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Rapid Onset Hydralazine-induced Antineutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis Presenting with Hemoptysis and Kidney Failure: Case Report

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Rapid onset hydralazine-induced antineutrophil cytoplasmic antibody (ANCA) associated vasculitis presenting with hemoptysis and kidney failure: case report

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Abstract

Hydralazine-induced vasculitis can be challenging to recognize and diagnose as presenting symptoms vary and can mimic other conditions or diseases, however, swift intervention and treatment is key in halting progression of the disease and providing patients with the best possible outcomes. A 71-year-old African American female presented to the emergency department with weakness, fatigue, anemia, blood-streaked sputum, fever, chills, and severe myalgias. Hydralazine was prescribed to treat resistant hypertension eight months prior to presentation. Hydralazine was discontinued on hospital day (HD) 4. Pertinent laboratory values showed elevated inflammatory markers, positive antinuclear antibody (ANA), negative rheumatoid factor (RF), normal complement levels, and positive anti-histone, anti-proteinase 3, anti-myeloperoxidase, anti-double stranded DNA, and p-ANCA. Renal biopsy confirmed chronic vascular injury, likely related to long standing hypertension, contributing to the development of chronic renal injury and stage 4 kidney disease. The patient was discharged on mycophenolate mofetil (MMF) and atovaquone. The patient was later readmitted with progressive renal failure, and treatment transitioned to cyclophosphamide (CYC) and sodium 2-mercaptoethane sulfonate (MESNA), plasmapheresis, and hemodialysis. This case illustrates the challenging presentation and course that patients with drug-induced vasculitis can face on initial presentation to the hospital and after discharge. The onset to disease in this case was faster than the average time to disease presented in the literature.

Background

Hydralazine acts as a direct vasodilator which decreases systemic resistance and results in the lowering of blood pressure. The medication finds a place in therapy not as a first-line antihypertensive agent but is more commonly used during episodes of hypertensive urgency or emergency and with treatment of resistant hypertension.[1,2] Hydralazine shows benefit in specific patient populations including pregnant patients and when used in addition with a nitrate for African American patients with heart failure and reduced ejection fraction[1,2], although data is unclear how race influences this benefit.[3]

Like any medication, clinicians should be mindful of the unique side effect profile for hydralazine. It is well known to be associated with immune-mediated syndromes. First documented in 1953, hydralazine-induced lupus-like syndrome has since been well documented with occurrence in up to 10% of patients and is more common in Caucasian patients on doses 200 mg daily or greater after 3 months to 3 years of therapy.[4,5] Of note, hydralazine-induced lupus-like syndrome rarely affects the kidneys and shows no ds-DNA antibody involvement.[6] From the 1980's to early 2000's, several case reports documented hydralazine-associated renal vasculitis, including several with pulmonary involvement, which was first termed as pulmonary-renal syndrome secondary to hydralazine use by Yokogawa *et al* in 2009. Their review identified 68 cases of hydralazine-induced vasculitis with all patients positive (100%) for MPO-ANCA when tested.[6]

While hydralazine is a commonly prescribed anti-hypertensive medication causing vasodilation, the presentation of hydralazine-induced vasculitis is rare and covers a broad spectrum of signs and symptoms. [7] Patient presentation varies, and symptoms can overlap with other conditions, slowing diagnosis and treatment.[8,9] ANCA-associated vasculitis (AAV) is an inflammatory autoimmune condition that affects the small blood vessels causing necrosis of capillaries, venules, arterioles, and small arteries. AAV typically involves more than one organ system, although single organ system presentations have been reported.[10-12] Systemic involvement can include a variety of organ systems, including kidneys, lung, skin, mucosa, heart, blood, and joints. [10,13] Onset of symptoms can also be delayed with 4.7 years being the average time duration to disease presentation after starting hydralazine.[8,14] It is noted in previous reports that patients with the earliest interventions tend to have the best outcomes.[10,15] Removal of hydralazine from the patient's formulary with subsequent symptom improvement can be a positive sign toward making the diagnosis, however, not all patients will display improvement and diagnosis relies on serology and kidney biopsy[7] The purpose of this case is to provide an example of an unusually rapid onset of hydralazine-induced ANCA-positive vasculitis presenting with pulmonary and renal dysfunction complicated by existing renal disease.

