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Case Report

Vasculitis manifested with multiple mass lesions in kidneys, lungs and soft tissue, mimicking malignant tumors

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ABSTRACT

We report a case of granulomatosis with polyangiitis (GPA) (Wegner's granulomatosis) who presented with multiple mass lesions in kidneys and lung lobes, as well as neck soft tissue, mimicking malignancies. This 71-year-old woman initially presented with sudden right foot drop, left calf pain and right eye vision loss. She was treated with corticosteroid for the diagnosis of possible temporal arteritis. Months after steroid was tapered to 2 mg per day, she developed increasing fatigue, weight loss, and shortness of breath. CT scan showed lung mass lesions in left upper lobe (3.8 × 2.4 cm), right mid lung with pleural extension (3.4 × 3.3 cm), and right lower lobe (1.1 × 1.0 cm); right neck (3.3 × 2.6 cm), right kidney (2.3 × 1.8 cm) and left kidney (2.0 × 1.6 cm). Right quadriceps muscle biopsy shows focal granulomatous inflammation. Lung biopsy showed necrotizing and poorly formed granulomatous inflammation. Biopsies of kidney mass lesions showed necrotizing and non-necrotizing granulomatous inflammation. No crescentic or necrotizing glomerular lesions were observed in the total 40 sampled glomeruli. No malignancy was identified in any of the biopsies. Her c-ANCA was found to be positive and PR3-ANCA antibody was 6.88 U/ml (normal 0–0.90 U/ml). She was diagnosed with granulomatosis with polyangiitis and treated with high dose corticosteroid and rituximab. Eight months later, follow-up showed resolved mass lesions by chest X-ray and CT and stable renal function. The case highlights the atypical clinical presentation of vasculitis and the significance of considering this possibility in differential diagnosis when confronting mass lesions present in multiple organ systems. Biopsy is critical for the correct diagnosis to initiate timely and appropriate treatment, and also important to avoid unnecessary surgical resection.

1. Introduction

Vasculitis is a group of diseases with protean presentations, many of which are vague and non-specific, causing broad clinical consideration and hence challenges in reaching the correct diagnosis [1,2]. Mass lesions in the kidneys and lungs often raise the concern of malignancy, while vasculitis is rarely come to differential diagnosis as a possible cause. Occasionally unnecessary resection including lung lobectomy or wedge resection and partial or total nephrectomy have been performed due to the mass lesions [3,4]. Here we report a patient with multiple mass lesions in the lungs and kidneys as well as in soft tissue of neck, which clinically were highly suspicious for malignant neoplasms, but pathology findings of biopsies along with additional laboratory tests are consistent with granulomatosis with polyangiitis (GPA) (Wegner's granulomatosis). Immunosuppressive therapy resulted in resolution of the mass lesions.

2. Case report

A 71 year old female patient with past history of hypertension, hypothyroidism and gastroesophageal reflux disease presented with sudden right foot drop, left calf pain and right eye vision loss on February 2016. Ophthalmologic examination showed right eye central retinal artery occlusion. Chest X-ray showed that lungs were negative with mild cardiomegaly. Biopsy on bilateral temporary artery was done which showed mild intimal fibrosis. She was started on high dose

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prednisone for possible temporal arteritis, which gradually tapered to 2 mg in February 2017. She developed increasing fatigue, weight loss, shortness of breath, abdominal pain and lower leg pain on August 2017. Chest CT showed solid masses in the lungs, including one in the left upper lobe, one in the right mid lobe with pleural extension and one in the right lower posterior lung. A partially visualized mass was also seen on the superior pole of the right kidney. Neck CT showed a 3.3 × 2.6 × 2 cm subcutaneous lesion. Abdominal CT showed a mass in the right superior kidney and a mass in the left inferior kidney; liver, spleen, pancreas and adrenals appeared normal. Radiology considered lung masses were compatible with malignant metastasis and renal mass lesions concerning for renal cell carcinoma. The right mid lung lobe mass and both kidney mass lesions were biopsied. Additional tests showed c-ANCA and PR3-ANCA antibody positive. She was then diagnosed as GPA, and received prednisone and rituximab treatments on October 2018.

