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A Case of Pulmonary Hemorrhage and Renal Failure

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Abstract: *Background*: Alveolar hemorrhage can be seen in many vasculitic disorders. However, granulomatosis polyangiitis (formerly Wegener's granulomatosis) uncommonly presents with life threatening alveolar hemorrhage and has only been discussed in a few case reports [1].

Case Presentation: A 53 year old Caucasian male presented with hemoptysis and profound anemia. Two weeks prior, he had presented with abdominal pain with normal renal function and numerous pulmonary nodules. During the current admission, the patient was hypoxic with acute renal failure requiring hemodialysis. Urine sediment demonstrated dysmorphic red blood cells. A bronchoscopy revealed diffuse alveolar hemorrhage. The diagnosis of pulmonary-renal syndrome was made and therapeutic plasma exchange was initiated. Laboratory studies were significant for a c-ANCA titer positive at 1:640 FIU and anti-proteinase (PR)-3 antibody titer positive with 78.3 U/ml. Renal biopsy demonstrated necrotizing crescentic glomerulonephritis. A diagnosis of granulomatosis vasculitis was determined.

Conclusion: Alveolar hemorrhage is rare to be the presenting symptom of granulomatosis vasculitis where the common presenting features are recurrent sinusitis, epistaxis, chronic otitis media or rhinitis. Physicians should consider granulomatosis vasculitis in the differential diagnosis of pulmonary-renal syndrome presenting with hemoptysis.

Keywords: Granulomatosis, vasculitis, pulmonary hemorrhage, renal insufficiency, Wegener's, dialysis, plamapharesis.

INTRODUCTION

Granulomatosis polyangiitis is one of three pulmonary-renal syndromes which are associated with antineutrophil cytoplasmic antibodies, either c-ANCA or p-ANCA, due to autoantibodies against target antigens proteinase-3 and myeloperoxidase (MPO), respectively. Classically, when a patient presents with pulmonary hemorrhage and necrotizing glomerulonephritis anti-glomerular basement membrane disease (anti-GBM disease) is thought of first. Granulomatosis polyangiitis is increasing in incidence and thus becoming aware and comfortable with the different clinical presentations of this disease process can be life saving. We describe a case of granulomatosis polyangiitis presenting with diffuse alveolar hemorrhage (DAH).

CASE PRESENTATION

This case is a 53 year old Caucasian male with a history of tobacco abuse was over the past few months been treated twice with azithromycin and prednisone for what was believed to be bronchitis. Six weeks later he presented to the Emergency Department (ED) with abdominal pain. The workup was significant for normal laboratory studies (Table **1**) and numerous pulmonary nodules, found on a chest x-ray and confirmed with a computed tomography scan (CT) of the chest. Subsequently, an outpatient positron-emission test (PET) scan showed metabolically active pulmonary nodules and a biopsy was scheduled. One week later and prior to the biopsy, he presented to the ED with hemoptysis. He was coughing black to bright red blood clots with whitish sputum for three days and, on the day of presentation, frank blood clots. He confirmed mild shortness of breath at rest and generalized weakness along with nausea and vomiting. He denied hematemesis. The patient worked as a maintenance worker and welder and had no history of exposure to

Table 1. Laboratory Findings from Two Weeks Prior to Current Admission

Laboratory	Value	Normal Value
Hemoglobin	12 g/dL	13-18 g/dL
Hematocrit	32%	40-52%
Potassium	3.9 mEq/L	3.5-5 mEq/L
BUN	22 mg/dL	6-20 mg/dL
Creatinine	1.1 mg/dL	0.6-1.2 mg/dL

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asbestos. Moreover, he had no recent travel outside the United States or sick contacts and NSAIDs on occasion He denied fever, chills, weight loss, loss of appetite, chest pain, abdominal pain, diarrhea, constipation, hematuria, changes in urine output, headaches, and rashes.

On examination, the patient was pale, afebrile with a blood pressure of 147/82 mmHg and tachycardic at 120 beats per minute. He was hypoxic (pulse oximtery reading of 83% on room air) and tachypneic (respiratory rate of 30 breaths per minute). The examination was also significant for coarse breath sounds bilaterally in all lung fields and generalized poor air movement.

