CLINICAL VIGNETTE

Diffuse Alveolar Hemorrhage in C-ANCA Vasculitis with Pulmonary/Renal Syndrome

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A 61-year-old man presented to the Emergency Department (ED) with headache for 2 weeks that was worse with exertion. This visit was his eighth ED visit for various complaints over the last 10 months. The first ED visit was for dyspnea on exertion and weakness. Work up was notable for CT chest that demonstrated "parenchymal abnormalities of both lungs." He was started on levofloxacin and asked to follow up with his primary care physician. Four months prior, he presented to the ED with cough productive of clear sputum with occasional bloody streaks as well as dyspnea on exertion. Labs were notable for a now abnormal creatinine of 1.49 mg/dL (up from 1.19 mg/dL), and CT pulmonary angiogram was notable for "diffuse bilateral infiltrates." He was started on oxygen and transferred to his contracted hospital. Details of that hospital admission are not known. Two months prior, he returned to the ED complaining of dyspnea on exertion. Oxygen saturation was 92% on ambient air. Chest X-Ray demonstrated "diffuse interstitial infiltrates-fibrosis unchanged in the mid and lower lung fields and improved in the upper lung fields." He was discharged home on an unspecified dose of prednisone for a possible inflammatory pulmonary process. He returned to the ED 4 more times before being admitted. Some of the complaints or findings included right shoulder pain, generalized weakness, rising creatinine from 1.19 to 1.49 to 2.19 to 2.80 mg/dL, and slowly decreasing hemoglobin going from 10.4 to 9.5 to 9.7 to 8.8 g/dL (no history of dark or bloody stool), and headache. X-ray of the shoulder was negative, stool guaiac was negative, neurological exam was non-focal, and CT brain was unremarkable.

During the current (8^{th}) visit for continued headache worse with exertion, he was admitted due to frequent ED visits, lack of a unifying diagnosis, and delays in obtaining prompt outpatient nephrology and pulmonary evaluations. Past medical history was negative for asthma but remarkable for hypertension controlled on amlodipine, losartan, and hydrochlorothiazide. Other medications included occasional NSAIDS for headache or shoulder pain, and more recently acetaminophen/hydrocodone for worsened headache. He was born in Mexico, moved to the United States many years ago, and worked with metal to make chairs. No asbestos or chronic bird exposure. He had a 10 pack a year smoking history and quit 3 years prior. Physical exam was notable for pallor, a non-focal neurological exam, and bilateral inspiratory crackles of the lungs. Creatinine was now 4.26 mg/dL. Urinalysis demonstrated 100 mg/dL protein, 2+ blood, and 11-20 RBC's per high power field. Anemia had worsened since the last ED visit with hemoglobin falling from 8.8 g/dL to 6.0 g/dL with a current MCV of 83.5 iron 18 mcg/dL (range 65-175), normal TIBC, slightly reduced iron saturation, and a normal ferritin. Admission Chest X-Ray is shown in Figure 1.

Kidney biopsy was done on hospital day #2. A non-contrast CT chest (Figure 2) on hospital day #3 showed a diffuse and markedly heterogeneous pattern of multiple small consolidations most pronounced in the upper lobes that had progressed from imaging 4 and 10 months prior. High dose methylprednisolone was initiated. Oxygen requirements worsened, and patient was transferred to the ICU on 100% high flow oxygen. Renal biopsy revealed pauci immune necrotizing glomerulonephritis with 40% glomerulosclerosis. There were acute on chronic findings with some active disease. Bronchoscopy demonstrated diffuse alveolar hemorrhage (DAH.) Plasmapheresis was initiated hospital day #4, and rituximab was started hospital day #5. Oxygen requirements and creatinine gradually improved, and urine output remained adequate. Over the next few days, additional labs revealed C-ANCA positive 1:256, P-ANCA negative, Anti-MPO (Myeloperoxidase Antibody) negative, but Anti-PR3 (Proteinase 3 Antibody) was misprocessed. Other labs including ANA, SS-A/Ro and SS-B/La Autoantibodies, Glomerular Basement Membrane IgG Ab, Citric Citrullinated Peptide Ab, Rheumatoid Factor, SPEP, Hepatitis Panel, Urine Toxicity Screen and HIV were negative. C3 and C4 were within normal limits. CRP was very elevated at > 19.00 mg/dL. Bacterial blood culture was negative. Bronchial washing microbiology assays were negative. After 16 days in the hospital he was weaned off O2 and discharged home. At discharge the creatinine was 3.29 mg/dL and the hemoglobin was stable at 8.1 g/dL after a total transfusion of 3 units PRBC. No EGD or colonoscopy was done. He received high dose methylprednisolone for 3 days, plasmapheresis 7 times, and rituximab 1 time. After methylprednisolone completion, he was started on prednisone 80 mg daily, and this was tapered off as an outpatient. He did not receive any more doses of rituximab. Details of outpatient treatment and decision making are not clear, but the patient is doing relatively more than 1 year after discharge. The latest creatinine is down to 2.25 mg/dL, he sees a nephrologist every 3 months, he denies dyspnea, and CT Chest report more than 1 year after discharge indicates minimal sub pleural fibrosis and two lung nodules.