2.1. Laboratory results

Serum creatinine 0.86 mg/dl (reference range 0.6–1.2 mg/dl), GFR 75.1 ml/min (> 59 ml/min), CRP 102.9 mg/L (0.3–5.0 mg/L), ESR 109 mm/h (0–30 mm/h), cryoglobulin test negative, antinuclear antibody negative, C3 148 mg/dl (88–201 mg/dl), C4 26 mg/dl (10–40 mg/dl), c-ANCA 1:40, p-ANCA negative, atypical ANCA negative, anti-PR3 IgG 6.99 U/ml (0–0.90 U/ml), anti-MPO IgG 0.09 U/ml (0–0.90 U/ml), tuberculosis Quantiferon Gold test negative. Urine protein 40 mg/dl (0–20 mg/dl), urine protein creatinine ratio 0.18 (0–0.19), RBC 0–2/HPF (0–2/HPF), WBC 1–5 /HPF (1–5/HPF).

2.2. Radiology results

CT of Chest on August 2017 showed a mass lesion in the left upper lobe of lung, measuring 3.8 × 2.4 cm, a mass in the right mid lung with pleural extension, measuring 3.4 × 3.3 cm, and a mass in the right lower posterior lung, measuring 1.1 × 1.0 cm. Neck CT on September 2017 showed a 3.3 × 2.6 × 2 cm subcutaneous lesion, superficial to the musculature in the right lateral neck. The parotid and submandibular glands and mucosal surfaces are unremarkable. CT of Abdomen on November 2017 showed a mass lesion in the superior lateral aspect of right kidney measuring 2.3 × 1.8 cm, a second mass in the inferior pole of left kidney measuring 2.0 × 1.6 cm. Liver, spleen, pancreas and adrenals appeared normal (see Fig. 1).

2.3. Pathology findings

The patient had biopsy of right and left temporal arteries on March 2017, which showed mild intimal fibrosis compatible with aging changes, and negative for inflammation in serial sections. The patient had right quadriceps skeletal muscle and sural nerve biopsies which showed focal granulomatous inflammation, mild type II fiber atrophy and moderate axonopathy. Right lung mass lesion biopsy showed necrotizing and focally granulomatous inflammation. There is no evidence of malignancy (see Fig. 2). Both right and left kidney mass lesions were biopsied which showed multi-focal necrotizing and non-necrotizing granulomatous inflammation. Vascular wall Fibrinoid necrosis or transmural inflammation was not identified. The glomeruli showed focal periglomerular fibrosis and compression of the glomerular capillary tufts, but no crescentic lesions or fibrinoid necrosis were observed in total 40 glomeruli. There was no infiltration of eosinophils or neutrophils (see Fig. 3). Grocott-Gomori methenamine stain and Ziehl-Neelsen stain did not reveal fungal or mycobacterial microorganisms, respectively. Immunohistochemical stain for cytomegalovirus and adenovirus are both negative. There was no kidney tissue submitted for immunofluorescence or electron microscopic studies. There is no evidence of malignancy in both kidney biopsies.

2.4. Therapy and follow-up

After the diagnosis of GPA, the patient received rituximab 1000 mg twice (two weeks apart) on October 2017, then 1000 mg on April 2018, with plan of maintenance treatment 500 mg per 6 months for two years. The patient received prednisone 40 mg daily from October 2017, then tapered until off on the end of Mach 2018. On the last follow up (August 2018), the patient had no symptoms, specifically, no shortness of breath, no cough, no hemoptysis, no hematuria, no fever or fatigue and no weight loss. Physical examination showed blood pressure 120/74 mmHg, no rashes or subcutaneous mass lesions, lungs clear, abdomen soft and non-tender, and extremities no edema. Lab tests showed serum creatinine 1.2 mg/dl, c-ANCA and p-ANCA negative, atypical ANCA indeterminate, anti-PR3-IgG 0.9 U/ml, anti-MPO IgG 0.1 U/ml, ESR 19 mm/h, CRP < 1.0 mg/L. Chest X-ray on May 2018 showed that lungs were clear, no pleural effusion, no mass lesions in the lungs or chest wall, cardiac silhouette size mildly enlarged. Chest CT performed on September 2018 showed focal small scar-like changes in the areas of pervious lung mass lesions (see Fig. 1).

