A Rare Case of Pulmonary Plasmacytoma with Multiple Myeloma Presenting with Bilateral Consolidative Cavitary Lung Lesions

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KEYWORDS
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ABSTRACT
Primary pulmonary plasmacytoma is a rare plasma cell neoplasm. Most reported cases involve the upper aerodigestive tract. Here, we report a 58-year-old male presenting with bilateral consolidative cavitary lung lesions. After an extensive investigation, the diagnosis of pulmonary plasmacytoma was suggested and then confirmed with histological and immunohistochemical examinations in addition to kappa light chain paraproteinemia that progressed to multiple myeloma. An autoimmune work-up showed that cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies (C-ANCA and P-ANCA) and other various antibodies being positive but without evidence of vasculitis or autoimmune disease. The patient was started on bortezomib, cyclophosphamide, and dexamethasone chemotherapy for three cycles but subsequently developed a respiratory infection that required intensive care management; he died after few months.

Introduction:

Rare cases of malignant plasma cell neoplasm are referred to as extramedullary plasmacytoma (EMP) of the soft tissues. Other entities include multiple myeloma, bone plasmacytoma and plasmablastic sarcoma [1]. Most reported cases of EMP involved the head/neck region, and upper respiratory tract. They rarely involve the lower respiratory tract. Clinical manifestations of EMP of the lung varies based on location of the lesion and present with non-specific respiratory symptoms. Radiological findings may include masses[2–6] nodules[1,7,8], endobronchial lesion[5,9–11], and alveolar consolidation[12]. Patients with EMP should undergo complete diagnostic workup to exclude concurrent multiple myeloma. Here, we present the case of a 58-year-old male patient with bilateral cavitary lung lesions found to have primary pulmonary plasmacytoma that progressed to multiple myeloma one year after initial presentation.

Case Presentation:

A 58-year-old male patient with unremarkable past medical history was referred to our center. He was admitted to an outside facility with bilateral cavitary consolidations in the lung and multiple mediastinal lymph node enlargement along with slightly impaired kidney function. The patient reported a history of chronic cough with minimal sputum production for the last seven months with subjective fever but denies hemoptysis, shortness of breath, chest pain, or other constitutional

symptoms. Further history was negative for epistaxis, chronic sinusitis, eye symptoms, or mucocutaneous manifestations. There were no gastrointestinal or neurological symptoms but occasional joint pain. Vital signs were stable. Examination revealed no palpable lymphadenopathy and equal breath sounds with bilateral crepitations. Cardiovascular and neurological examination was normal. The patient had left big toe dry gangrene.

Basic initial laboratory tests showed white blood cell count of 7.45 × 10^9/L with normal differentials, hemoglobin of 108 g/L, platelets at 1136 ×10^9/l. The urea was 11.8 mmol/l, creatinine was 181 micromol/l, calcium was 2.19 mmol/l, albumin was 33 g/l, and total protein was 101 g/l (Ref 65-81g/l). C-reactive protein was 86 mg/L, and the ESR was 122 mm/h. Peripheral blood smear showed normocytic anemia with marked thrombocytosis and rouleaux formation. Hepatitis B, C, and HIV tests were all negative.

The initial chest X-ray (*Figure 1)* showed multiple pulmonary nodules of variable sizes in both lung fields with left-sided pleural effusion. Computed tomography (CT) scan of the chest revealed significant mediastinal and hilar lymphadenopathy and multifocal consolidative and cavitary lung lesions with left sided pleural effusion (*Figure 2).* CT angiography of the lower extremities indicated complete popliteal artery occlusion bilaterally consistent with an embolic event versus thrombosis rather than atherosclerotic disease. No destructive lesions were seen on the skeletal survey. No abnormalities were seen on echocardiography. Further diagnostic tests were commenced, and autoimmune work up detected positivity of autoantibodies as shown in *Table 1*. No proteinuria was noted.

Serum protein electrophoresis (SPEP) and immunofixation showed monoclonal gammopathy (IgG kappa). The M spike was 28.6% of the total serum protein and 74.5% of the total gamma globulin. Urine protein electrophoresis (UPEP) and immunofixation were normal and negative for the Bence Jones protein. Ig free light chain in urine was negative. Immunoglobulin analysis revealed IgG at 41 g/l (Ref. 7-16 g/l) as well as normal IgM, IgA, and IgE levels. Beta 2-microglobulin was 10.3 g/l (0.80 – 2.20mg/l). Serum free light chain showed Ig free light chain kappa at 122 mg/l and Ig free light chain kappa of 31.30 mg/l; the JAK2 mutation not detected.

