

A Rare Case of Overlapping Syndrome of ANCA-Associated Glomerulonephritis and Systemic Lupus Erythematosus

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Abstract

Introduction: Two very interesting rheumatologic diagnoses include Systemic Lupus Erythematosus (SLE) and Anti-Neutrophil Cytoplasmic Antibody (ANCA)-negative Vasculitis. It is rare to see these two conditions diagnosed in the same patient. This case analyzes the complex interactions between these two disease states.

Case: This is the case of a 69 year old female who presented with shortness of breath, hematuria, and renal failure. Lab work was significant for elevated ANA (1:1280), positive double-stranded DNA antibody, normal complement levels and a negative Vasculitis panel. Renal biopsy was consistent with ANCA-associated Vasculitis (AAV). Thus the patient met diagnostic criteria for both SLE and AAV and was treated accordingly.

Conclusion: A review of the literature reveals that these typically separate disease entities when diagnosed together may actually represent a completely new, overlapping syndrome. This case is unique in that there have not been any other cases of a simultaneous diagnosis of SLE and ANCA-negative Vasculitis without evidence of lupus nephritis reported in the literature. A deeper understanding of the mechanism driving these rare diseases can lead to improved prognostication and treatment of these conditions.

Keywords: Systemic lupus erythematosus; ANCA; Vasculitis; Autoimmune

Introduction

Systemic Lupus Erythematosus (SLE) and small vessel vasculitides such as Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis are both uncommon diseases. Typically, SLE and ANCA-Associated Vasculitis (AAV) are two distinct clinical entities, and rarely occur simultaneously [1]. The renal manifestations of SLE are classically characterized by an immune complex glomerulonephritis with endocapillary proliferation [2, 3]. In contrast, the renal manifestations of AAV are characterized by glomerular necrosis and crescent formation in the absence of cellular proliferation or immune complex deposition [4]. There is evidence in the literature that there may be some association between ANCA vasculitides and SLE, but it is still unclear exactly what this association is [5]. Through the following case report, we aim to discuss the pathophysiologic

mechanisms, prognosis, and management of these two conditions, especially in context of one another.

Case Report

We present the case of a 69 year old female with two simultaneous new diagnoses of SLE and ANCA-negative Vasculitis. Her past medical history was significant for hypothyroidism, gastro esophageal reflux disease, and recently diagnosed pulmonary hypertension. Her presenting symptoms included one week of increasing shortness of breath, pleuritic chest pain, and joint pain. She was seen at an outside hospital and found to have acute kidney injury as well. She was transferred to our hospital with initial workup revealing of a positive ANA, positive lupus anticoagulant, and positive anticardiolipin antibody. Vitals on admission, patient had a temperature of 37.2 degrees Celsius, heart rate 77, respiratory rate 18, blood pressure 153/70, and oxygen saturation 90% on room air. On examination, she was oriented to person, place, and time, and appeared to be in mild respiratory distress. Her mucous membranes were moist. On auscultation, her heart sounded regular in rate and rhythm and her lungs had diffuse crackles in her lower left lung with good aeration of her right lung. Her abdomen was soft and non-tender to palpation and bowel sounds were hypoactive. Skin was warm and dry with no rashes or lesions noted and her extremities had no clubbing, cyanosis, or edema. Continued workup at our hospital revealed that the patient met the criteria for lupus: she had bilateral pleural effusions on chest x-ray, red blood cell casts in urinalysis, thrombocytopenia (values ranged from 43 to 117), and lymphopenia (absolute lymphocyte count ranged from 0.24 to 1.37). In addition, laboratory results were significant for a positive double-stranded DNA antibody IgG with a value of 551 (more than twice normal the reference value), and positive ANA (1:1280). Kidney function continued to worsen throughout her hospital stay, requiring dialysis. Eventually a biopsy of the kidney was performed which revealed focal necrotizing glomerulonephritis, red blood cell casts, and arteriosclerosis with severe intimal fibrosis, suggestive of an ANCA-associated Vasculitis (Figure 1). There was no evidence

