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Pulmonary Metastasis in a Patient with Simultaneous Bladder Cancer and Relapsing Granulomatosis with Polyangiitis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 70
Final Diagnosis: Metastatic micropapillary urothelial carcinoma
Symptoms: Dry cough • dyspnea • hematuria
Medication: Cyclophosphamide
Clinical Procedure: Pulmonary wedge resection
Specialty: Pulmonology

Objective: Unusual clinical course
Background: Granulomatosis with polyangiitis (GPA) relapse can complicate the differential diagnosis of pulmonary lesions.
Case Report: A 70-year-old male smoker with GPA and emphysema presented with dyspnea, dry cough, and a right upper lobe pulmonary ground-glass opacity that persisted despite antibiotics. A trans-bronchial biopsy did not reveal active vasculitis, malignancy, or infection. He was treated for presumed GPA relapse based on pulmonary manifestations, renal failure, and elevated PR3-ANCA. Later, hematuria led to the cystoscopic discovery of a bladder wall lesion, which was diagnosed as micropapillary urothelial carcinoma not involving the muscularis propria. The patient developed an increasing pulmonary infiltrate with a new solid component, satellite lesions, and regional lymphadenopathy. A right upper lobe wedge resection showed metastatic urothelial carcinoma.

Conclusions: The simultaneous presentation of a pulmonary lesion and GPA relapse is a diagnostic challenge. The differential diagnosis should include the rare possibility of metastatic urothelial carcinoma, regardless of how the lesion appears radiographically.

MeSH Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis • Antibodies, Antineutrophil Cytoplasmic • Hematuria • Solitary Pulmonary Nodule • Wegener Granulomatosis

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/893406>

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Background

Granulomatosis with polyangiitis (GPA), formerly called Wegener's granulomatosis, is the most common ANCA-associated vasculitis. The diagnosis of GPA relapse is often challenging.

Cyclophosphamide, a cornerstone in achieving GPA remission, is strongly associated with bladder cancer [1–3]. We report the first case of pulmonary metastatic urothelial carcinoma presenting atypically as a single and progressive ground-glass opacity in a patient with GPA relapse and prior cyclophosphamide exposure.

Case Report

A 70-year-old Caucasian male smoker with emphysema presented with a 2-month history of dyspnea and a dry cough. Five years previously, he was diagnosed with GPA when he presented with diffuse alveolar hemorrhage and acute glomerulonephritis. Serology and renal biopsy were consistent with GPA at that time. He received cyclophosphamide and prednisone followed by mycophenolate, with clinical improvement. His cumulative cyclophosphamide dose was 19 grams (1 gram in a single intravenous dose and 18 grams in 6 months of daily oral dosing).

During his present workup, serology studies revealed significant increases in proteinase-3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) and C-reactive protein (CRP) levels: his PR3-ANCA, which had been undetectable on 25 preceding tests, was now 3,712 EU/ml; his CRP, consistently within normal range on prior tests, was now 64 mg/L. The patient also had developed acute-on-chronic renal insufficiency with new-onset nephrotic-range proteinuria, consistent with GPA renal flare. Chest computer tomography (CT) revealed a new right upper lobe (RUL) ground-glass opacity (Figure 1A, 1B). Despite levofloxacin therapy, a chest CT 5 weeks later showed enlargement of the RUL opacity (Figure 1C). A RUL trans-bronchial biopsy did not demonstrate alveolar hemorrhage, vasculitis, or malignancy, and cultures were negative. High-dose steroids were therefore started for presumed relapsing GPA, and mycophenolate was continued.

One month later, routine urinalysis revealed microscopic hematuria. Cystoscopy revealed a flat, erythematous bladder wall lesion. A biopsy showed micropapillary urothelial carcinoma (MUC) invading the lamina propria and lymphovascular spaces (Figure 2A, 2B), flat urothelial carcinoma *in situ*, and no tumor in the muscularis propria. Pelvic magnetic resonance imaging showed a 4-cm tumor involving the bladder left anterolateral wall with retroperitoneal aortocaval and pelvic lymphadenopathy.

Five weeks later, serology showed persistently elevated levels of PR3-ANCA (816 EU/ml) and CRP (52 mg/L). A follow-up chest CT revealed enlargement of the RUL lesion, now with a solid component as well as satellite nodules and pre-vascular lymphadenopathy (Figure 1D). A RUL wedge resection was performed and high-grade metastatic MUC carcinoma was found (Figure 2C, 2D; immunostains were positive for CK7 and CK20, and negative for p63, TTF-1, and CDX-2). Large vessels were filled with tumor cells and the surrounding lung parenchyma showed extensive ischemic necrosis without evidence of active vasculitis or granuloma. After the pulmonary wedge resection, the patient developed severe refractory hypoxemia followed by cardiopulmonary arrest and death.