Case Presentation

A 71-year-old African American female presented to the emergency room with complaints of weakness, fatigue, fevers, chills, myalgias, and bloody sputum. Eight months prior, the patient presented for stroke due to uncontrolled hypertension. Blood pressure at the time of stroke was 229/118; diabetes was moderately controlled with A1C of 7.1%, and baseline creatinine was 1.9-2.0mg/dL with GFR of 29-30 L/min/1.73m^{2}xL. Patient was then treated for resistant hypertension, hyperlipidemia, Type 2 diabetes mellitus, and chronic kidney disease, then discharged on amlodipine, aspirin, atorvastatin, carvedilol, doxazosin, isosorbide mononitrate, losartan, hydrochlorothiazide, and hydralazine 100 mg three times daily. Based on patient self-report and medication fill history, she was determined to be mostly adherent to her regimen. The patient reported never having been treated for hypertension before and no changes to medications were made after discharge. The patient was not aware of any family history of autoimmune conditions.

On presentation to the ED eight months later, the patient's blood pressure was 155/85, pulse 71 bpm, and respiratory rate 22 br/min with 99% saturation on room air. The patient was fatigued and experiencing alternating fevers and chills. On a physical exam, she was noted to be hypovolemic. She had unintentionally lost weight, with BMI decreasing from 44.34 kg/m^2 to 33.7 kg/m^2. WBC count was 5.8 x 10e9/L, hemoglobin 6.2 g/dL, and MCV 75.7 fl L. Hemoglobin A1C was 6.3%. Electrolyte panel showed sodium 133 mmol/L, potassium 4.4 mmol/L, chloride 103 mmol/L, carbon dioxide 22 mmol/L, glucose 129 mg/dL, blood urea nitrogen (BUN) 54 mg/dL, creatinine 2.24mg/dL, and estimated GFR of 25 mL/min/1.73m^{2}xL. Urinalysis showed clear, yellow urine, 30 mg/dL of protein, pH 5.0, specific gravity of 1.013, 6 RBCs/HPF, 3 WBCs/HPF and absence of bacteria, gross blood, leukocytes, or nitrites. Blood microbiology and respiratory cultures showed no growth.

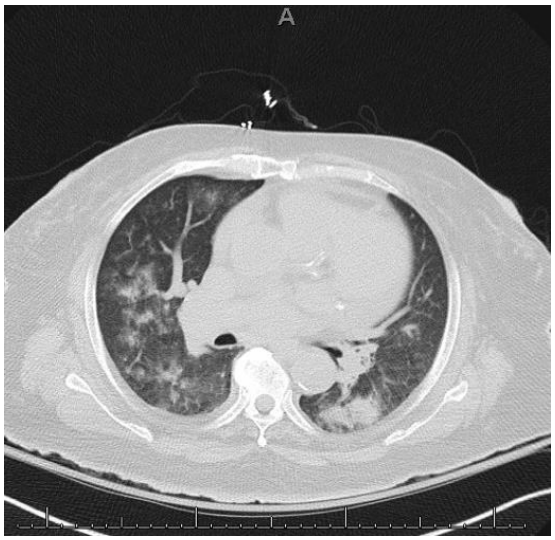

Figure SEQ Figure * ARABIC 2 Day 2 of hospital admission - CT scan of chest shows diffuse multifocal mixed irregular ground-glass and consolidative airspace disease, most prominent at the lung bases with concern for atypical infection

On CT scan, the patient's lungs were shown to have diffuse multifocal areas of ground-glass opacities and consolidative airspace disease, with area of greatest concern at the lung bases (Figure 2). Bronchoscopy and bronchoalveolar lavage (BAL) of the left lower lung was performed which resulted in unremarkable findings. Upper GI endoscopy was performed, also resulting in unremarkable findings. The patient received multiple blood transfusions during her hospital stay due to dangerously low hemoglobin levels.

A kidney biopsy was ordered on hospital day 6. To prepare for light microscopy, sections prepared from the submitted sample were stained with H&E, PAS, Masson's trichrome and Jones silver stains. Microscopic examination showed renal cortex and medulla with 17-19 glomeruli per level section, of which 9-10 glomeruli showed global sclerosis (approx. 52%). Approximately 5 glomeruli per section demonstrated segmental sclerosis/scarring (approx. 27%). A few remaining patent glomeruli showed mesangial expansion and mesangial hypercellularity. Significant endocapillary hypercellularity, necrotizing lesions and crescent formation were not seen. There was acute tubular injury visualized. A few tubules demonstrated luminal casts with degenerated red blood cells. There was variable, mild-to-moderate tubular atrophy and interstitial fibrosis with associated

lymphocytic interstitial inflammation. Arterial vessels showed moderate to severe intimal sclerosis. There was focal hyalinosis. No vasculitis was observed.