Initial laboratory studies were significant for profound anemia and acute renal failure (Table **2**). Urine sediment

Table 2. Laboratory Findings from this Admission

Laboratory	Value	Normal Value
White Blood Cell	15 k/uL	4.5-11 k/uL
Hemoglobin	5.7 g/dL	13-18 g/dL
Hematocrit	16.1%	40-52%
Platelets	185 k/uL	150-440 k/uL
Sodium	132 mEq/L	135-145 mEq/L
Potassium	7.1 mEq/L	3.5-5 mEq/L
Chloride	102 mEq/L	99-19 mEq/L
Bicarbonate	18 mEq/L	22-33 mEq/L
BUN	208 mg/dL	6-20 mg/dL
Creatinine	12.11 mg/dL	0.6-1.2 mg/dL
Glucose	121 mg/dL	70-105 mg/dL
Calcium	8.7 mg/dL	8.5-10.5 mg/dL
Phosphorus	10.3 mg/dL	2.9-4.8 mg/dL
Magnesium	2.1 mg/dL	1.6-2.6 mg/dL
AST	9 U/L	10-37 U/L
ALT	12 U/L	10-49 U/L
Alkaline Phosphatase	63 U/L	41-120 U/L
Total bilirubin	0.4 mg/dL	0.3-1.2 mg/dL
Total protein	6 g/dL	6.2-8.3 g/dL
Albumin	2.8 g/dL	3.4-4.9 g/dL
Lactate dehydrogenase	256 U/L	118-273 U/L
Ferritin	782 ng/mL	22-322 ng/mL
Transferrin	144 mg/dL	203-362 mg/dL
Haptoglobin	146 mg/dL	40-240 mg/dL
Iron	22 ug/dL	35-194 ug/dL
Iron Binding Capacity	209 ug/dL	250-450 ug/dL
Transferrin Saturation	11%	20-50%
Complement C3	128 mg/dL	90-170 mg/dL
Complement C4	27 mg/dL	12-36 mg/dL
INR	1.0	
PT	10.6 seconds	9.7-11.3 seconds
aPTT	27.5 seconds	23-31 seconds
Urine analysis	Cloudy, Straw, specific gravity 1.010, pH 5, 2+ proteins, negative glucose, negative ketones, negative bilirubin, too numerous to count RBCs, 3+ hemoglobin, no WBC, negative leukocyte esterase, negative nitrites, normal urobilinogen, amorphous sediment	Clear, Yellow, specific gravity 1.005-1.030, pH 4.5-8, negative proteins, negative glucose, negative ketones, negative bilirubin, 0/HPF RBCs, negative hemoglobin, 0/HPF WBC, negative leukocyte esterase, negative nitrites, normal urobilinogen

demonstrated a moderate amount of dysmorphic red blood cells (RBC) with no RBC casts but a moderate amount of muddy brown casts. The chest x-ray (Fig. **1**) showed diffuse bilateral airspace opacities that were non-specific concerning for pulmonary edema, pulmonary hemorrhage, ARDS, or pneumonia. Given the presence of hemoptysis, urinary red cell casts and acute kidney injury, the possibility of a pulmonary-renal syndrome was considered. He was intubated and placed on mechanical ventilation and bronchial lavage was initially sent from the patient confirming pulmonary hemorrhage seen in Fig. (**2**). The patient was started on a course of plasmapheresis and supportive hemodialysis. Immunologic studies were done and are reflected in Table **3**. Significant findings included c-ANCA titer of 1:640 FIU, and a negative anti-GBM antibody titer. A renal biopsy was performed and was significant for necrotizing crescentic glomerulonephritis with fibrocellular crescents in nine of sixteen glomeruli along with acute tubular injury (Figs. **3**, **4**) with a lung biopsy (Figs. **5**-**7**) indicating the presence of acute and organizing infarct with numerous vascular thrombi and necrotizing vasculitis.

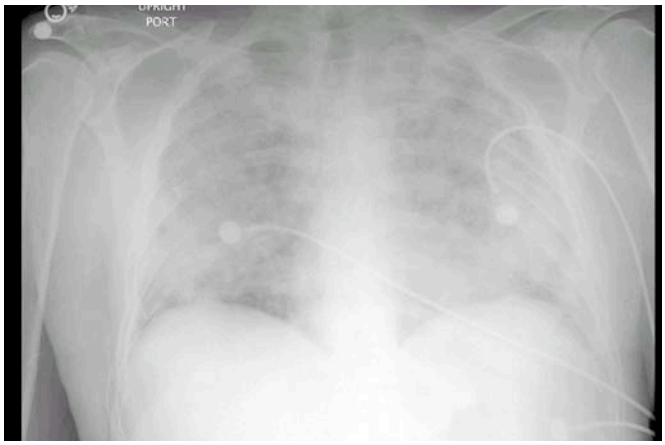


Fig. (1). Portable upright AP view showing diffuse bilateral airspace opacities. Differential diagnosis includes pulmonary edema, pulmonary hemorrhage, ARDS, and pneumonia.