Discussion

GPA is a small-vessel vasculitis in which autoantibodies (c-ANCA) are produced against cytoplasmic antigens found in neutrophils, usually proteinase-3 (PR3-ANCA). Although the specificity of elevated c-ANCA titers for the initial diagnosis of GPA can be up to 99%, its role in measuring disease activity and predicting relapse is controversial [1–3]. Rarely, PR3-ANCA has been detected in hematopoietic malignancies, but it has not been detected in urothelial or other solid tumors from patients with GPA [4].

In our patient, GPA relapse was suggested by elevated PR3-ANCA titers, worsening respiratory function with new pulmonary infiltrate, worsening renal failure with associated proteinuria to nephrotic levels, and newly elevated acute-phase reactants.

Some of the pulmonary manifestations of GPA overlap with those of many other pulmonary diseases – cough, shortness of breath, upper airway disease, alveolar hemorrhage, a single mass, multiple nodules, cavities, and infiltrates [5].

While chest imaging findings in patients with GPA can mimic lung primary and secondary malignancies, the patient's initial chest CT (Figure 1B) was not characteristic of a metastatic lesion. Whereas the patient had a single ground-glass opacity, pulmonary metastases are usually discrete oval or rounded lesions, multiple, peripherally located, and often sub-pleural. Moreover, there was no mediastinal or hilar adenopathy, pleural effusion, or evidence of lymphangitic spread. Furthermore, an upper lobe location is an unusual presentation of metastasis. The patient's pulmonary lesion turned out to be a metastatic cancer despite all the above evidence to the contrary on his initial presentation.

Bronchoscopy was chosen as the initial diagnostic modality because it has a relatively low risk of complications and can help rule out infection. However, the trans-bronchial biopsy