CT-guided biopsy of the right lower lobe lesion was performed. The examined sections showed dense lymphoplasmacytic infiltrate composed predominantly of plasma cells. There was no evidence of granuloma. IHC showed that CD138 highlighted the numerous plasma cells. The lymphocytes are composed of mixed B-cell (CD20+) and T-cell (CD3+). Kappa and Lambda light chains were inconclusive. The study was not supportive of IgG4 related disease and no clonality was confirmed to support light chain disease. Infectious etiologies were ruled out. Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy showed dense bronchial wall plasma cell rich infiltrate. Molecular testing for IgH rearrangement was negative excluding a neoplastic nature to the plasma cells. Infections and malignancy were excluded. Congo Red stain for amyloidosis was negative. Bone marrow aspirate showed normal cellularity with no infiltrative process noted. Bone marrow trephine biopsy confirmed normal cellularity with plasma cells less than 1%. Open lung wedge biopsy was attempted with pleural fluid aspiration—pleural fluid showed many plasma and plasmacytoid cells. Histopathology revealed patchy lymphohistocytic infiltration that was negative for malignancy, granuloma, and vasculitis.

The patient underwent angioplasty of the lower extremities and commenced on anticoagulation. He was given a provisional diagnosis of lupus nephritis versus ANCA-associated vasculitis by

rheumatology. In addition to anti-phospholipid antibody syndrome and monoclonal gammopathy. Renal biopsy was deferred due to atrophic kidney on images. Due to the overall clinical picture with positive serology, he was treated empirically with prednisolone and azathioprine but later switched to mycophenolate mofetil by nephrology to possibly treat lupus nephritis. However, his condition was deteriorating, and he was given pulse methylprednisolone and initiated on cyclophosphamide, which dramatically improved his condition. He was thus discharged from the hospital with further plans of continuation on cyclophosphamide.

Two months later, the patient was re-admitted with respiratory symptoms, hemoptysis, anorexia, weight loss, and subjective fever. He had multiple repeated respiratory infections with mucormycosis, invasive pulmonary aspergillosis, and bacterial pneumonia. Chest CT revealed interval progression of lung disease and consolidation of the left upper lobe. CT-guided lung biopsy was repeated and demonstrated a brisk plasmacytic infiltrate with positive clonality of kappa light chain-restricted plasma cell neoplasm. IHC was diffusely positive for CD138, CD43, CD20, CD3, and IgG. It was negative for CD20 and CD3. Repeated bone marrow aspiration and biopsy showed many plasma cells estimated around 17%. The patient was started on VCD chemotherapy consisting of bortezomib (Velcade), cyclophosphamide, and dexamethasone. He completed three cycles, however, his course evolved into multiple complicated episodes of bacterial/viral pneumonia that required intensive care management and invasive ventilation. He was deemed not candidate for any further systemic chemotherapy, and he died few months later.

Table. 1: ***Serological Testing:***

Test	**Result**	**Reference range**
ANA	Positive	Negative
ANA Titer	A Speckled 1:160	
Anti-DsDNA	>800 U/mL.	0-200 U/mL
Anti-Smith	16.1 U/mL	0-5 U/mL
Anti-SCL-70 antibody	8.8 U/mL	0-3 U/mL
Anti-RNP antibody	12.1 U/mL	0-10 U/mL
Anti-SSA (Ro)	35.8 U/mL	0-20 U/mL
Anti-SSB (La)	13.3 U/mL	0-4 U/mL
ANCA IF	Positive	Negative
C-ANCA, (PR3 Antibodies)	28.9 U/ml	0-10 U/ml
P-ANCA, (MPO antibodies)	50 U/ml	0-6 U/ml
C3	1.55g/l	0.90-1.80 g/l
C4	0.50g/l	0.10-0.40 g/l
Lupus Anticoagulant	Positive	Negative
Anti B2-Glycoprotein IgM	5.2 U/mL	0-12 U/mL
Anti B2-Glycoprotein IgG	11.4 U/mL	0-10 U/mL
Cryoglobulins	Absent	Absent
Rheumatoid Factor	<10 IU/mL	0-14 IU/mL
Cyclic citrullinated peptide antibodies	1.3 U/mL	0-4.9 U/mL
Anti-GBM antibodies	Negative	Negative