This patient has ANCA Associated Vasculitis with pulmonary/renal syndrome based on the acute and chronic renal failure, the immunological lab results, pulmonary infiltrates on imaging, kidney biopsy results, and the bronchoscopy finding of DAH. There were no significant ENT or skin findings. The antineutrophil cytoplasmic antibody (ANCA) – associated vasculitides (AAV) are a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels.[1] The AAV comprise granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1] The relative rarity and non-specific presentation of the AAV pose diagnostic challenges and often result in a significant diagnostic delay of more than 6 months in a third of patients.[1] This patient's diagnosis was delayed by almost 11 months due in part to frequent ED visits and difficulty obtaining specialist referrals. Other autoimmune and infectious conditions were ruled out.

The positive C-ANCA at 1:256 changed the diagnosis to C-ANCA Vasculitis with pulmonary/renal syndrome. Although MPO Antibody was negative, PR3 Antibody was mis-processed. The combination of a C-ANCA pattern on immunofluorescence testing and PR3-ANCA is associated with [GPA].[2] Positive immunofluorescence assays without confirmatory enzyme immunoassays for anti-PR3 or antimyeloperoxidase antibodies are of limited utility.[2] A 2017 study[3] evaluated 395 patients with nonidentified ANCAs, and only 1.8% of these patients were diagnosed with GPA. Notable in this study was that GPA patients with anti MPO or anti PR3 had much higher CRP values and systemic forms of GPA compared to GPA patients with non-identified ANCA who were more likely to have lower CRP values and localized forms of GPA.[3] This patient had a very elevated CRP of >19.00 mg/dL and systemic disease making GPA with PR3 Antibody positive more likely.

If the patient was Anti PR3 positive, then the diagnosis would more likely be Granulomatosis with Polyangiitis (GPA), although Microscopic Polyangiitis (MPA) would be possible. MPA and GPA share the clinical features caused directly by capillaritis and small-vessel vasculitis, although GPA can be differentiated from MPA by characteristic clinical features caused by necrotizing granulomatous inflammation, usually affecting the respiratory tract. PR3-ANCAs are present in about two-thirds of patients with GPA, but also in one-quarter of patients with MPA, whereas MPO-ANCAs are present in the majority of patients with MPA, but also in up to one-quarter of patients with GPA (as defined by the 1994 Chapel Hill Consensus Conference)[4] Samples from patients diagnosed as having GPA or MPA can also be negative for both types of ANCA. [4]

A recent review article[5] mentioned that DAH presents with dyspnea in 65-100% of patients, hemoptysis 40-100%, and hemoglobin drop of 0.6 to 2.0 g/dL. Greater than 50% of patients required mechanical ventilation, and most of them had renal failure.[5] Chest X-ray features of DAH are ground-glass diffuse opacities and/or consolidation, and sometimes mosaic-type perfusion pattern, which indicates arteriolar vasculitis. High-resolution tomography (HRCT) has higher sensitivity and the classic features include ground glass opacities with a random distribution.[5] This patient had a non-contrast CT Chest that showed a diffuse and markedly heterogeneous pattern of multiple small consolidations most pronounced in the upper lobes. Bronchoscopy and bronchoalveolar lavage (BAL) are other diagnostic tools. In BAL, the pathologist must search for hemosiderin laden macrophages which usually appear 24-48 hours after the DAH has started.[5] The diagnosis of DAH is challenging and even more difficult to identify the specific cause. The most common cause of DAH was an autoimmune disease mostly AAV[5] like in this patient.