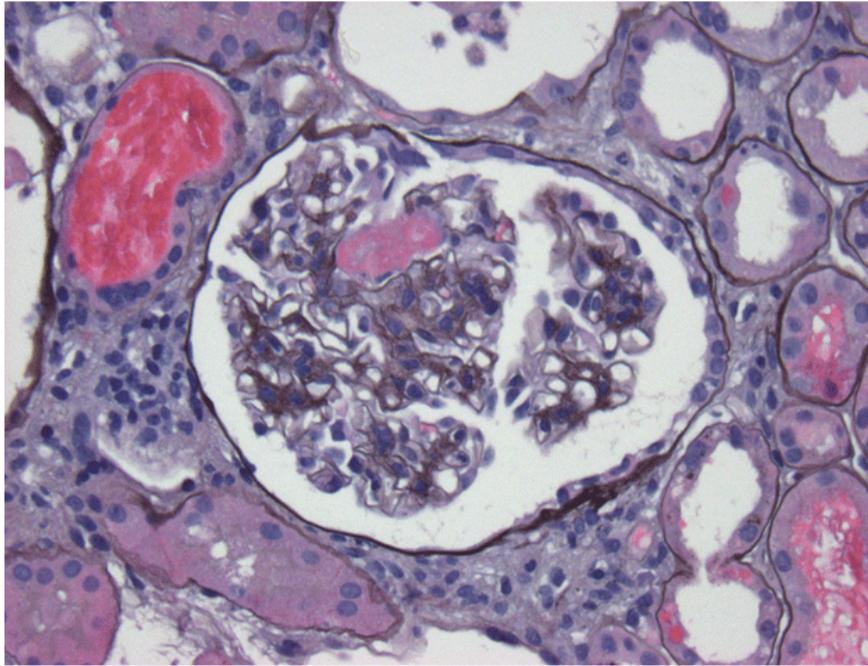


Figure 1: Patient's renal biopsy in a Jones silver stain demonstrating a glomerulus with a focus of fibrinoid necrosis and a red blood cell cast in the tubule next to it, 400 x magnifications.

of endocapillary proliferation or immune complex deposition. Patient had a negative C-ANCA, indeterminate P-ANCA, and follow up myeloperoxidase and proteinase-3 labs were negative. In addition, other pertinent negative labs included negative complement 3 (C3), complement 4 (C4), Anti-Sjogren's Syndrome A (SSA), Anti-Sjogren's Syndrome B (SSB), Rheumatoid Factor (RF), and anti-glomerular basement membrane antibody. Based on this workup, the patient met the criteria for both SLE and AAV. She was given a course of high dose steroids while in the hospital and subsequently started on cyclophosphamide. Her symptoms improved and she was suitable for discharge. She continued to be followed by rheumatology and nephrology as an outpatient with tri-weekly dialysis sessions. After two months, our patient's disease stabilized on azathioprine and cyclophosphamide and she no longer required dialysis. She remained stable without requiring dialysis for another 10 months. However, about a year after her diagnosis, she developed pancytopenia and had to be readmitted to the hospital. Unfortunately, it was a complicated hospital course involving neutropenic fever which did not improve with antibiotics and pancytopenia which did not improve with multiple transfusions of blood products. She additionally had severe metabolic acidosis thought to be secondary to splenic infarctions and required intubation and pressor support. Family ultimately decided to pursue a comfort measures approach. Thus the patient was compassionately extubated and she passed away shortly thereafter.

Discussion

Based on the Chapel Hill consensus conference in 2012, this patient's Vasculitis diagnosis is most consistent with the

microscopic Polyangiitis subtype because her biopsy reveals necrotizing Vasculitis of the small vessels without immune deposits and no evidence of granulomatous inflammation or eosinophils. Our patient also met 6 of the 11 criteria for SLE as defined by the 1997 Update of the 1982 American College of Rheumatology Revised Criteria: nonerosive arthritis, pleuritis (bilateral pleural effusion seen on CXR), renal disorder (red blood cell casts), hematologic disorder (lymphopenia and thrombocytopenia), immunologic disorder (anti-DNA and anti-phospholipid antibodies), and positive antinuclear antibody. Thus, she fulfilled diagnostic criteria for both AAV and SLE.