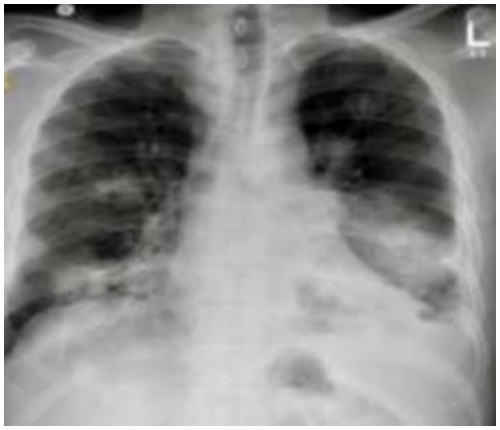

Figure 1

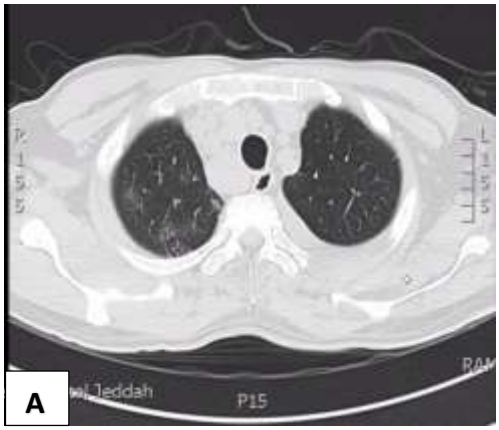

Figure 2. A

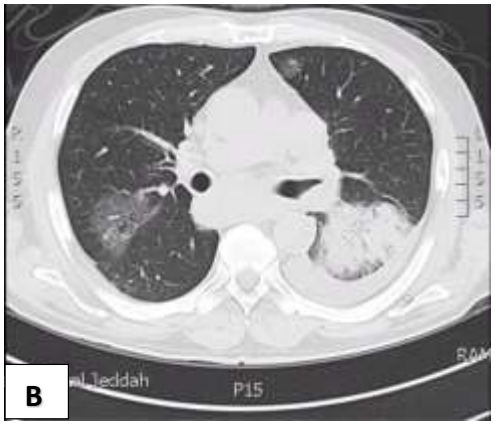

Figure 2. B

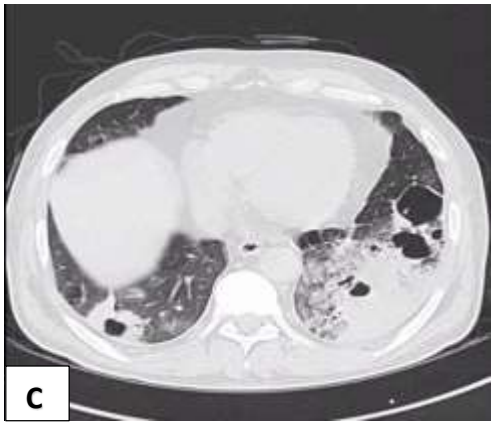

Figure 2. C

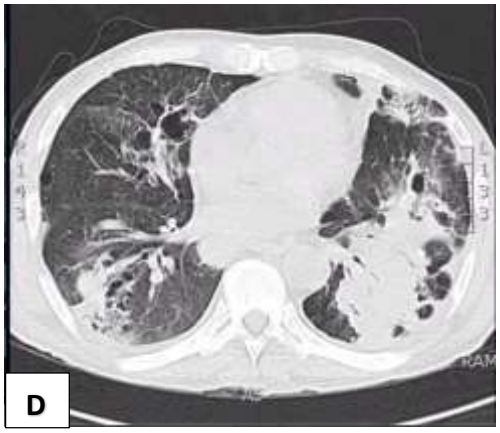

Figure 2. D

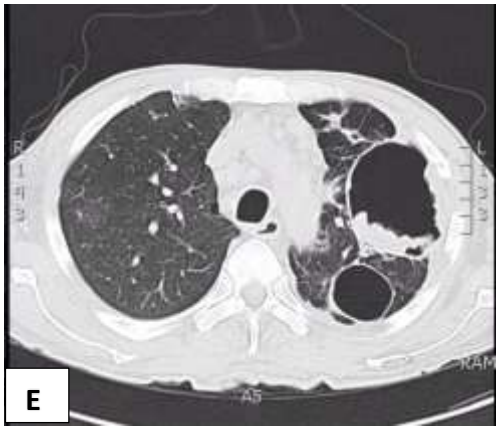

Figure 2. E

Figure 1.
Multiple pulmonary nodules of variable sizes are seen in both lung fields.

Figure 2.
Serial computed tomography (CT) of the chest showing significant mediastinal and hilar lymphadenopathy (A), multifocal consolidative lung lesions with reactive pleural effusion on the left side, and bilateral patchy consolidations with cavitation (B,C). Multiple cavitatory lesions were seen with surrounding ground-glass opacities in the both lungs but predominantly in the left lung (D,E).

