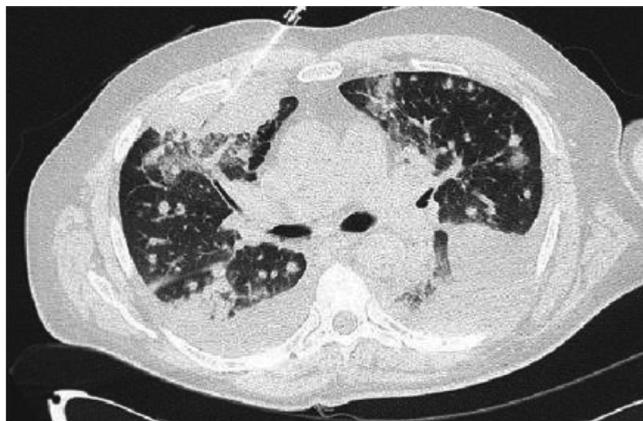


Figure 2. CT-guided transthoracic biopsy. The bioptic needle is sampling the right upper lobe lesion.

The post mortem examination revealed a diffuse monoclonal T cell infiltrate (immunohistochemistry: CD3+, CD30+, CD20 -, CD56 -, ALK1 -, pan-cytokeratin (MNF116) -, CK7-, CK20-, TTF1-, chromogranin-, synaptophysin-) diagnostic for a high grade anaplastic large cell lymphoma (ALCL) with cardiac, pulmonary, splenic, hepatic, renal, pancreatic and gastric localization.

## Discussion

Multiple pulmonary nodular lesions and/or masses with lung cavitations with hilar/mediastinal adenopathy need a careful and active differential diagnosis. Once infectious diseases are excluded, the main causes to be detected could be sarcoidosis, lymphoma, pulmonary lymphomatoid granulomatosis, Wegener's and other vasculitis, metastatic cancer/melanoma and less commonly primitive lung cancer (Table 1). In this case tissue samples obtained by CT scan guided lung biopsy and EBUS-TBNA were not diagnostic and the possibility of a solid neoplasia was not confirmed. The eventual diagnosis of granulomatosis with polyangiitis, was suggested by prior crusty rhinitis, Anti-Neutrophil Cytoplasmic Antibodies (ANCA) and the presence of necrotic nodular areas at lung CT. However, lack of microscopic haematuria and the typical small vessel angiitis, usually adjacent to major inflammatory lesions, lacked [1]. The occurrence of a rare form of lymphoproliferative disorder, specifically pulmonary lymphomatoid granulomatosis was suspected. This disease typically affects men between the ages of 30 and 50 and presents with poorly defined nodules throughout both lungs was suspected [2]. Lymphomatoid granulomatosis is associated in most cases with a Epstein-Barr virus (EBV)-associated B cells proliferation, but it may present a distinct form of T cell lymphoma, with no evidence of EBV infection [3]. Nonetheless, the diagnosis requires surgical biopsy, because transthoracic needle aspirate and transbronchial biopsy samples are too small for adequate evaluation of the classic triad of polymorphic lymphoid infiltrates, lymphatic transmural infiltration of vessels by lymphoid cells, and focal areas of necrosis [4]. Primary pulmonary

lymphomas are very rare accounting for only 3.6% of extranodal lymphomas, less than 1% of all NHL and less than 0.5% of all primary pulmonary malignant tumours [5] and are frequently misdiagnosed. In a recent report of 19 patients, most of these rare lung lymphomas were B-type and only 1 was an anaplastic large T-cell lymphoma [6].

Anaplastic Large Cell Lymphoma (ALCL), which affected our patient, is aggressive and rare forms of NHL [7] presenting with systemic symptoms as fever, night sweats, weight loss, rapidly progressive adenopathy, and early extranodal involvement (skin, liver, lung, bone) [8]. These lymphomas are classified according to the translocation of the *Anaplastic Lymphoma Kinase* (ALK) gene: *ALK*-positive forms affect children and young adults and have a better clinical outcome while *ALK*-negative tumours mainly affect older male patients [9]. Other variants are those associated to breast implants, characterized by good prognosis [10], and primary cutaneous ALCL. Recent studies showed that autoimmune disorders like celiac disease, as in this case, and psoriasis [11] may contribute to the risk of T-cell ALCL development suggesting chronic antigenic stimulation with local antigenic drive as a possible pathogenic mechanism ultimately leading to the development of lymphoma [12].

The diagnosis of primary systemic ALCL is best made by excisional tissue biopsy, most commonly a lymph node. At histology, large cells, often with horseshoe-shaped nuclei (so-called "hallmark" cells), with prominent nucleoli, mostly growing in cohesive-appearing sheets that sometimes cluster within lymph node sinuses are seen, an appearance that can mimic solid metastasis of carcinoma [13]. As in this case, nearly all ALCL express CD30, which could have been targeted by brentuximab vedotin, a CD30-directed antibody. An association of CD30-directed antibody and cyclophosphamide, doxorubicin and prednisone is the treatment of choice in these cases [14].

In conclusion, diffuse pulmonary consolidations in middle-aged patients could implied multiple differential diagnosis including from infectious, inflammatory and neoplastic diseases. Clinical and laboratory findings may give false clues and should be interpreted on the basis of a defined pathology. When less-invasive techniques, such as transbronchial needle biopsy and transthoracic biopsy, are not diagnostic, surgical approach is mandatory.

**Table 1. Differential diagnosis.**

Condition	Risk factors	Radiologic features	Histology
Metastatic solid neoplasia	Smoking history Colo-rectal and kidney cancer, melanoma	Bilateral nodules/masses, peripheral distribution with predilection of lung bases Mediastinal adenopathy Possible: pleural effusion, lymphangitic carcinomatosis	Depending on the primary lesion histology, frequently Necrotic
Granulomatosis with polyangiitis	Unknown, probable genetic predisposition to infective triggers	Scattered uni- or bilateral opacities up to 10 cm of diameter Cavitation with thick and irregular walls	Necrosis Vasculitis Mixed inflammatory infiltrates
Lymphomatoid granulomatosis	EBV infection B-cell lymphoproliferative diseases	Multiple bilateral nodules, mostly <1 cm along the bronchovascular bundles or interlobular septa Possible: cystic lesions	Polymorphic lymphoid infiltrates, Transmural vascular infiltration by lymphoid cells Focal necrosis
Anaplastic large cell lymphoma	Celiac disease, psoriasis, breast implants	Multiple opacities with speculated appearance Possible: cavitation, mediastinal adenopathy, pleural effusion	"Hallmark" cells: large cells with horseshoe-shaped nuclei

EBV, Epstein-Barr virus.

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