The definitive diagnosis of granulomatosis polyangiitis was made. As the diagnosis was being confirmed renal replacement therapy was begun as well as four treatments of plasmapharesis were completed. Once the diagnosis was confirmed, plasmapharesis was stopped and the patient was started on cyclophosphamide and prednisone along with dialysis support. Immunologically he achieved remission, but failed to recover renal function and remains dependent on hemodialysis (Graph **1**).

DISCUSSION

Granulomatosis polyangiitis is a pauci-immune vasculitis, and is one of the many causes of pulmonary-renal syndrome. Etiologies of pulmonary-renal syndrome include anti-GBM disease, and microscopic polyangiitis (MPA), and granulomatosis polyangiitis. This patient's clinical presentation of DAH with necrotizing crescentic glomerulonephritis was atypical but immunologically consistent with granulomatosis polyangiitis due to high titers of c-ANCA and PR-3 antibodies.

The incidence of granulomatosis polyangiitis has almost doubled from since 1990 to 1 in 64.8 million in 2005 and mean age range at presentation is 40 to 60 years [2]. Granulomatosis polyangiitis is a systemic vasculitis that affects both medium and small vessels. Typically, granulomatosis polyangiitis involves the upper respiratory tract, lungs, kidneys and joints and is frequently an indolent disease [3]. Most of these patients have c-ANCA positive antibodies and less commonly myeloperioxidase positive antibodies [4]. Approximately 99% of patients with granulomatosis polyangiitis will develop upper respiratory tract involvement during the disease process [2,4]. Pulmonary involvement ranges from 60-85%, classically as capillaritis or granulomatosis masses, which could lead to diffuse alveolar hemorrhage (DAH) [2]. DAH has been reported over a wide range from 7-40%, and usually the results of a mass or untreated capillaritis [4,6]. DAH is characteristically not the presenting symptom, as seen in our

Table 3. Immunologic Studies

Laboratory	Value	Normal Value
Antinuclear antibody	< 7.5 IU/mL	< 7.5 IU/mL
Antineutrophil cytoplasmic Antibody	Total: ≥ 1:640 FIU c-ANCA pattern	Total: < 1:20 FIU
Glomerular Basement Membrane Antibody	< 1.0 AI	< 1.0 AI
Total Hepatitis B Core Antibody	Negative	Negative
Hepatitis B Surface Antigen Antibody	Postitive	
Hepatitis C Virus Antibody	Negative	Negative
Neutrophil Myeloperoxidase Antibody	< 9.0 U/mL	< 9.0 U/mL
Neutrophil Proteinase-3 Autoantibody	78.3 U/mL	< 3.5 U/mL
Rheumatoid Factor	80 IU/mL	< 10 IU/mL
Anti-Streptolysin (ASO) Antibody	53 IU/mL	≤ 200 IU/mL

