



Case Report

# Predicament of classification: Multisystem small vessel vasculitis with crescentic Glomerulonephritis

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## Case History

The patient is a 28-year old Caucasian man with six month history of arthralgia and crampy abdominal pain who presented with acute dyspnea and cough for 6 months associated with migratory polyarthralgias involving his knees, ankles, wrists, and shoulders. Three months prior to admission he noted an episodic crampy abdominal pain with intermittent diarrhea and constipation. The arthralgia persisted and was more associated with two hours of morning stiffness. During this time he also noted occasional nose bleeds and difficult hearing out of his left ear.

He was seen in the emergency department with the above complaints. Physical examination showed no evidence of joint swelling or erythema and his laboratory evaluation is seen in table 1.

Two weeks later, he returned to the outpatient medical clinic for follow-up. He

**Table 1:** Laboratory values

Test	1 encounter	2 encounter	3 encounter
BUN	7	21	17
Creatinine	1.0	1.3	1.2
WBC			6.5
Hematocrit	45	39	28-23
Platelets			332
PT			13
INR			
PTT			20
ESR	27	56	56
RF	43, 1:80		186: 1-2560
Cryoglobulins			negative
ANA	Negative	Negative	
ANCA	Negative	Negative	
CH50			310
Hep. A serology			negative
Hep B serology			negative
Hep C serology			negative
AST		103	46
LDH		236	189
T.bili/D.bili		1.2	1.2/0.6
AP			129
URINE:			
RBC	20-30	TNTC	TNTC
WBC	3-5	7-10	3-5
Protein	trace	+1	+2 (multiple granular and RBC casts)
24 h protein		1.4 gram	
Cr. clearance		109	



complained of persistent crampy abdominal pain and episodic loose stools occasionally streaked with blood. He noted worsening arthralgia and approximately one hour of morning stiffness which was not relieved by Motrin. His right ankle aspiration was attempted without success. A Lyme titer was negative. He was sent home on Indocin.

He returned to the outpatient clinic with swollen left calf, persistent arthralgia not relieved by Indocin, and new oral ulceration. Physical examination at this encounter revealed bilateral conjunctivitis, oral ulcers, tender bilateral ankle swelling, and swollen left calf. Lower extremity Doppler ultra-sound showed no evidence of DVT. An x-ray of the sacroiliac joints was unremarkable. His laboratory investigation is shown in table 1.

Seven days later he returned to the ER with acute shortness of breath (SOB), and cough productive of brown and blood streaked sputum. He complained of new proximal leg muscle weakness, three days of fever to 100F, persistent loose stools, and 20 Lb. weight loss over the prior 2 months. The abdominal pain had resolved. He denied a history of rash, nausea, hematemesis, dark stools, dysuria, flank pain or gross hematuria. There was no history of chronic bronchitis, sinusitis, and tuberculosis exposure. He denied homosexual contact, IV drug abuse, or prior blood transfusion. His only medication was Naprosyn 500 mg twice daily. He was allergic to penicillin. Physical examination revealed pale young male in mild respiratory distress. BP 110/60 mmHg. Heart rate 130 beats per minute (BPM) regular, respiratory rate 24 per minute, temperature 100.1 F, oxygen saturation on room air 84%. Skin examination showed no erythema or rash. Oral examination revealed oral ulcerations. Bibasilar crackles on lung examination. Abdominal and cardiac examination were unremarkable. Extremities showed no evidence of arthritis, erythema, or swelling. Neurological examination showed mild proximal muscle weakness of both lower extremities, and mild weakness of the dorsiflexion of the left foot. Laboratory investigation is shown in Table-1. The urine microscopy showed an active sediment with red blood cells (RBC's) and granular casts and too many RBCs to count (TNTC). His chest-x ray revealed patch pulmonary infiltrates with consolidation at both bases. His kidney-ureters-bladder (KUB) and sinus x-rays were unremarkable.

Patient was admitted to the hospital. The Naprosyn was stopped and he received two units of packed RBC with increase in his hematocrit (Hct) to 31. However, transfusion was associated with worsening SOB and he required 100% oxygen to maintain an oxygen saturation of 90%. He was started on Bactrim and erythromycin empirically and solumedrol 1 gram IV. The relevant tests are shown in table 1.

On the second hospital day a renal biopsy was performed. Ear nose and throat consultation and neurological consultation were requested. That revealed mild hearing loss in the left ear. Neurological examination with EMG revealed evidence of mononeuritis multiplex. He was started on cyclophosphamide orally and prednisone 60 mg daily. He was discharged home on the 11 hospital day with blood urea nitrogen (BUN) 32 and creatinine of 1.5.

A final diagnosis was focal necrotizing glomerulonephritis, pauci-immune due to ANCA negative granulomatosis with polyangiitis (GPA).

## Discussion of the Case

Small vessel vasculitis is a multi-system disease involving the kidneys, gastrointestinal tract, central nervous system, upper and lower respiratory system, and skin to name a few. There have been multiple efforts to define the diagnostic criteria and classification of the disease with no perfect system materialized yet. The American college of Rheumatology (ACR) classification criteria in 1990 were aimed at defining and classifying small vessel vasculitis to facilitate diagnosis and research



on the subject [1] however, these criteria were introduced before the discovery of anti-neutrophil cytoplasmic anti-bodies (ANCA) testing as a diagnostic tool [1,2]. The sensitivity and specificity of the criteria put forward by the ACR are 88% and 92% respectively [1].