There are three possibilities to explain the ultimate diagnoses of both AAV and SLE in this patient: she had a Vasculitis that happened to meet SLE criteria, she had a separate renal Vasculitis in the setting of SLE, or the two together represent a single new and unique disease entity: an overlapping syndrome.

This case is significant for many reasons. First, it raises the question of the underlying mechanisms driving these two diseases. Since there are many features of SLE and AAV that overlap, it is possible that they are triggered together by similar mechanisms. Indeed, one study found that in 9% of cases, there was some underlying chronic inflammatory process that triggered the ANCA associated Vasculitis to develop into rapidly proliferating glomerulonephritis [7]. The path physiologies underlying the renal manifestations of each of these diseases are complex. Although classic lupus nephritis is thought to be secondary to immune complex deposition, it has been suggested in the literature that class IV lupus may be caused by a different mechanism [3]. Class IV lupus nephritis often exhibits prominent

glomerular necrosis and little or no immune complex deposition. Some studies have suggested that crescentic necrotizing pauci-immune glomerulonephritis may be a very rare variation of lupus nephritis [2]. However, it is also hypothesized that this manifestation of lupus nephritis is driven by ANCA via activation of neutrophils that release cytokines, leading to endothelial damage and the resultant necrosis and crescent formation [4]. The significance of ANCA seropositivity in lupus workup therefore requires further examination.

ANCA seropositivity is detected in up to 30% of all SLE patients [5, 8]. Typically, SLE patients with ANCA positivity are found to have p-ANCA, and rates of ANCA seropositivity are even higher in patients with renal involvement, suggesting some association [8]. There is conflicting information regarding the importance of testing for ANCA in SLE. Some studies have suggested that the degree of seropositivity in SLE patients does not significantly differ from the general population and is not associated with a different clinical presentation, so therefore the routine measurement of ANCA in SLE patients is not generally recommended [9]. However, other studies have suggested that ANCA seropositivity correlates with disease duration, severity of symptoms including alveolar hemorrhage, and response to specific treatments [4,5]. Therefore ANCA testing in lupus is of some value. The role of ANCA in lupus renal disease is further complicated by the fact that in up to 10-20% of pauci-immune glomerulonephritis cases, ANCA is seronegative [2]. This subgroup of pauci-immune glomeronephritis patients is much rarer and less studied. In addition, this subgroup of ANCA negative patients with pauci-immune glomerulonephritis challenges the theory that ANCA is the driving factor in pauci-immune glomerulonephritis as a rare manifestation of lupus nephritis. One review found that ANCA negative patients had a higher prevalence of nephrotic syndrome, more severe renal glomeruli lesions, and overall poorer outcome compared to ANCA positive patients [10]. The underlying pathophysiology of ANCA-negative pauci-immune glomerulonephritis is not clear at this time, but it has been suggested that neutrophil infiltration plays a key role even in the absence of ANCA antibodies [2, 10-12].

The idea of an "overlapping syndrome" where SLE and AAV coexist has been reported in the literature [1, 11, 13]. The vast majority of overlapping cases that have been reported are ANCA positive, and 96% of those cases are p-ANCA positive [13]. Indeed, one recent literature review found that when excluding patients that had only extra renal manifestations of SLE, only 8 cases of SLE/AAV overlap syndrome were reported, and of these all were p-ANCA positive [11]. The overlapping syndrome is thought to be a unique disease entity where neither disease state predominates nor the sum of their symptoms determines severity. Typically, patients with overlapping syndrome have more severe presentations than patients with either disease alone and it is associated with a higher prevalence of pericarditis, arthritis, necrotizing and crescentic glomerulonephritis, and cytopenia [13]. There also may be an association between overlap syndrome and antiphospholipid antibody syndrome [13].