3. Discussion

Vasculitides are a group of diseases defined as inflammation of blood vessels with structural injury, necrosis or occlusion of the vessels [5,6]. The presentation of vasculitis can be very non-specific and differs considerably from patient to patient due to its variable involvement of the vascular systems in different organs, which makes its often diagnostically challenging. Vasculitis can manifest as organ-specific but more often demonstrates multisystemic involvement. Large vessel vasculitis including Takayasu arteritis and giant cell arteritis shows granulomatous arteritis and is localized to aorta and its major branches. Polyarteritis nodosa and Kawasaki disease involves medium-sized and small arteries. Small vessel vasculitis (SVV) involves small arteries, capillaries and venules. It can be primary, but can also be secondary to other systemic disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Henoch-Schönlein purpura or cryoglobulinemia. Non-immune complex-mediated SVV is also called pauci-immune vasculitis. The majority of pauci-immune SVV are associated with anti-neutrophilic cytoplasmic antibody (ANCA), which is related to a variety of autoantigens including myeloperoxidase (MPO), proteinase-3 (PR3), lysosomal membrane protein 2 (LAMP2), elastase, and others [7]. The major forms of ANCA-associated small vessel vasculitis encompass microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) (Wegner's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss), separated by integrated clinical and pathological findings [2,8].

The organ systems involved by GPA most commonly are upper respiratory tract including nasal cavity and nasal sinuses, lungs and kidneys. Upper airway symptoms including sinusitis, recurrent epistaxis, mucosal ulceration, nasal septal perforation, are responsible for presentation symptoms in 73% of patients in a large study of 158 cases [9]. However, many patients, including our patient do not have upper respiratory symptoms. Vasculitis can present as mononeuritis multiplex, which was likely the cause of sudden right foot drop and left calf pain in this patient at presentation. The etiology of sudden right eye vision loss might be obliterative vasculitis associated with GPA which showed central retinal artery occlusion by ophthalmologic examination. Pulmonary symptoms of GPA include cough, hemoptysis, shortness of breath and chest pain (pleuritis), and radiology may show lung infiltrates in 45% of patients. Occasionally lung changes can present as distinct mass lesion(s), which closely mimics neoplastic process. Biopsy is important for diagnosis before considering lobectomy or wedge resection, which may further compromise the lung function. However, interpretation of the lung biopsy in these patients can be very challenging. It may only show focal acute and chronic inflammation. The finding of focal acute inflammation is the subsequent response to the