Table 2: Comparison of pulmonary presentation of PPP as described by various authors:

Author	Age/Sex	Presentation (Radiological/Hematological)	Treatment	Outcome
Shi-Ping Luh[1]	42/F	Right anterior mediastinal shadow with multiple pulmonary nodular lesions. No evidence of MM.	Chemotherapy	Improved after two months of treatment
Agrawal S[2]	50/M	Lobulated mass of left lower lung lobe with endobronchial extension. No evidence of MM.	Radiotherapy	Significant symptomatic and radiological improvement after 4 weeks.
Rahim Y[3]	55/M	Right upper lobe lobulated mass. IgG lambda monoclonal gammopathy.	Radiotherapy, Chemotherapy	Reduction of tumor size at six months follow up.
Si Nie[4]	48/M	Left lower lobe lung nodule No evidence of MM.	Chemotherapy	Disease free during 1.5 years follow up
Montero C[5]	59/M	Left main bronchus tumor and enlarged subcarinal lymph nodes. No evidence of MM.	Surgical resection, Radiotherapy	Disease free during 10 years follow up
Montero C[5]	64/M	Right upper lobe mass. IgG kappa monoclonal gammopathy	Radiotherapy	Disease free during 15 years follow up
Montero C[5]	56/M	Right upper lobe bronchial tumor with mediastinal lymph node disease. IgA kappa monoclonal gammopathy.	Radiotherapy, Chemotherapy	Death
Yi Zhou[6]	61/F	Right middle and lower lobe lung mass. No evidence of MM.	Surgical resection and postoperative chemotherapy.	Treated with no evidence of recurrence.
Kumar S[7]	80/M	Right lower lobe solitary lung nodule. No evidence of MM.	Radiotherapy	Complete resolution
Sang-Heon Kim[8]	26/F	Bilateral multiple lung nodules with ground glass opacities. No evidence of MM.	Chemotherapy	Near complete resolution
Evgeny Edelstein[9]	47/M	Left main bronchus mass. No evidence of MM.	Endoscopic debulking followed by laser ablation	No recurrence after eight months
Jong Il Park[10]	86/M	Endobronchial mass obstructing the left upper lobar bronchus with obstructive pneumonitis. No evidence of MM.	Radiotherapy	Treated with no evidence of recurrence at six months.

Taheri Z[12]	60/F	Hilar and mediastinal lymphadenopathies. Right lung alveolar consolidation and left lung nodular infiltration. No evidence of MM.	Chemotherapy	Free of symptoms with normal chest x-ray after treatment.
Present Case	58/M	Mediastinal and hilar lymphadenopathy and multifocal consolidative and cavitary lung lesions. Progressed to MM after 1 year.	Chemotherapy	Death

Discussion:

Extramedullary plasmacytoma (EMP) is characterized by a neoplasm derived from plasma cells occurring outside the bone marrow and lacks specific features of multiple myeloma (MM). It accounts for around 3-5% of all plasma cell neoplasms. Males are predominantly affected (three- to four-fold more than females)[14]. We present here a case of a patient diagnosed with pulmonary plasmacytoma that subsequently progressed to multiple myeloma one year after his initial presentation with bilateral cavitary lung lesion and impaired kidney function. Although MM can initially present as renal failure, the concomitant presentation with lung involvement and digital ischemia mimicked autoimmune disease such as systemic lupus erythematosus versus ANCA-associated vasculitis. Even though kidney biopsy was deferred due to atrophic kidney, there was no evidence of vasculitis on the biopsied lung lesions. Our patient had serologic positivity of ANA, anti-dsDNA, anti-Smith, and ANCA. He had elevated PR3 and MPO antibodies by ELISA. Only a few reported cases in literature have demonstrated the probable association between AAV and MM. Kapoulas[15] reported a patient who was diagnosed with MM and had confirmed MPO-ANCA-associated necrotizing crescentic glomerulonephritis proven by renal biopsy but eventually died from fatal pulmonary hemorrhage. Roper et al.[16] reported a 60-year-old male with acute renal failure due to cast nephropathy from MM who had positive perinuclear ANCA (p-ANCA) and MPO antibodies. Cheta[17] reported a patient with MM presented with acute renal failure and positive PR3 and MPO antibodies but whose serum ANCA was negative with no evidence of vasculitis on kidney biopsy.

