New-Onset Rheumatologic Disease in an Elderly Patient Initially Presenting as Worsening Sequelae of Longstanding Peripheral Vascular Disease

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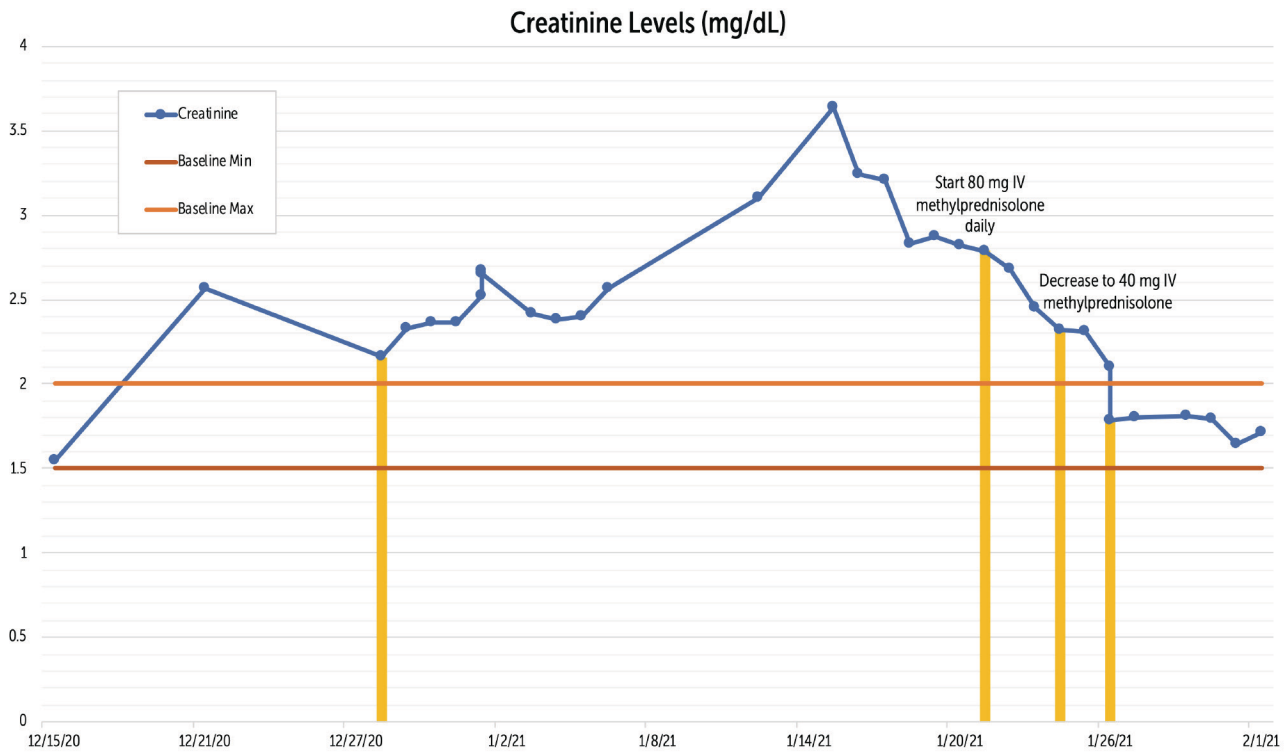
INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that is believed to activate and attack nuclear antigens in genetically susceptible individuals after exposure to environmental factors causing cell damage.[1,2] Although it is most common in females of child-bearing age, initial presentation is not strictly limited to this population, as onset over the age of 50 years is reported in 3-18% of cases.[2] The common manifestations of SLE affect nearly every system of the body and may include arthralgia, myalgia, fever, rash, hepatosplenomegaly, lymphadenopathy, pleuritis, glomerulonephritis, pericarditis and neuropsychiatric manifestations.[1-3] Common laboratory findings in SLE with varying degrees of sensitivity and specificity include anti-nuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), anti-histone antibodies, elevated inflammatory markers, and decreased levels of complements C3 and C4.[1] Treatment is typically aimed toward symptom management and prevention of organ damage; thus, treatment regimens are typically dictated by the organ systems involved and symptoms experienced.[1]