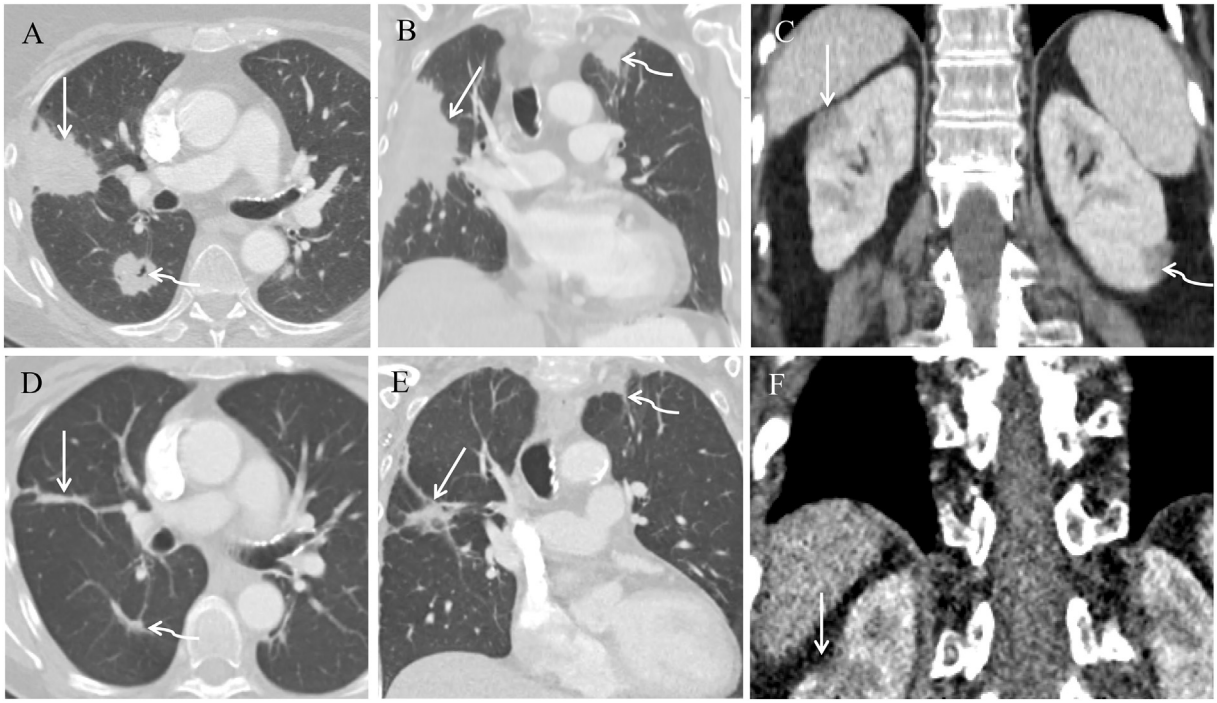

Fig. 1. Radiology imaging (CT) of chest and abdomen: A–C: Before biopsy and treatment in 2017: A. Chest CT shows an anterior mid lung mass (straight arrow) and lower posterior lung nodule (curved arrow). The posterior nodule has central hypodensities suggestive of cavitation. B. Chest CT shows large right mid lateral lung mass with pleural extension (straight arrow) corresponding with the anterior mass on previous picture, and an irregular mass of the left lung apex (curved arrow). C. Abdominal CT shows right upper pole (straight arrow) and left lower pole (curved arrow) renal mass lesions. D-F: Chest CT in 2019 after prednisone and rituximab treatment: D. Previous sites of right anterior mid mass (straight arrow) and lower posterior nodule (curved arrow) show that they have resolved with a small amount of residual scarring at the sites. E. Previous sites of right lung mid lateral mass (straight arrow) and left apex mass (curved arrow) show that they have resolved with a small amount of residual scarring at the sites. F. 2019 chest CT– Contour deformity of the upper pole of right kidney at the site of the previous mass lesion (straight arrow), consistent with cortical scarring. The mass is no longer seen. There is no abdominal CT from 2019, and this is the best image available to look at the renal lesions seen in 2017. The left lower pole kidney is not included in the CT field of view.

necrosis instead of due to infection. But the more suggestive feature of granulomatous inflammation can be very vague and very poorly formed. In addition, the characteristic necrotizing granulomatous change can be very focal and may not well sampled. Therefore, the biopsy findings can be misinterpreted as an infectious process or as aspiration pneumonitis. The latter was suggested in the comment of the lung biopsy report of this case. Therefore, it is important to pay close attention to the histiocytic clusters and small focus of necrosis which