Pulmonary involvement with plasma cell neoplasm can be either solitary primary pulmonary plasmacytoma (PPP) without marrow involvement or with extramedullary involvement of the lungs[10,18]. Disseminated MM to the lung is more common compared to PPP[14]. Plasmacytoma of the lung can be the initial presentation preceding the diagnosis of multiple myeloma as in our case. While several reports have shown that symptoms of pulmonary plasmacytoma varies based on location of the lesion, they mostly present with cough, shortness of breath, and chest pain; they may also be asymptomatic. Radiological signs may include pulmonary nodules, mass adjacent to the hilum, diffuse bilateral reticulonodular infiltration, and lobar consolidation as shown in *Table 2*. Some studies revealed that both lungs are equally involved with lesions occurring most predominantly at the upper lobes[19].

Due to non-specific symptoms and signs on imaging, pulmonary plasmacytoma diagnosis requires both histological examination of the neoplasm, and immunohistochemical markers to exclude other differential diagnoses. Plasmacytoma carries positivity of CD138 and CD38, especially CD138[4,20]. In some cases where patients were presented with parenchymal involvement rather than mass or nodules, BAL was used for diagnosis with findings of monoclonal plasma cells[18]. Bone marrow examination has to be performed to exclude multiple myeloma as plasma cells must be less than 5% with no dyscrasia, normal skeletal survey, and no bone lesions. Diagnosis was

difficult to yield in our case due to multiple inconclusive lung biopsies despite the fact that they showed plasma cells.

Histopathology did not support the presence of neoplastic cells. Furthermore, the disease course was complicated by repetitive superimposed fungal, viral, and bacterial infections that led to worsening respiratory conditions and worsening of the cavitary lung lesions. AAV is a group of vasculitic disorders predominantly affecting small vessels causing necrotizing vasculitis, which can be furtherly classified into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). GPA frequently involves upper, lower respiratory systems, and kidneys causing necrotizing granulomatous inflammation. SLE is a multisystem autoimmune disease. There is a well-known association between development of lymphoproliferative diseases (mainly lymphomas) during the course of some autoimmune rheumatological diseases such as Sjogren's syndrome, dermatomyositis, and systemic lupus erythematosus.

In contrast, solid malignancies can cause paraneoplastic syndromes with symptoms mimicking that of rheumatological conditions. Lupus-like syndromes can occur as paraneoplastic phenomenon with clinical and serological features similar to those in primary SLE[21]. A reported case described a 47-year-old male who presented with rapid progressive decline of kidney function due to acute interstitial nephritis associated with rheumatoid arthritis (RA)-like symmetrical polyarthritis, but he eventually was diagnosed with multiple myeloma[22]. Paraneoplastic vasculitis was found to be associated with solid malignancies especially those involving lung, gastrointestinal, and renal systems[23–25] as well as hematological malignancies like lymphoproliferative disorders, and myelodysplastic syndromes[21]. The most common presentation of vasculitis in association with malignancy is cutaneous leucocytoclastic vasculitis[25,26]. Paraneoplastic vasculitis may antedate the diagnosis of malignancy, occur simultaneously, or follow the diagnosis of malignancy[23,25]. However, some factors including the patient's age at diagnosis, acuity of symptoms, and response to treatment might be suggestive of an occult malignancy and further work up should be undertaken.

There are several reported cases demonstrating the development of AAV and hematological malignancies—mainly lymphoproliferative diseases[26,27]. However, association of vasculitis with MM remains rare. A case has been described for a 37-year-old male with MM presented initially with polyarteritis nodosa (PAN)-like features who eventually required small bowel resection due to perforation with histopathology, thus disclosing PAN-associated necrotizing vasculitis[28]. As mentioned in the literature, different modalities were used for treatment of pulmonary plasmacytoma including surgical resection, radiotherapy, systemic chemotherapy, or a combination (*Table 2*).

In conclusion, the occurrence of pulmonary plasmacytoma as an initial presentation preceding multiple myeloma diagnosis remains challenging due to the rarity of disease as well as a lack of specific manifestations. We present here a case of EMP in the form of pulmonary plasmacytoma presenting uniquely with cavitary lung lesions and Kappa light chain paraproteinemia but that eventually progressed to MM. We reported this case to emphasize the need for serial follow-up to rule out systemic disease with bone marrow involvement in the setting of pulmonary plasmacytoma. Positivity of specific autoantibodies and ANCA serologies does not necessarily indicate the presence of autoimmune disease or ANCA-associated vasculitis. Histopathological

examination of the affected organ remains the cornerstone for diagnosis. Differentiation between these two entities is critical because it will implicate further therapeutic decisions.

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