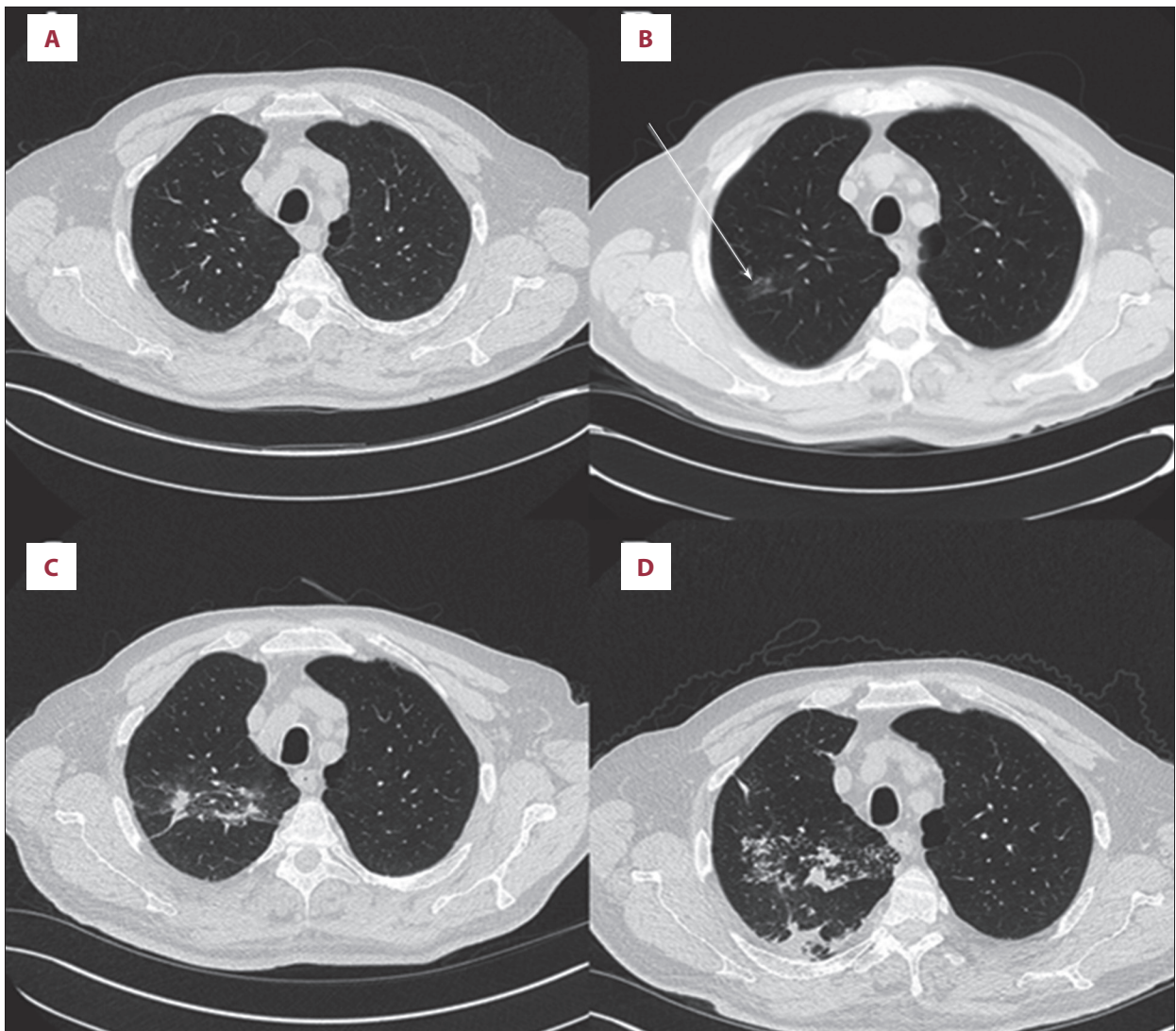


Figure 1. CT Chest. (A) One year prior to presentation. (B) New right upper-lobe ground-glass opacity (arrow) at initial presentation. (C) Progression of lesion 5 weeks later. (D) Worsening primary lesion with prominent satellite lesions 14 weeks after initial presentation.

result was inconclusive; it neither confirmed active vasculitis nor provided an alternate explanation for the lung lesion (such as an infection). Although the role of bronchoscopy in the diagnosis of active vasculitis is questioned [6], CT-guided percutaneous transthoracic biopsy of the lung was not chosen as the initial diagnostic approach due to its higher risk of iatrogenic pneumothorax, particularly in a patient with emphysema. Open-lung biopsy is often required for a definitive diagnosis of active vasculitis [6], as well as to rule out other potential diagnoses like cancer in our patient.

Patients with GPA are at an overall increased risk of cancer [4,7]. While their risk of bladder cancer is strongly associated with cyclophosphamide duration and cumulative dose [8,9], a few retrospective studies have also suggested an association

between GPA itself and solid malignancies, specifically bladder and renal carcinomas [4,7]. In the latter studies, which excluded malignancies secondary to immunosuppressive therapy, most cases of malignancy were diagnosed at the onset of vasculitis. Therefore, although our patient was diagnosed with GPA 5 years ago and had received cyclophosphamide, we cannot completely rule out the possibility that his vasculitis was related to a predisposition for malignancy. Since hematuria is common to both GPA renal flare and bladder cancer, its cause must be investigated in these high-risk patients. Cystoscopy in our patient led to the initial diagnosis of the primary urothelial carcinoma.

In our literature search, we identified only 1 other report of a patient with GPA and pulmonary metastatic bladder cancer.