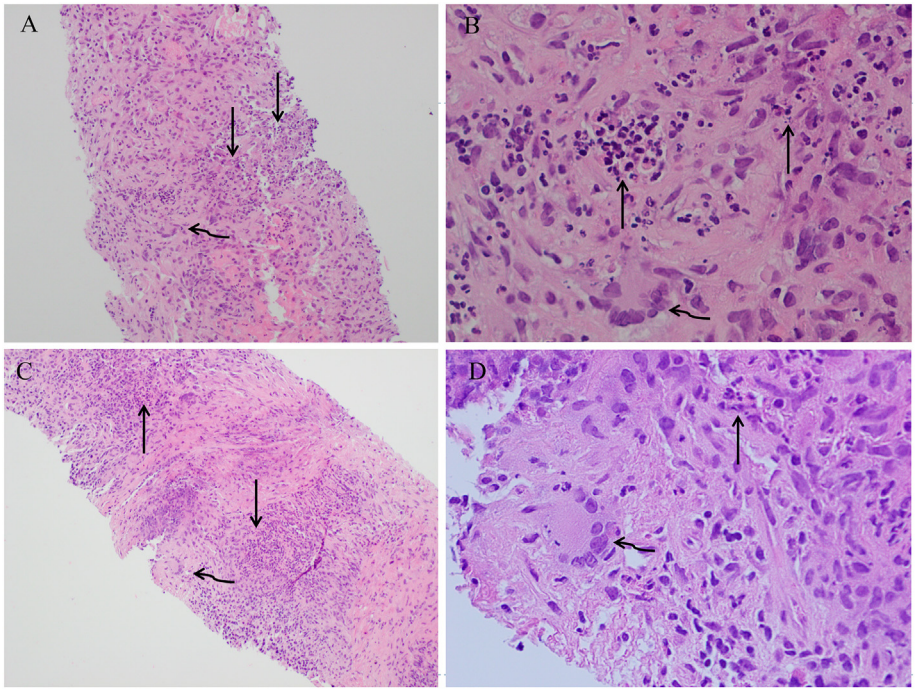

Fig. 2. lung biopsy (hematoxylin and eosin stains): A and C: intermediate power views show necrosis and acute inflammation (straight arrows), and vague granulomatous inflammation with multi-nucleated giant cells (curved arrows). B and D: high power views show necrosis and acute inflammation (straight arrows), and granulomatous inflammation with multi-nucleated giant cells (curved arrows).

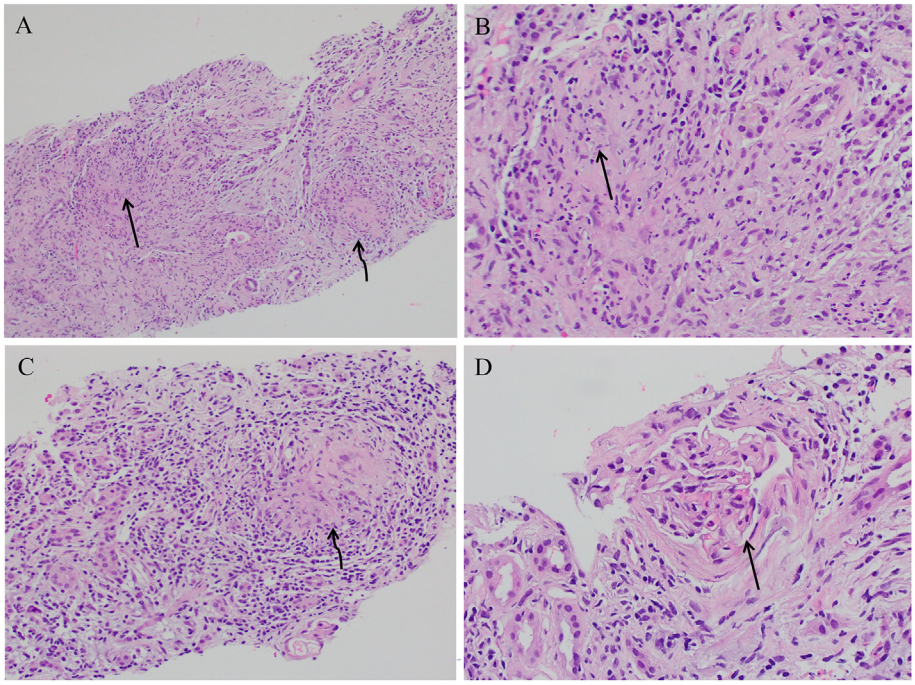

Fig. 3. kidney biopsy (hematoxylin and eosin stains): A Intermediate power view of kidney shows necrotizing (straight arrow) and non-necrotizing granulomatous (curved arrow) inflammation involving the tubulointerstitium. B High power view of necrotizing granuloma. C High power view of non-necrotizing granuloma. D Glomerulus (straight arrow) shows intact capillary tufts with no crescentic or necrotizing lesions. There is mild periglomerular fibrosis and interstitial inflammation.