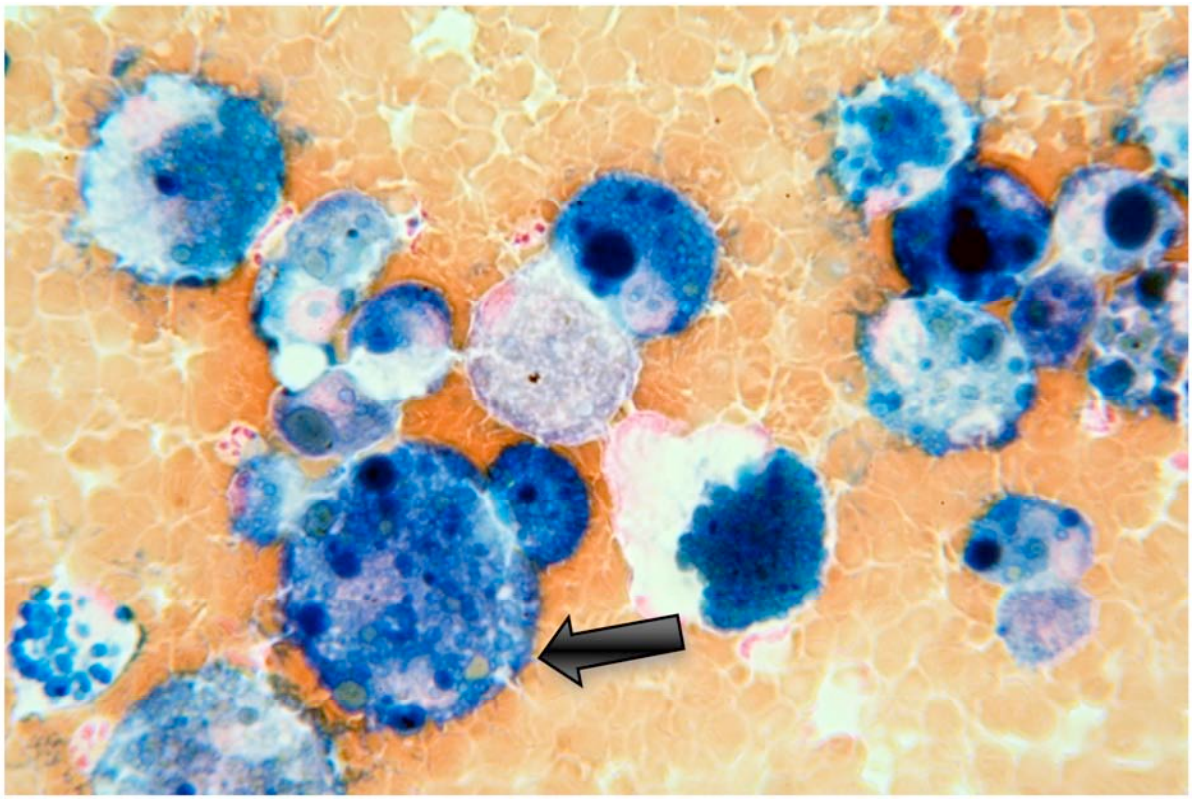


Fig. (2). Bronchial lavage showing hemosiderin laden macrophages with an index of 77% indicative of pulmonary hemorrhage seen on light microscopy with magnification at 40x with an iron stain.

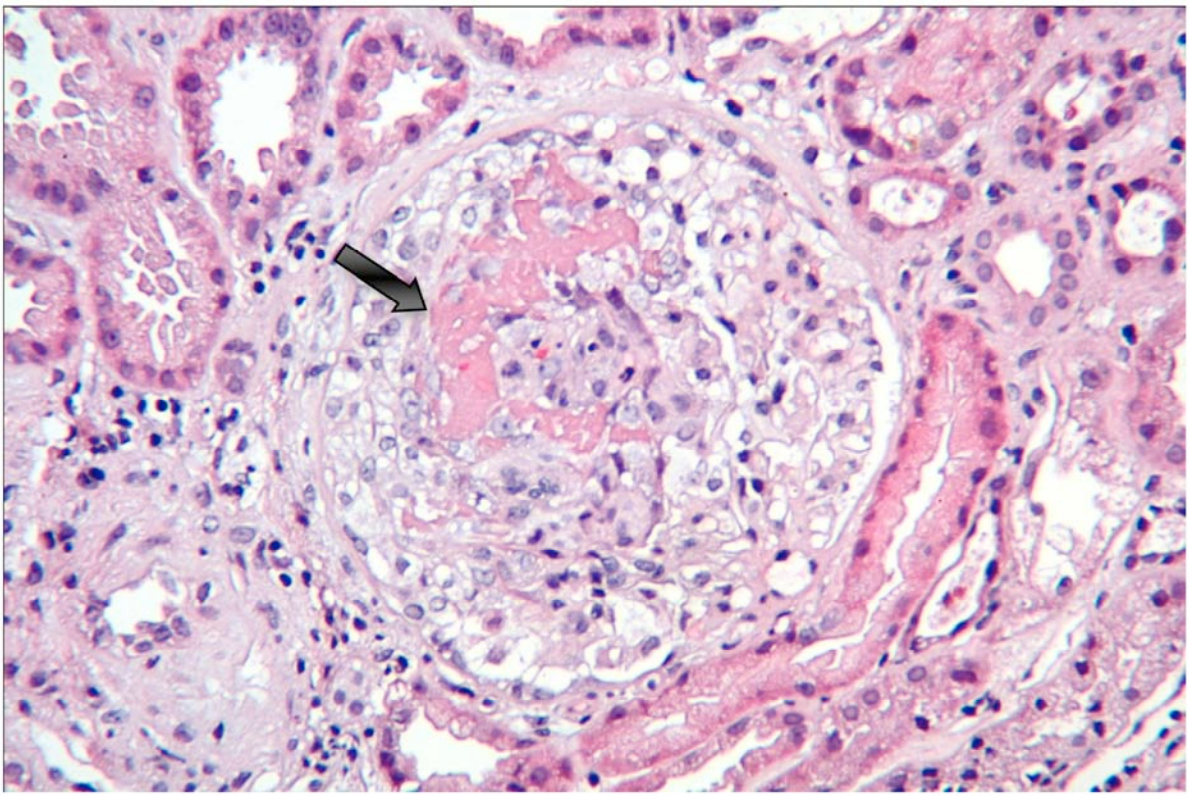


Fig. (3). Kidney biopsy showing necrotizing glomerulonephritis in the glomerulus with crescents seen on light microscopy with magnification at 20x with a hematoxylin and eosin stain.