On immunofluorescence, examination of the frozen sections prepared from the submitted material showed 1-3 glomeruli of which up to 2 glomeruli showed global sclerosis. The glomeruli showed non-specific, focal and segmental staining for IgM, kappa and lambda light chains. In addition, there was trace granular staining in the glomeruli for C3 and C1q. There was no significant staining in the glomeruli for IgG, IgA, fibrinogen/fibrin, and albumin. Tubular cast stain for IgA, IgM, kappa and lambda light chains. There is focal granular staining in the peritubular capillaries and tubular basement membranes for C1q. There was no significant staining in the interstitium for any of the above immunoreactants tested. Arteries and arterioles demonstrate staining for C3 only.

	Prior Hospital Admission		F/up Appointment
	On prior admission s/p stroke	*2 weeks s/p stroke*	*One month s/p stroke*
	Novemeber 2020	--	--
Renal Function			
Blood urea nitrogen	39 mg/dL	23	27
Glomerular filtration rat	24 mL/min/1.73m^2	29	29
Creatinine	2.02 mg/dL	1.95	1.97
Urinalysis			
Blood	Negative		
Protein	100 mg/dL		
White blood cells	1/HPF		
Red blood cells	1/HPF		
Pulmonary			
Hemoptysis	Negative	Negative	Negative
Labs			
Hgb A1C		7.1%	
Ferritin			

Table 1 Laboratory values and symptoms on prior hospital admissions

Electron microscopy was submitted but did not show glomeruli and examination was not performed.

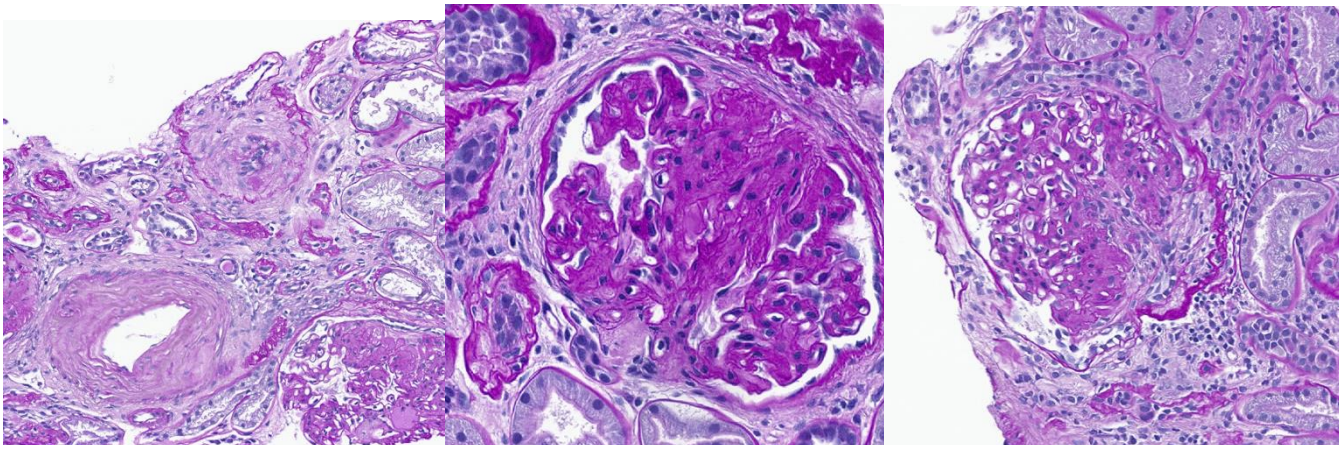

Figure 3 Kidney biopsy findings with PAS stain demonstrating general sclerosis and scarring with some mesangial expansion and hypercellularity. Severe arteriolosclerosis and focal hyalinosis observed, likely the result of uncontrolled hypertension.

Biopsy noted significant chronic vascular injury in the form of moderate to severe arteriosclerosis and focal arteriolar hyalinosis, likely to be related to the patient's hypertension, contributing to the development of chronic renal injury. Focal segmental glomerulosclerosis (FSGS) could be due to a primary condition, however attribution to a secondary condition could not be ruled out.