As the patient was becoming acutely ill, he was started on high-dose corticosteroids. The reported prognosis of DAH is poor, with in-hospital mortality ranging from 20% to over 50%.[6] In an article by de Prost et al[6] a scoring system was used to help determine urgency of treatment. It is important to initiate treatment in [DAH] patients as soon as possible before results of immunological markers and/or tissue biopsy have been obtained due the life threatening nature of DAH.[6] This patient scored high (based on respiratory symptoms and proteinuria), so immediate treatment was warranted.

It is important to stratify the vasculitis disease severity. Usually DAH in a patient with AAV is considered as a severe disease.[5] First line therapy is high-dose glucocorticoids and cyclophosphamide. Plasmapheresis can be another option for induction in DAH.[5] Induction of remission with rituximab is another treatment option, and the efficacy is non-inferior to cyclophosphamide.[5] The RAVE trial included 51 patients with DAH, 27 received rituximab; the remission rates were similar between groups.[5] This patient was felt to have severe disease because of the DAH and ANCA Associated Vasculitis. He received high-dose methylprednisolone and plasmapheresis (7 sessions) in the hospital. He received one dose of rituximab. He was discharged home on a prednisone taper, but he did not get any further treatments of rituximab. Fortunately, he has done well. He has stable chronic kidney disease, no respiratory symptoms, and a significantly improved CT Chest. Continued close follow up is needed. The percentages of patients who suffer disease flares after appropriate courses of treatment have been estimated to be 25-40%.[7]

Figures

Figure 1. PA Chest X-Ray on day of admission.

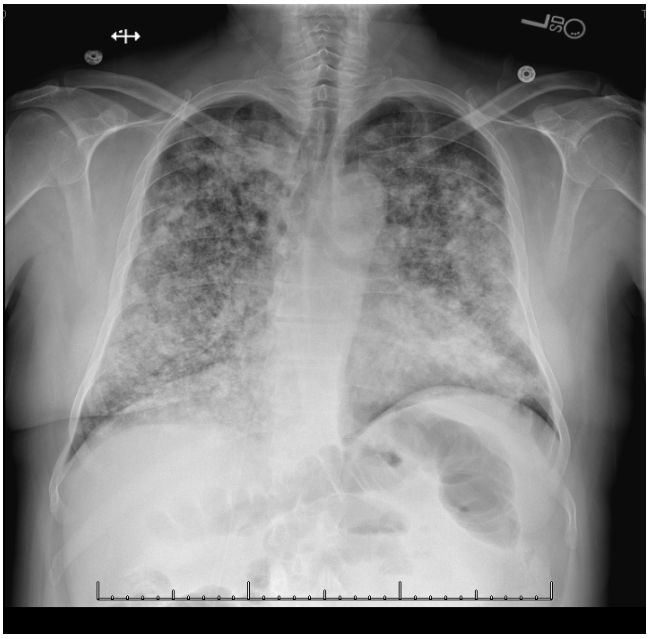
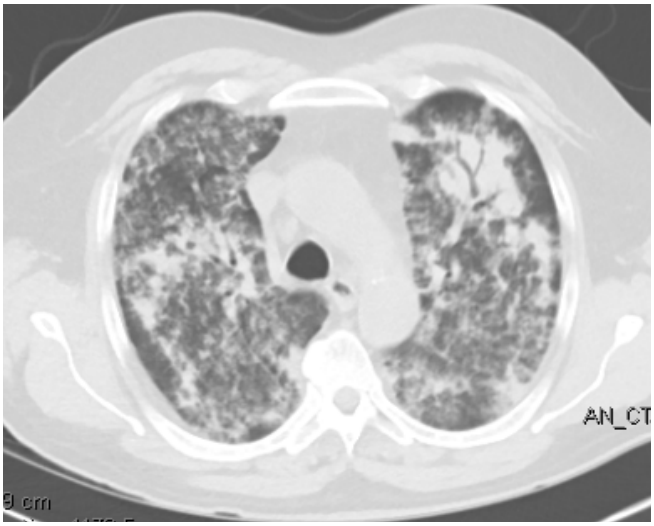


Figure 2. Lung window of CT Scan of Chest on hospital day #3.



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