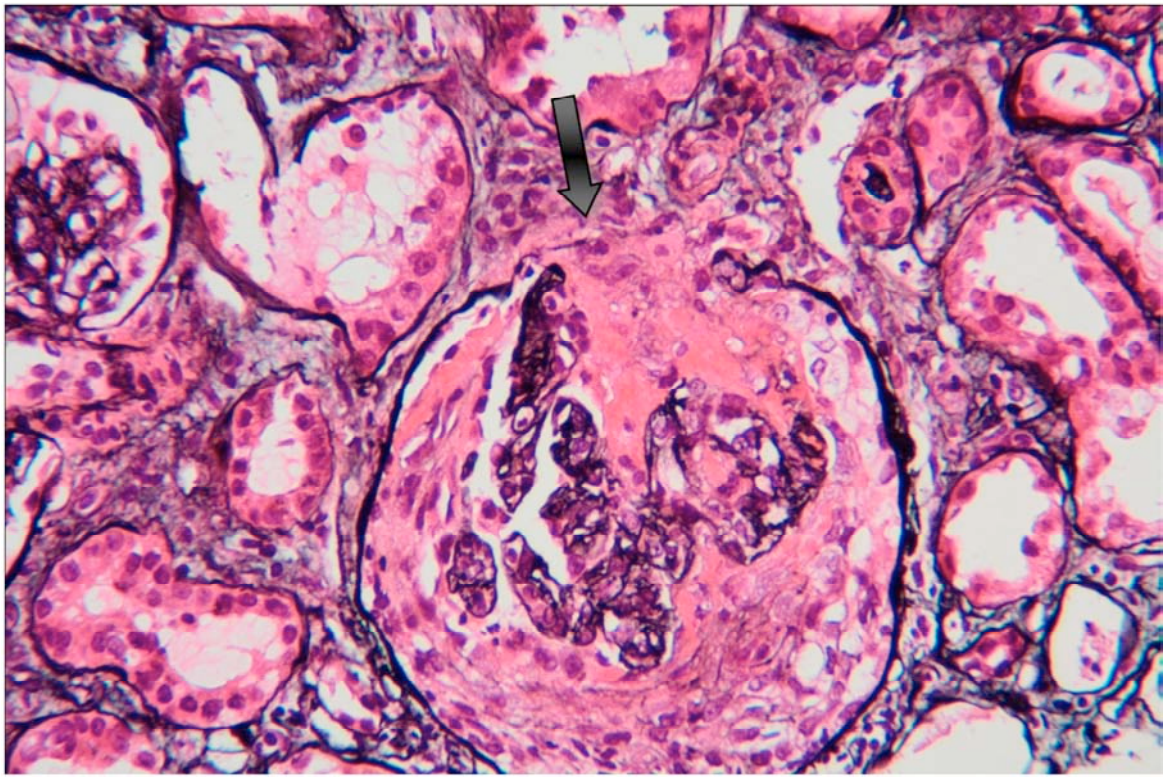


Fig. (4). Kidney biopsy shows glomerular tuft rupture seen on light microscopy with magnification at 20X with a Jones methenamine silver stain.