The Chapel Hill Consensus Conference criteria (CHCC) provided definition of the disease but no classification attempts were provided [3,4]. Defining the disease by pathology, vessel size, and organ involved have made some strides, however, the ANCA serology was not included as a criteria for the diagnosis.

The European Medicine Agency Algorithm (EMA) tried to combine the ACR and CHCC criteria for GPA, eosinophilic granulomatosis with poly-angiitis (EGPA), and microscopic poly-angiitis (MPA) and ANCA was included in the algorithm. This classification did away with tissue diagnosis if the features and the ANCA are consistent with GPA disease process. This system permitted the classification of patients with a correlation among observers of 91.5% [5]. Though, none of the EMA algorithms reliably distinguish between GPA and MPA without a tissue biopsy. There has been significant overlap in the signs and symptoms and in the ANCA serology between MPA and GPA. Even though the clinical definition of GPA and MPA did not predict long term outcome and relapse as compared to ANCA serology (MPO-ANCA Vs PRO3-ANCA) [6]. Sometimes, the tissue pathology and the extent of the organ involved are not enough to make the distinguishing between the different clinical disease entities [7].

The alternative classification based on ANCA serology along with tissue biopsy may be the best way to characterize these syndromes. The differences between proteinase-3 (PRO3-ANCA) and myeloperoxidase (MPO-ANCA) can more precisely distinguish the underlying disease. The PRO3-ANCA disease have a specific ANCA serology subtypes, a better predictive value with respect to outcome and relapse of the disease, when compared to MPO-ANCA. Even though the treatment of these diseases in many occasions are the same [6,8]. Approximately 82-94% of patients with either GPA or MPA are ANCA positive [9,10]. GPA is commonly associated with PRO3-ANCA and MPA with MPO-ANCA. However, 20% of patients with GPA or MPA have the alternative ANCA, and at least 10% of patients are ANCA negative [11-13]. The majority of patients (75-80%) with renal limited vasculitis (RLV) are MPO ANCA positive.

By using PRO3-ANCA, MPO-ANCA, and ANCA-negative disease, this classification can overcome the shortcoming of using the diagnostic criteria for each disease entity. The PRO3-ANCA and MPO-ANCA have more prognostic significance than the terms MPA and GPA as far as response to therapy, relapse, and patient outcome are concerned [6,14].

The patient under discussion is presented with multi-system involvements, with overlap of the criteria characteristic for each GPA and MPA. The kidney biopsy did not reveal a granuloma formation which is an essential criteria for the diagnosis of GPA. This can be explained by a sampling error. The patient had involvement of the upper and lower airways which are consistent with GPA. The negative ANCA serology can be observed in 20% of patients with GPA [11,13]. This picture makes it difficult if not impossible to assign the patient's disease to a designated entity. The description of ANCA negative vasculitis with involvement of the kidney would be much easier if the treatments applied for the 3 diseases are the same. However, in many occasions the treatment strategy is different. His final diagnosis should be ANCA-negative focal necrotizing glomerulonephritis consistent with GPA.

Ear, nose and throat involvement is common in GPA (90%) Vs MPA (35%) [15-17]. Tracheal and pulmonary disease can be seen in the majority of ANCA associated vasculitis, (AAV) [16,18-20]. Tracheal or subglottic stenosis, pulmonary consolidation or fibrosis, and pulmonary arterial hypertension are some of the manifestation of the disease [18,21].

Renal involvement is common in GPA and MPA [16,17,22]. In a series of cases glomerulonephritis was present in 18% at presentation and up to 77-85% of patients within the first 2 years of the disease [17,22]. When the disease is presented with asymptomatic hematuria, IGA nephropathy and thin basement membrane disease (TBMD) should be considered in the differential diagnosis. Proteinuria is usually sub-nephrotic (<3 grams/day) and is due to fibrosed glomeruli or tubular fibrosis [17,20]. More advance disease with focal and segmental glomerulosclerosis (FSGS) can present with nephrotic range proteinuria (>3 grams/day) the other possibility would be a second diagnosis like membranous nephropathy on top of vasculitis which is not uncommon in these occasions [23,24].

Non-specific laboratory abnormalities like, leucocytosis, thrombocytosis, high ESR, C-reactive protein, and normocytic normochromic anemia are some of the non-specific presenting findings in ANCA-associated vasculitis (AAV), [17]. The presence of anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-glomerular basement membrane antibodies (anti-GBM) are sometimes associated with AAV.

ANCA-negative pauci-immune crescentic glomerulonephritis are considered to be part of the spectrum of GPA and MPA. They have similar biopsy findings and prognosis [25].

The diagnosis of the AAV should rest on the clinical manifestation, ANCA serology, and tissue biopsy to confirm the conclusion. As is illustrated in the case under discussion the presence of ANCA positivity is not necessary if the clinical picture and the tissue diagnosis are consistent with the underlying disease process.

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