In addition to these cases of overlap syndrome reported

in the literature, there have also been cases of ANCA positive glomerulonephritis in the setting of SLE as well as ANCA negative glomerulonephritis outside the setting of SLE [1, 4, 7, 10-12,14]. There have also been cases of pauci-immune glomerulonephritis reported in the setting of concurrent lupus nephritis [4, 8, 15]. Our case demonstrated no evidence of lupus nephritis since there was no evidence of immune complex deposition on biopsy. What makes our case unique is that, to our knowledge, there has only been one other case of pauci-immune ANCA negative glomerulonephritis without renal manifestations of lupus nephritis occurring in the setting of SLE reported in the literature [2]. In addition, whereas in other cases patients already carried one diagnosis and later went on to develop symptoms consistent with a second diagnosis; this is the first case of a simultaneous diagnosis of SLE and pauci-immune ANCA negative glomerulonephritis.

An understanding of the underlying mechanism is important because knowledge of the driving factor responsible for the patient's symptoms can influence both prognosis and treatment. One study found that there is a 35% mortality rate over 5 years in patients with ANCA negative glomerulonephritis [12]. Prognosis also changes in the context of each disease. For example, creatinine at the time of presentation is the best predictor of mortality in AAV, whereas the class of lupus nephritis is often used for SLE prognosis [12, 16]. A recent European multicenter study that looked at 160 patients with ANCA-associated Vasculitis determined that the serum creatinine at the time of initial presentation was the best predictor of renal function and prognosis of the disease after the first year [12]. In contrast, the prognostic indicators for SLE include male gender, a positive lupus anticoagulant, and the class of lupus nephritis at the time of diagnosis [16]. Our patient did have a positive lupus anticoagulant which would worsen her SLE prognosis. However, our patient also had a creatinine of 1.6 on presentation which would be predictive of a favorable prognosis in AAV. From a similar standpoint, differentiating SLE from AAV can also have an impact on treatment options. One limited study suggested that mycophenolate mofetil had higher remission rates and better prognoses in patients with ANCA-positive lupus nephritis as compared to cyclophosphamide [5]. Such an observation suggests that further research needs to be done to determine if induction and maintenance therapy in patients with ANCA-negative pauci-immune glomerulonephritis should be different than in either SLE or AAV alone. More invasive treatment, such as renal transplant, has different outcomes depending on which disease is being treated: renal transplantation resolves systemic symptoms in AAV whereas there is improvement in renal but not systemic symptoms of SLE [7]. We hope this patient's case will shed light on these two important rheumatologic diseases. Indeed, further exploration of the rare AAV and SLE overlapping phenomenon can lead to improved management of these conditions in the future.

Conclusion

In summary, SLE and AAV are two distinct diseases that are likely related by some underlying mechanism. This underlying

mechanism is worth further exploration with future studies, but may be driven by neutrophils. Based on our patient's presentation, we would recommend checking serum ANCA in patients with SLE because review of the literature suggests ANCA seropositivity does change prognosis and treatment options. The clinical impact of ANCA seropositivity remains to be elucidated. Further investigation into pauci-immune ANCA associated glomerulonephritis in the setting of SLE is warranted so that we may continue to improve care of these patients in the future.

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Declarations

The authors have no conflicts of interest to report. Informed consent was obtained from the patient's next of kin at the time of the submission process of this case report. This case report has been written in accordance with CARE guidelines.