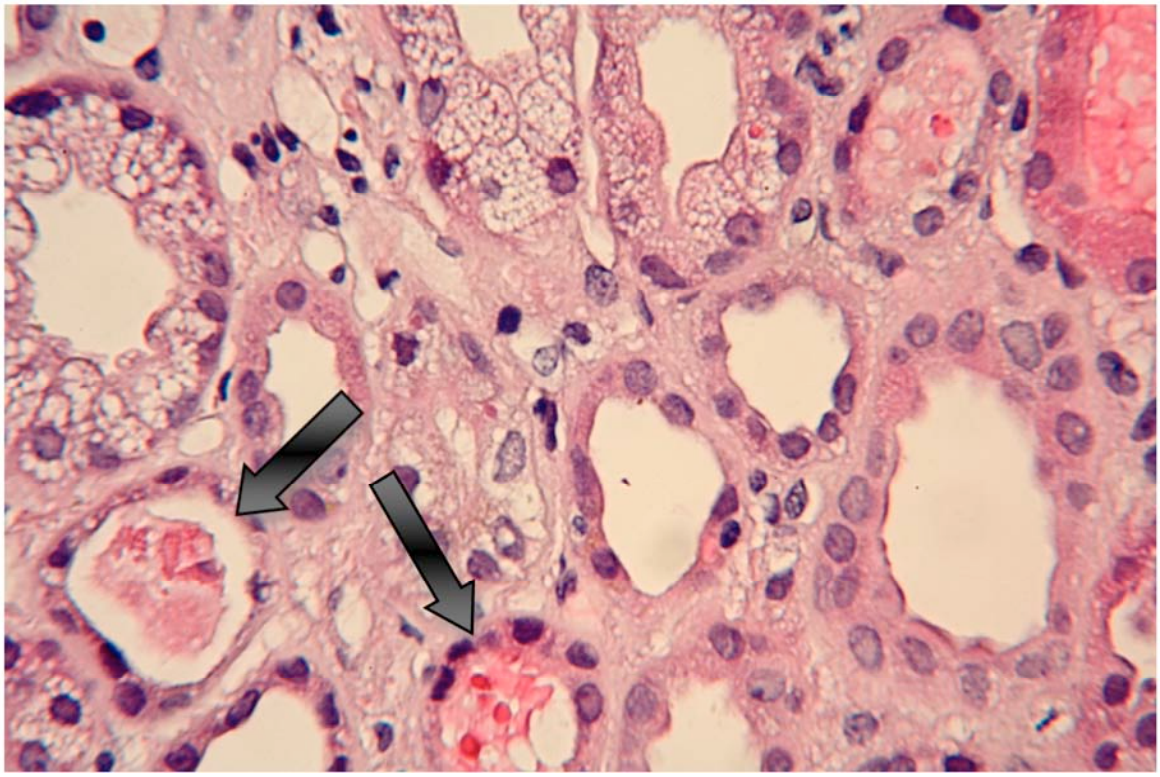


Fig. (5). Lung biopsy shows a necrotizing vasculitis that is associated with hemorrhagic infarct in the lung parenchyma seen with light microscopy with magnification at 10x with a hematoxylin and eosin stain.

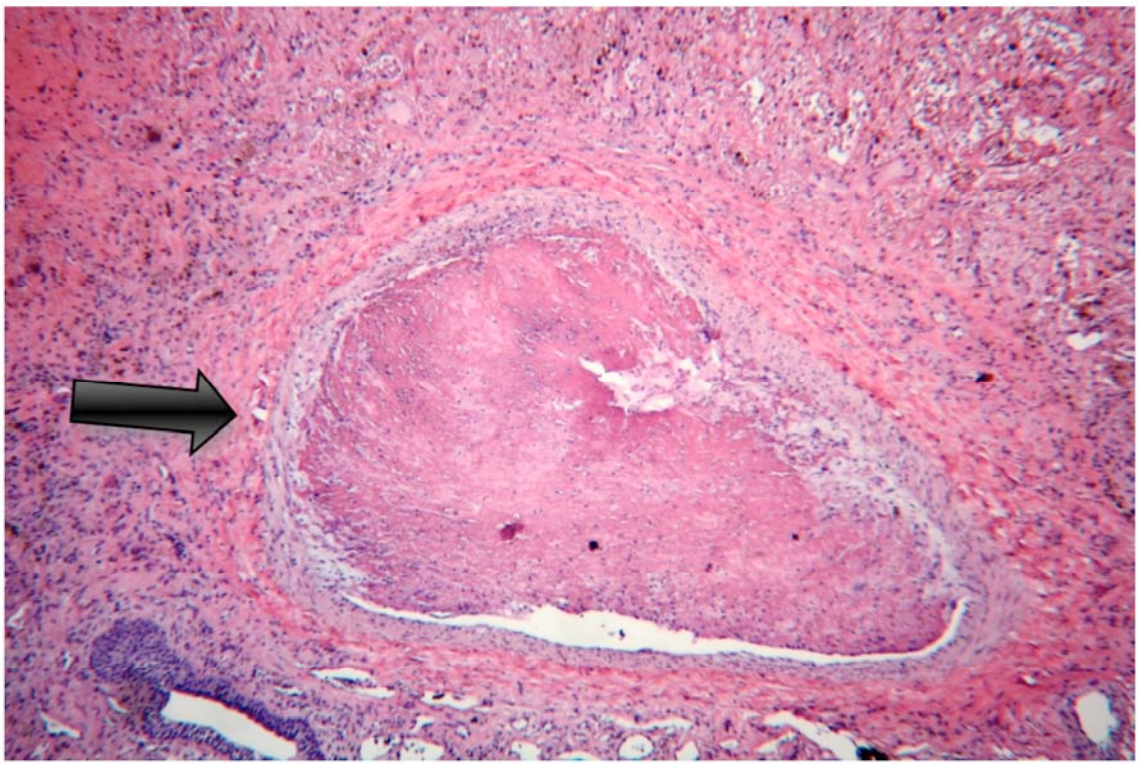


Fig. (6). Lung biopsy shows vascular thrombi in the lung seen with light microscopy with magnification at 4x with a hematoxylin and eosin stain.