Differential Diagnosis

- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- ANCA associated vasculitis
- Polymyalgia rheumatica
- Systemic lupus erythematosus (SLE)
- Pulmonary infection (tuberculosis, pneumonia)
- Underlying malignancy
- Anemia of chronic kidney disease

Treatment

On HD 6, cefepime was discontinued, pulse dose methylprednisolone was started, and patient was consented for renal biopsy. While the biopsy was unable to rule out FSGS completely, there was not sufficient activity to confirm the presence of active crescents in the tissue. There was, however, extensive damage to the glomeruli from the patient's long-standing and poorly controlled hypertension and Type 2 diabetes mellitus. Hyalinization and arteriolar thickening were grossly apparent throughout the sample. On HD 6, 1000mg/d IV methylprednisolone was given for 3 days, then the patient was transitioned to 60mg PO prednisone daily. There remained the question about whether to treat with additional immunosuppressive therapies. Given the positive anti-PR3, MPO, and ds-DNA antibodies in a geriatric patient with significant bilateral lung involvement with ground-glass opacities and air space disease, it was felt that the benefit of trying a low dose immunosuppression regimen outweighed the risk of monitoring on just the steroid. Thus, MMF 1000mg once daily, was initiated on HD 13. With the initiation of immunosuppressive therapy, prophylaxis for pneumocystis pneumonia (PJP) was initiated with 1500mg atovaquone, once daily.

Recurrence and subsequent treatment

The patient was discharged from the hospital to her home on HD 20 and then readmitted 4 days later, presenting with Stage III AKI and worsening symptoms due to medication non-compliance and difficulty taking care of herself at home. The patient's kidney function had declined significantly with GFR of 10 and Cr of 4.17 on readmission. In the setting of oliguria and complete renal failure, dialysis was begun. At the same time, the patient developed worsening air space disease and had recurring hemoptysis requiring multiple blood transfusions. CT chest showed diffuse airspace disease, and bronchoscopy confirmed significant diffuse alveolar hemorrhage. Pulse dose steroids were started and MMF was discontinued. The patient was started on cyclophosphamide (CYC) and sodium 2-mercaptoethane sulfonate (MESNA) with plans to continue ongoing infusions in an outpatient setting every 4 weeks. The patient remained in the hospital for 22 days then was discharged home to family care.

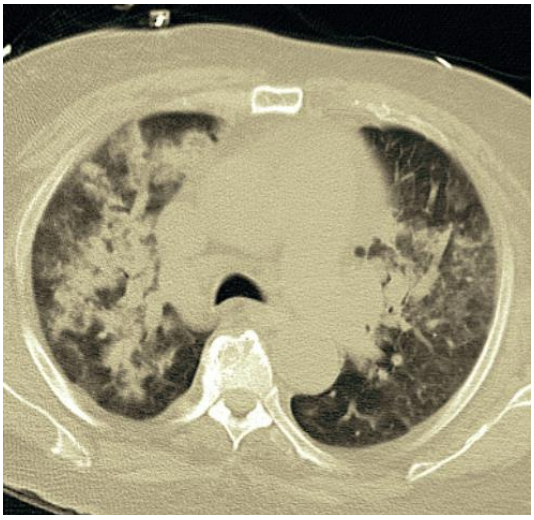

Figure 4 Day 4 of hospital readmission - CT scan of chest shows worsening diffuse multifocal mixed irregular ground-glass and consolidative airspace disease in all lung fields

Discussion

Mechanism of Action

Due to the rarity of AAV with the use of hydralazine, the pathogenesis of the disease is not fully understood. One proposed mechanism that is well accepted hypothesizes that hydralazine accumulates inside the cytoplasmic granules of neutrophils and subsequently binds to myeloperoxidase and induces cytotoxic products and apoptosis.[13] After cell death, the once sequestered antigens are exposed to antigen-presenting cells which leads to anti-neutrophil cytoplasmic antibodies (ANCA) and anti-nuclear antibodies (ANA).[14] Another proposed mechanism suggests antibodies target neutrophil-derived antigens which then complex and attach to the vascular endothelium. Once attached, the neutrophils degranulate MPO and PR3 into the cytoplasm.[16] It is hypothesized that hydralazine interacts with MPO and forms a reactive intermediate that interacts with ANCA, releasing anti-histone antibodies that go on to form neutrophil extracellular traps.[16,17]

Risks

Review of literature indicates hydralazine-induced AAV has a dose-dependent relationship to severity of disease;[13] literature suggests doses vary between 50-300 mg daily and onset of disease is within weeks to years of beginning regimen.[5,6,12]

Several risk factors for developing hydralazine-induced AAV have been identified. Patients who are female sex,[6] thyroid disease,[18] human leukocyte antigen (HLA)-DR4 genotype, and/or who are slow hepatic acetylators are at high risk for developing hydralazine-associated AAV.[12,19]

Diagnosis and treatment challenges

The case presented here is of a rapid onset of vasculitis after starting hydralazine. According to the analysis by Yokogawa et al of 66 case reports documenting hydralazine induced vasculitis, only 5 cases reported a time to onset of 1 year or less after starting hydralazine; the average time to presentation was 4.7 years.[6]