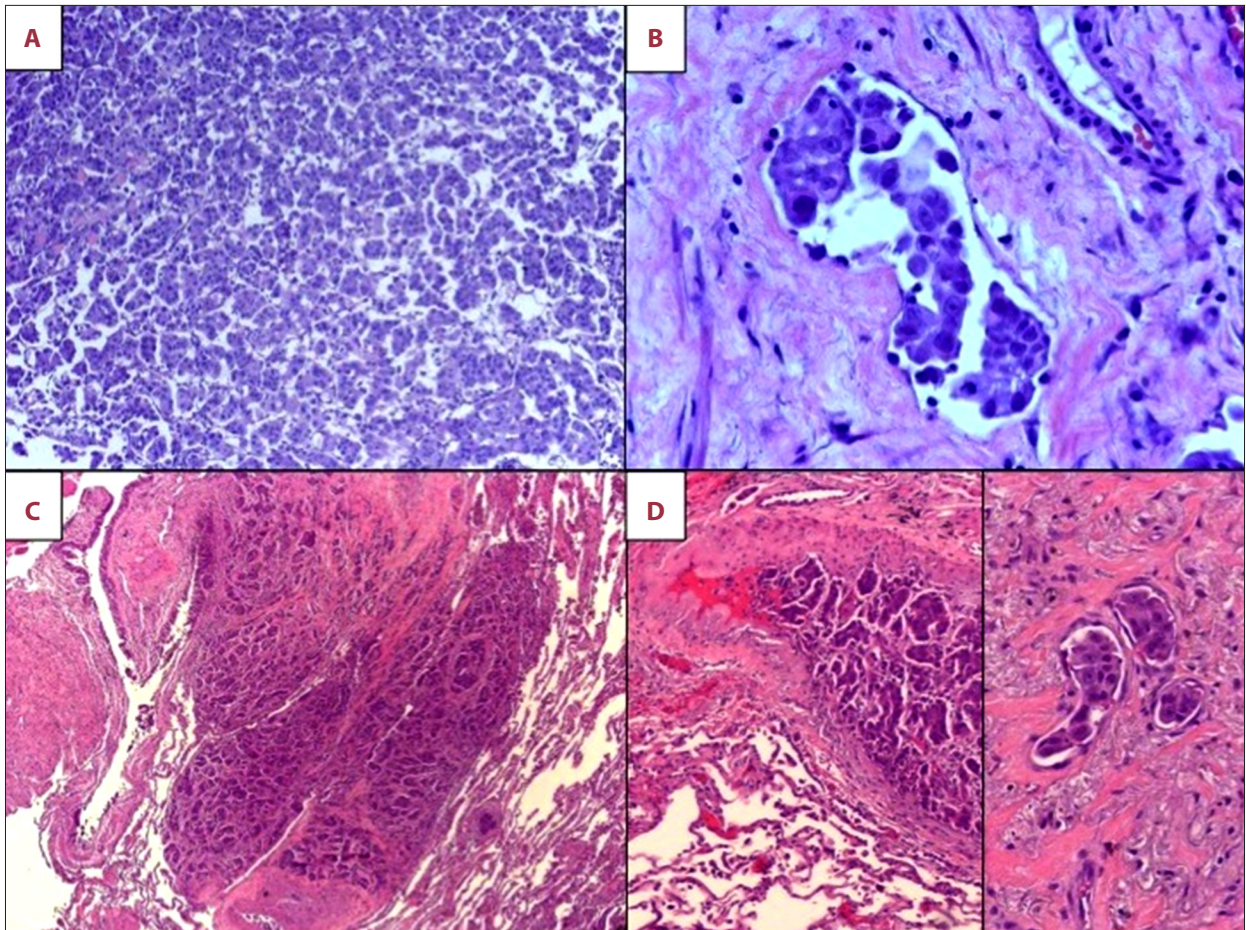


Figure 2. Hematoxylin and Eosin-stained sections of bladder and lung pathology. (A) (10 \times), (B) (40 \times): Bladder biopsy showing micropapillary urothelial carcinoma with lymphovascular invasion in the lamina propria. (C) (10 \times), (D) (20 \times): Lung wedge resection showing metastatic micropapillary carcinoma with extensive lymphovascular invasion.

The patient had received cyclophosphamide, and presented classically with multiple, bilateral, small (<1.5 cm) pulmonary nodules [10].

Bladder malignancy and other bladder diseases are the usual causes of non-glomerular hematuria; however, active renal involvement by GPA can also cause the same [8]. Our patient's non-glomerular hematuria posed not only a diagnostic challenge, but also the opportunity to diagnose the primary neoplasm.

The patient's new bladder cancer diagnosis, subsequent radiographic suspicion for pulmonary malignancy, and rapid pulmonary lesion progression despite immunosuppressive therapy prompted us to pursue a RUL wedge resection, which was diagnostic for metastatic MUC. The absence of histologic evidence for vasculitis in the resection could have been related to increased immunosuppressive therapy, necrotic masking, sampling limitation, or absence of GPA pulmonary flare.

Micropapillary urothelial carcinoma is a high-grade variant seen in 0.7% of urothelial carcinomas [11]. Its presence, even focally, is associated with extensive lymphovascular invasion and poor prognosis [12–16]. In metastases from mixed urothelial carcinomas, the micropapillary component predominates, as demonstrated in our patient's disease course [15]. Urothelial carcinoma metastasis without muscularis propria invasion is unusual, but muscularis propria involvement may have been missed in the limited biopsy sample [17].

Ours is the first report of a pulmonary metastatic urothelial carcinoma potentially masquerading as GPA pulmonary flare. Our case illustrates some of the clinical challenges in diagnosing and managing a patient with GPA flare. Elevation of GPA-associated serologic markers can be used to guide initial management, but their utility in defining vasculitis activity or relapse is limited. Clinical correlation is essential. The initial diagnostic approach should include ruling out pulmonary infections, since the treatment of a vasculitis relapse with high-dose immunosuppressive agents could be detrimental to a patient with an underlying infection.

If bronchoscopy is non-diagnostic, an open-lung biopsy should be considered for a patient with a non-resolving progressive infiltrate and clinical deterioration despite empirical treatment.

Conclusions

GPA relapse is a diagnostic challenge and can mask pulmonary metastasis from micropapillary bladder carcinoma.

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