Hydralazine, a vasodilating drug used for treatment of hypertension, has been demonstrated to cause various rheumatologic complications, including a lupus-like syndrome and an anti-neutrophil cytoplastic antibody (ANCA) vasculitis, which tend to present with overlapping features.[3-5] Notably, both of these hydralazine-induced rheumatologic diseases tend to present similarly to their primary counterparts but with less severity and less organ involvement; however, hydralazine-induced lupus is particularly prevalent in the elderly population whereas the limited data available regarding hydralazine-induced ANCA vasculitis is inconclusive regarding a predominant age-group affected.[3-5] The definitive treatment of both of these complications of hydralazine therapy is early identification and intervention with cessation of hydralazine therapy, given that in both diseases, symptoms typically resolve upon cessation of the offending agent.[3,4] With this treatment in mind, cessation of the offending agent can also be diagnostic in terms of determining whether a patient's clinical presentation is due to primary or drug-induced rheumatologic disease. Here, we present a 78-year-old woman, Mrs. J, who was on long-term hydralazine therapy with apparently worsening complications of her known peripheral artery disease, chronic kidney disease, and type 2 diabetes mellitus and was subsequently found to have several findings concerning for new-onset underlying rheumatologic disease, possibly hydralazine-induced.

CASE PRESENTATION

Mrs. J is a 78-year-old woman who presented to Thomas Jefferson University Hospital (TJUH) from an outpatient rehabilitation facility for transient altered mental status. She has a medical history of coronary artery disease with right coronary artery stent, type 2 diabetes mellitus (T2DM), hypertension previously controlled with hydralazine until December 2020, chronic kidney disease, permanent pacemaker secondary to complete heart block, interstitial lung disease (ILD) diagnosed in January 2020 and complicated by severe pulmonary hypertension leading to cor pulmonale, and stage 1A invasive ductal carcinoma of the breast previously treated with Anastrazole and partial mastectomy in August of 2020. She had been discharged for one day after being admitted to TJUH for 19 days for weakness and generalized pain. During that admission, she was also found to have an acute kidney injury (AKI), which was concerning for underlying rheumatologic etiology. Workup at that time demonstrated elevated PL-12 antibody, which is commonly associated with myositis, but her presentation was not consistent with dermatomyositis or polymyositis. Rheumatologic studies also showed elevated anti-nuclear antibody (ANA) with titer of 1:320 and homogenous pattern, positive anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3) antibodies with titer of 1:640, and anti-double stranded DNA (dsDNA) antibody elevated to 889 IU/mL (normal = < 200 IU/mL). Nephrology concluded that her AKI was most likely due to nonsteroidal anti-inflammatory drug (NSAID) use, poor oral intake, and secondary autoregulatory failure due to angiotensin receptor blocker (ARB) use at home. She also had a sacral decubitus ulcer determined by dermatology to be most likely due to



reactivation of latent herpes simplex virus (HSV) infection and exacerbated by decreased mobility and failure to thrive, so she was prescribed a one-week course of valacyclovir. Lastly, she had painful discoloration of her bilateral toes, most likely due to cholesterol emboli. Vascular surgery obtained an ankle brachial index (ABI) pulse volume recording (PVR) study due to concern for ischemia, which showed right ABI of 0.50 and left ABI of 0.53, indicating severe and mild to moderate peripheral vascular disease respectively. They recommended continuing dual antiplatelet therapy and high-intensity statin and following up with them as an outpatient.

During the present admission, her previously identified medical problems persisted with her acute kidney injury worsening as indicated by persistent microscopic hematuria and proteinuria on urinalysis and creatinine rising to a maximum of 3.64 mg/dL, approximately double her baseline of 1.5-2.0 mg/dL. She was additionally found to have oral ulcers on the hard palate that were not previously noted. She was empirically treated with vancomycin and piperacillin-tazobactam for broad-spectrum coverage of her suspected infection without improvement. CT head and MRI brain performed due to acute change in mental status showed findings consistent with vascular dementia. She received another course of valacyclovir for concern for HSV infection, but HSV 1 and 2 PCR were negative, so this medication was discontinued.