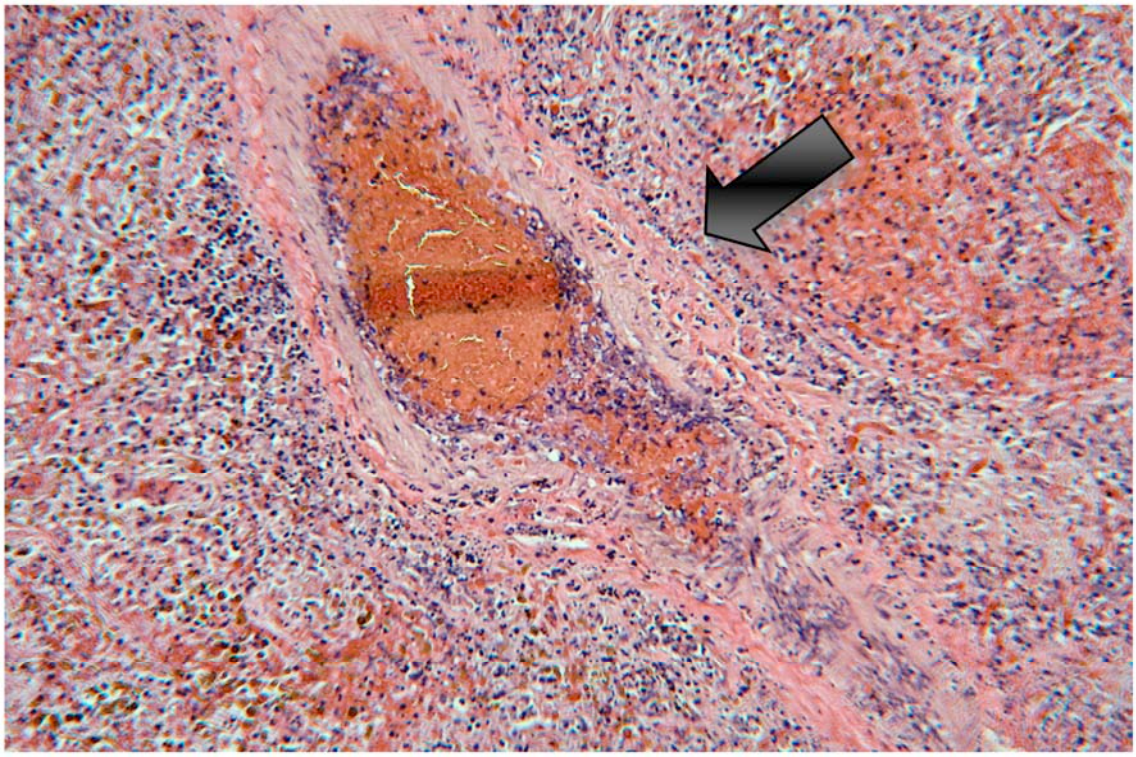
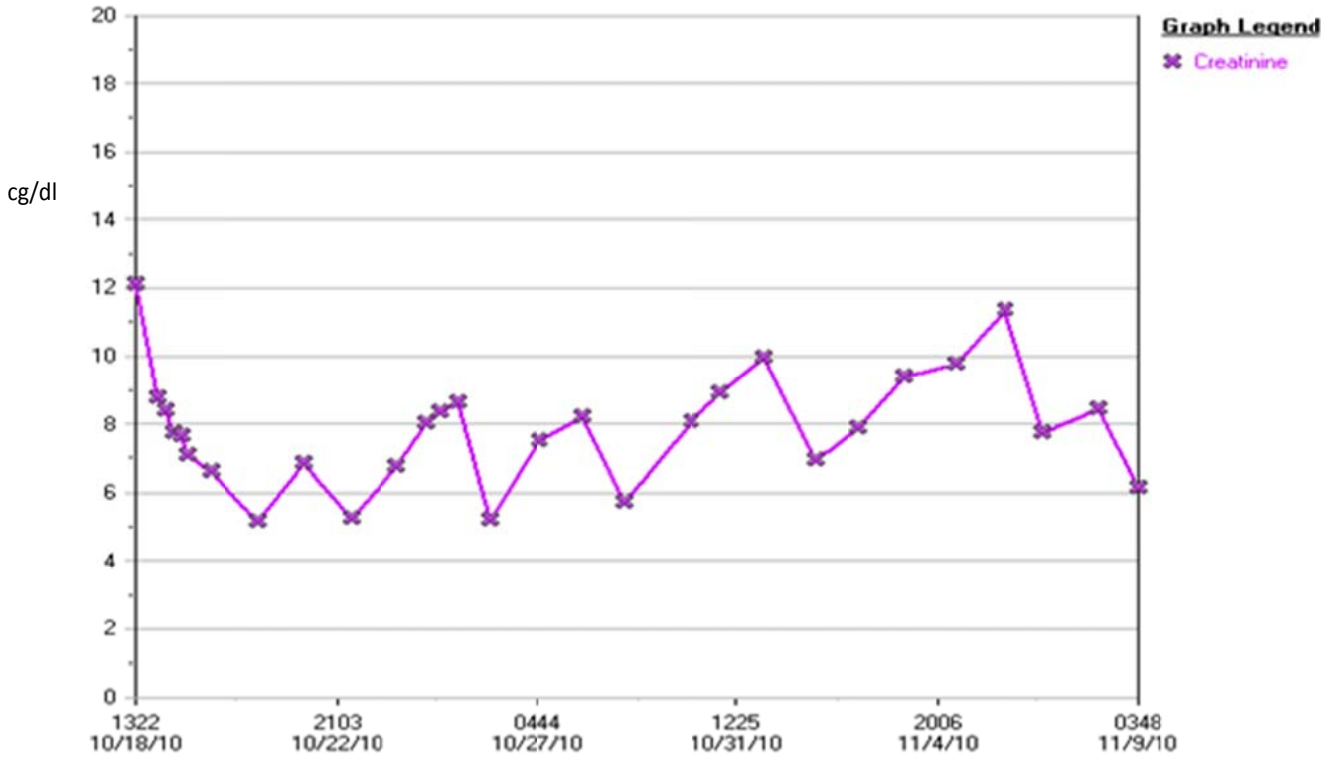