would give a hint for the diagnosis of necrotizing granulomatous inflammation. Special stains for fungal or mycobacterial organisms, or viral immunohistochemical stains can be used to rule out other causes of necrotizing granulomatous inflammation such as fungal, mycobacterial or viral infection. Polarization microscopy may be applied to rule out foreign material. Clinical and radiologic correlation can be also important. Keeping an open mind with broad differential diagnosis is essential. Base on the pathologic finding, the pathologist can offer suggestions for additional workup such as serology tests, so as to obtain further supportive evidence to reach a definite diagnosis.

The characteristic finding from kidney biopsy in patients of GPA is most often pauci-immune necrotizing crescentic glomerulonephritis [10]. Vasculitis outside of glomerular capillary tufts is seen in 8% to 13%, and granulomatous changes are seen in about 3% [9,11]. Very rarely, a renal mass lesion is reported [3,4,12]. The kidney biopsy of our patient demonstrates no glomerular changes such as fibrinoid necrosis or crescentic lesions. In the 40 sampled glomeruli, the glomerular tufts are either intact with no significant change or show compression by surrounding extraglomerular inflammation and fibrosis. This patient's urinalysis shows minimal hematuria or proteinuria with normal or near normal renal function, which is consistent with the pathologic findings of no glomerular involvement by vasculitis. The kidney mass lesions showed multifocal necrotizing and non-necrotizing granulomatous inflammation in the interstitium. Definite arterial or arteriolar fibrinoid necrosis or transmural inflammation is not identified. The differential diagnosis for kidney granulomatous inflammation is broad, which can include infection, drug reaction, autoimmune processes, sarcoidosis, among others. There is no interstitial infiltration of eosinophils which argues against a drug reaction. The stains for infectious agents such as fungal, mycobacterial, CMV and adenovirus infection are also negative. In this patient with c-ANCA and PR3-ANCA antibody positivity, the biopsies of lung, kidneys and quadriceps showed similar granulomatous inflammation. Putting the clinical, laboratory and pathological findings together, it is most consistent with a diagnosis of GPA which manifested as multiple mass lesions in organs and soft tissue.

Mass lesions in vasculitis have been reported in the lung, nasal sinus, mediastinum, kidney and even brain. In this patient, multiple mass lesions involving lungs, kidneys, and neck soft tissue are particularly remarkable. Clinically and radiologically these lesions can well mimic malignant neoplasm with metastasis. It has been reported that resections including wedge excision or lobectomy for lung mass, and total or partial nephrectomy for kidney mass have been performed for these lesions, which can be detrimental to the organ function [3,4,12]. Therefore, it is important to know the unusual presentations of vasculitides and keep them in the differential diagnosis clinically and pathologically. Biopsy plays a significant role for the diagnosis which may help initiate appropriate medical therapy. Proper and timely treatment often results in complete resolution of the mass lesions in these patients, which happened in our patient.

4. Conclusion

The presentation of granulomatosis with polyangiitis can be very unusual, including multiple mass lesions in organs and soft tissue, mimicking malignant neoplasms with metastasis. Knowledge of its uncommon presentations can help broaden the radar of clinical thought process so that vasculitis may be considered among the differential diagnosis. Perform relevant laboratory tests and biopsy for pathologic examination will help establish the correct diagnosis, initiate timely and appropriate treatment, and also importantly, avoid unnecessary surgery of resection which may compromise organ function.

Disclosure

The authors report no conflicts of interest in this work.

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