Hepatitis B and C antibodies were also negative. MRI of the feet was not concerning for osteomyelitis secondary to gangrenous foot wounds, and biopsy with direct immunofluorescence microscopy was not indicative of vasculitis. Repeat autoimmune studies showed persistently elevated anti-MPO/PR3 antibodies, improving but persistently elevated anti-dsDNA antibody to 562, elevated anti-cardiolipin IgM antibodies, and anti-histone antibody elevated to 3.8 U (strong positive = > 2.5 U). Her C3 complement was low on two occasions to 77 and 79, but C4 complement was within normal limits. Because the consulting rheumatology team had such strong suspicion for a rheumatologic process given her antibody titers, decreased C3, lack of resolution with other therapies, and presenting symptoms, she was started on a course of alprostadil, a vasodilating prostaglandin E1 analog, and 80 mg of IV methylprednisolone daily, which led to improvement of both her bilateral foot wounds and her acute kidney injury as indicated by creatinine returning to her baseline range. The IV methylprednisolone was decreased to 40 mg daily due to upper GI bleed possibly due to bleeding gastric ulcer, but despite this change, her improvement remained steady. A renal biopsy was performed about a week after beginning immunosuppressive therapy which demonstrated findings consistent with diabetic glomerulonephritis and pan-negative immunofluorescence.

DIFFERENTIAL DIAGNOSIS

At the time of presentation, it was suspected that Mrs. J's toxic metabolic encephalopathy was due to an infection of her bilateral gangrenous foot wounds with possible osteomyelitis and worsened by her concurrent vascular dementia. Given her history of positive p-ANCA, anti-dsDNA, and anti-histone antibodies, lack of improvement on antibiotics, negative imaging studies for osteomyelitis, and concurrent acute kidney injury on chronic kidney disease that was refractory to fluid boluses and markedly improved along with healing of bilateral foot wounds with corticosteroids and alprostadil respectively, it is far more likely that the primary disease process leading to her worsening clinical presentation was rheumatologic in nature. It is also important to note that it is likely that her overall clinical presentation was exacerbated as a result of several disease processes acting in tandem with one another, including rheumatologic disease, T2DM, peripheral vascular disease, and chronic kidney disease.

Given that Mrs. J also met both EULAR/ACR and SLICC criteria for SLE with her positive ANA, positive anti-dsDNA antibodies (95% sensitivity for SLE), and oral ulcers, late-onset SLE was at the top of our differential diagnosis despite her negative biopsy results.[1,6] Anti-histone antibodies are commonly thought to be associated primarily with drug-induced lupus; however, their presence has been noted in up to 75% of both drug-induced and primary SLE.[3] Additionally, anti-dsDNA antibodies are seen in more than 50% of SLE cases but only up to 5% of drug-induced lupus cases.[3]

On the other hand, her history of hydralazine-use with decreasing anti-dsDNA antibody titers in the few weeks following cessation of the drug would suggest the possibility of a hydralazine-induced ANCA vasculitis versus lupus, given that drug-induced rheumatologic diseases typically have a resolution of findings within weeks to months of drug cessation. Drug-induced lupus and SLE are not always distinguishable based on clinical presentation, and pharmacologic therapies tend to be similar when required; the hallmark of drug-induced lupus is that it would resolve with cessation of the drug.[3] In this case, it is difficult to determine whether her condition improved from cessation of hydralazine, initiation of corticosteroids, or a combination of the two given the timeline of her clinical course. Based on her clinical presentation, the severity of her symptoms would point more towards primary disease, given that neither drug-induced lupus nor ANCA vasculitis tend to present with organ involvement.[3,4] It is also important to note that her comorbid conditions likely played a role in the severity of her presentation, making severity of presentation a less reliable parameter due to confounding.

Lastly, without a renal biopsy confirming classic pathologies of either SLE, such as "full-house" staining for immunoglobulins and complement, or ANCA vasculitis, such as pauci-immune crescentic glomerulosclerosis, it is difficult to distinguish between these two pathologies based on clinical presentation and laboratory findings alone.[7,8] Positive ANCA serologies are associated with both ANCA vasculitis, and up to 20% of patients with SLE also have positive ANCA on serologic studies.[3] This patient's extrarenal manifestations are similarly minimally helpful in differentiation between the two. For example, she has interstitial lung disease (ILD) that was diagnosed only a year prior to her current presentation, but this disease has been associated with both ANCA vasculitis and SLE.[1,9] This finding is also confounded by the fact that she formerly used tobacco products, which may also lead to interstitial lung disease.