Fig. (7). Lung biopsy shows necrotizing vasculitis that is associated with hemorrhagic infarct seen with light microscopy with magnification at 10x with a hematoxylin and eosin stain.

case. It has been agreed upon that DAH does have an increase mortality rate of 60%, however, if granulomatosis polyangiitis is left untreated the mortality rate is 91% [1,5,7-9].

Glomerulonephritis is also been reported in varying frequencies from 40-70% [2]. Typically only about 25% require dialysis and only half of those will progress to end-stage renal disease [1,2]. Severe renal disease has been



Graph 1. Trend of creatinine from admission during treatment and renal replacement until discharge when patient went home with three times a week hemodialysis.

classified by the European Vasculitis Study Group as a presenting creatinine of over 5.8mg/dL [12]. Persistent renal impairment despite adequate treatment also leads to poor prognosis [2].

The prognosis of vasculitic disease is worse with concomitant renal impairment and pulmonary manifestations at initial presentation with the absence of upper respiratory tract involvement [2]. Those individuals that are admitted to the intensive care unit (ICU) with a suspected alveolar hemorrhage have a mortality of 25 to 50% [4]. Therefore, it is imperative to have a high index of suspicion in order to improve the outcomes. This disease is often confused with anti-GBM disease or microscopic polyangiitis (MPA). The only way to differentiate these diseases is by serology testing and confirmed with either lung or kidney biopsy. Goodpasture's syndrome is associated with high titers of anti-GBM antibody and DAH is a common presenting symptom. Goodpasture's disease is treated with plasmapheresis. MPA typically presents with capillaritis then subsequently develops Granulmatous vasculitis, but these diseases are treated very similarly with glucocorticoids and cyclophosphamide. However, in the presence of diffuse alveolar hemorrhage, immunosuppressive therapy alone can be inadequate and therefore plasmapheresis is instituted in some cases. There has been a randomized study that has shown benefit with plasmapharesis in addition to immunosuppressive therapy which includes the traditional high dose methylprednisolone with patients in severe renal diseae [12]. Due to the high mortality rate, associated with DAH and severe renal disease, our patient was plasmapheresed even before intravenous cyclophosphamide and glucocortiocoids were given and biopsy results were available. Recent evidence suggests that patients with severe ANCA-associated vasculitis, defined by the presence of DAH and/or severe renal involvement (creatinine greater than 5.7 mg/dL), might benefit from this combination [5,10,11].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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