References

1. Randa EY, Arrayhani M, Sqalli T. Cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) in systemic lupus erythematosus: An overlapping syndrome? *J Med Case Rep.* 2014; 2 (2): 22-23.
2. Cansu DU, Temiz G, Acikalin MF, Korkmaz C. Pauci-immune lupus nephritis: possibility or co-incidence? *Eur J Rheumatol.* 2017; 4(1): 73-75. DOI: 10.5152/eurjrheum.2016.013
3. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al., The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol.* 2004; 15(2): 241-250.
4. Nasr SH, D'Agati VD, Park HR, Sterman PL, Goyzueta JD, Dressler RM, et al., Necrotizing and crescentic lupus nephritis with antineutrophil cytoplasmic antibody seropositivity. *Clin J Am Soc Nephrol.* 2008; 3(3): 682-690. DOI: 10.2215/CJN.04391007
5. Li C, Zhou ML, Liang DD, Wang JJ, Yang J, Zeng CH, et al., Treatment and clinicopathological characteristics of lupus nephritis with anti-neutrophil cytoplasmic antibody positivity: a case-control study. *BMJ Open.* 2017; 7(7): DOI: 10.1136/bmjopen-2016-015668
6. Joel J, Gagnier, Gunver Kienle, Douglas G. Altman, David Moher, Harold Sox, David Riley. The CARE guidelines: consensus-based clinical case reporting guideline development. *Glob Adv Health Med.* 2013; 2(5): 38-43. DOI: 10.7453/gahmj.2013.008
7. Hedger N, Stevens J, Drey N, Walker S, Roderick P. Incidence and outcome of pauci-immune rapidly progressive glomerulonephritis in Wessex, UK: a 10-year retrospective study. *Nephrol Dial Transplant.* 2000; 15(10): 1593-1599.
8. Park EJ, Kim S, Kim H, Kim J. A case of true renal lupus vasculitis combined with pauci-immune glomerulonephritis in a patient with systemic lupus erythematosus. *J Rheum Dis.* 2015; 22(1): 34-38. DOI:10.4078/jrd.2015.22.1.34
9. Molnar K, Kovacs L, Kiss M, Kiss M, Husz S, Dobozy A, Pokorny G. Antineutrophil cytoplasmic antibodies in patients with systemic lupus erythematosus. *ClinExpDermatol.* 2002; 27(1): 59-61. DOI: 10.1046/j.0307-6938.2001.00964.x
10. Chen M, Yu F, Wang SX, Zou WZ, Zhao MH, Wang HY. Antineutrophil cytoplasmic autoantibody-negative pauci-immune crescentic glomerulonephritis. *J Am Soc Nephrol.* 2007; 18(2): 599-605. DOI:10.1681/ASN.2006091021
11. Jarrot PA, Chiche L, Hervier B, Daniel L, Vuiblet V, Bardin N, et al., Systemic lupus erythematosus and antineutrophil cytoplasmic antibody-associated vasculitis overlap syndrome in patients with biopsy-proven glomerulonephritis. *Medicine (Baltimore).* 2016; 95(22): e3748. DOI:10.1097/MD.0000000000003748
12. Eisenberger U, Fakhouri F, Vanhille P, Beaufile H, Mahr A, Guillevin, et al., LANCA-negative pauci-immune renal vasculitis: histology and outcome. *Nephrol Dial Transplant.* 2005; 20(7): 1392-1399. DOI:10.1093/ndt/gfh830
13. Hervier B, Hamidou M, Haroche J, Durant C, Mathian A, Amoura Z. Systemic lupus erythematosus associated with ANCA-associated vasculitis: an overlapping syndrome? *Rheumatol Int.* 2012; 32(10): 3285-3290. DOI:10.1007/s00296-011-2055-z
14. Burkhart R, Shah N, Abel M, Lewin M, James DO. Pauci-immune necrotizing and crescentic glomerulonephritis with membranous lupus nephritis, fifteen years after initial diagnosis of secondary membranous nephropathy. *Case Rep Nephrol.* 2015; 2015: DOI: 10.1155/2015/120762
15. Moeckel GW, Jabs K, Fogo AB. An 11-year-old African-American girl with systemic lupus erythematosus and ANCA-negative renal vasculitis. *Am J Kidney Dis* 2002;39(2)433-438.
16. Doria A, Iaccarino L, Ghirardello A, Zampieri S, Arienti S, Sarzi-Puttini P. Long term prognosis and causes of death in systemic lupus erythematosus. *Am J Med.* 2006; 119(8): 700-706. DOI:10.1016/j.amjmed.2005.11.034