OUTCOME & FOLLOW-UP

Despite the biopsies being negative, given her clinical presentation and improvement on immunosuppressive therapy, she was discharged back to the outpatient rehabilitation facility with a steroid taper, mycophenolate mofetil for long-term immunosuppression and plans to follow up with rheumatology as an outpatient in two weeks.

DISCUSSION

Although Mrs. J presented with many symptoms concerning for possible sequelae of her prior-known medical problems, such as her peripheral vascular disease and T2DM, a bird's eye view of her constellation of symptoms makes it clear that there was a rheumatologic process that was largely confounded by her other medical problems, irrespective of whether it was primary or induced by hydralazine use. Her case provides an opportunity to explore setting a precedent for determining whether the etiology of a patient's rapidly declining clinical presentation is rheumatologic in nature. In patients with persistently worsening multiorgan disease and new findings classically associated with rheumatologic disease, such as mucocutaneous ulcers, a rheumatologic workup is warranted to rule out the possibility of new-onset rheumatologic disease. Additionally, this case presents an opportunity to stress the importance of a thorough history and physical exam in order to determine appropriate interventions as early as possible in the disease course.

One of the most intriguing aspects of this case, and simultaneously one of the most prominent limitations, is the lack of findings consistent with rheumatologic disease on biopsy of both the foot and the kidney, with the kidney being of particular interest. It is difficult to determine

whether the lack of findings consistent with lupus nephritis or vasculitis on renal biopsy are due to true lack of renal involvement, presence of long-standing comorbid diabetic glomerulonephritis confounding the biopsy results, or initiation of immunosuppressive therapy prior to renal biopsy. Despite this limitation, Mrs. J's presentation was likely still primarily rheumatologic in nature given that although diabetic glomerulosclerosis can lead to chronic kidney disease, a rapid deterioration of kidney function is not typical and should be a warning sign that there may be a secondary etiology at play.[8]

The major question that remains is whether a renal biopsy would reliably show manifestations of a more acute rheumatologic process on top of her existing diabetic glomerulosclerosis, irrespective of prior immunosuppressive therapies. Given that it is widely accepted that renal biopsy is the gold standard for diagnosis of both lupus nephritis and renal vasculitis, there is a lack of literature describing cases in which patients had primary or drug-induced lupus or vasculitis with negative renal biopsy, as well as a predominance of literature describing similar cases with diagnostic renal biopsies. In one retrospective study of 12 patients with diagnosed drug-induced ANCA vasculitis, all 6 patients who had renal biopsies showed the classic pauci-immune crescentic glomerulonephritis.[5] Similarly, a recent review of evidence for utility of renal biopsy in patients with lupus nephritis found that the presence of two, three, or four of the five commonly encountered pathologic findings on renal biopsy of lupus nephritis had specificities of 0.89, 0.95, and 0.98, respectively, and sensitivities of 0.92, 0.80, and 0.66, respectively.[7] These criteria include intense C1q staining, full-house staining, extraglomerular deposits, tubuloreticular inclusions, and combined subendothelial and subepithelial deposits, none of which Mrs. J's renal biopsy revealed.[7]

The assertion that patients with drug-induced lupus or vasculitis should have findings consistent with such diagnoses on renal biopsy seems contrary to the notion that it is quite rare for these conditions to have extensive renal involvement, especially given that resolution often begins after cessation of the offending drug.[3,4] An argument against such an assertion could be made based on the clinical correlate of the approach to biopsy for giant cell arteritis after corticosteroid initiation. For giant cell arteritis, evidence suggests that temporal artery biopsy can be performed up to four weeks after starting high-dose corticosteroids without degradation of the accuracy of the study.[10] If we choose to use this as a model for our case, it stands to reason that if administration of the offending drug is ceased and immunosuppressive therapy is begun prior to renal biopsy, it becomes less likely that consistent findings will be seen on biopsy, with the accuracy of the results being significantly affected after some unknown time period.

KEY POINTS

- Unlike primary rheumatologic disease, drug-induced rheumatologic disease tends to have less severe presentation than primary rheumatologic disease and typically resolves with cessation of the offending medication.
- Comorbid medical conditions can convolute the diagnosis of an underlying rheumatologic disorder based on severity of symptoms and organ involvement alone.
- Although renal biopsy is the gold standard of diagnosing both lupus nephritis and renal vasculitis, further research is needed regarding whether clinical judgement should be used in cases when renal biopsy is negative but clinical presentation is consistent with rheumatologic disease.

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