Hydralazine-induced vasculitis poses a challenge for any treating care team, because many of the symptoms of vasculitis overlap with those of infection. This challenge held true for the patient in this case report, as infection could not be totally excluded from the differential, and it was a difficult decision to discontinue antibiotic therapy to instead pursue steroid therapy for immunosuppression. Laboratory results were crucial in determining the likelihood of infectious versus autoimmune disease. Using data from previous case studies and analyses, results indicated a high likelihood of drug-induced pauci-immune glomerulonephritis. Previous studies have demonstrated that high MPO antibody levels,[20] multiple positive autoimmune serologies,[7,21,22] and positive anti-histone antibodies[21] are frequently obtained in these patients. Our patient was pan-positive for anti-histone, PR3, MPO, ds-DNA, and p-ANCA which further guided the treating team's care plan. Ultimately, the decision was made to discontinue antibiotics and begin aggressive immunosuppression, as indicated in literature.

While removal of the drug can lead to reversal of disease in some,[21,23] many patients may need more supportive care and immunosuppressive therapies. Hydralazine-induced AAV often requires aggressive immunosuppression, despite the offending drug having been removed from the patient.[6] Treatment is patient specific and tailored to the severity and extent of the presentation, however, the general treatment plan consists of a) removal of the drug, b) high dose steroids, and depending on disease severity, an c) immunosuppressive agent. Cyclophosphamide has typically been considered first-line treatment; however, rituximab has been shown to be effective.[24] Mycophenolate mofetil has also been shown to be an effective treatment, yet patient tend to have less severe side effects compared to CYC.[8,10,25] When the patient was readmitted with worsening, recurrent disease, MMF was discontinued and a different regiment of CYC and MESNA was started. The patient responded well to the CYC infusions and achieved remission. Prognosis varies based on comorbidities, age, severity of disease, and response to treatment. Future areas of study could include exploring if slow acetylation is a predisposing factor to autoimmune changes due to hydralazine use. Additionally, evaluating the use of hydralazine in certain populations based on racial profile should be evaluated to avoid racial bias in the administration of this drug.

Apparent absence of kidney biopsy finding consistent with typical ANCA vasculitis could perhaps be explained by non-kidney involvement (pulmonary limited) at the time of kidney biopsy. When the patient was readmitted with what appeared to be rapidly progressive glomerulonephritis, it is possible that a repeat biopsy would have had findings consistent with ANCA vasculitis, such a crescentic glomerulonephritis.

Conclusion

After thorough workup and consideration of clinical presentation, lab values, imaging, and kidney biopsy findings, the patient presentation was determined to most likely represent pauci-immune ANCA vasculitis induced by use of hydralazine for the proceeding eight months. Treatment with a combination of steroids and MMF is shown to be an effective primary treatment with the potential for fewer side effects when compared with CYC. Differential diagnosis for patients taking hydralazine who present with declining renal function alone or with pulmonary renal syndrome should include hydralazine-induced vasculitis. Further research into the race-based use of hydralazine for African Americans is also warranted.

Conflicts of Interest Disclosure: Authors report no conflicts of interest in the writing of this manuscript. Authors received no funding.

Keywords

Pauci-immune GN
Hydralazine
Drug-induced vasculitis

Hospital Course

Admitted ~8 months after last hospital admission

Hospital Day	1	2	3	4	6	7	9	10	13	17	20
Renal Function											
Blood urea nitrogen	54	53	50	41	44	47	80	93	112	81	69
Glomerular filtration rate	25	24	25	29	27	27	22	20	24	29	26
Creatinine	2.24	2.26	2.23	1.97	2.08	2.11	2.46	2.69	2.26	1.94	1.9
Urinalysis											
Blood	Negative	Moderate									
Protein	30 mg/dL	100 mg/dL									
White blood cells	3/HPF	40/HPF									
Red blood cells	6/HPF	3/HPF									
Pulmonary											
Hemoptysis	Positive	Positive	Positive	Positive	Positive	Scant	Scant	Negative	Negative	Negative	Negative
Labs											
Hemoglobin	6.8	8.4	7.7	7.9	6.8	8.4	8.1	8.2	8.2	8.4	8.6
Hgb A1C										6.3%	
Ferritin	342ng/mL										
Interventions	1u PRBCs	1uPRBCs	Hydralazine d/c		1uPRBCs cefepime d/c methylpred started	atovaquone prophylaxis started		switched to prednisone	MMF started	pending discharge to SNF	pred tapered, MMF increased SNF denied pt, dc to home

Table 2 Laboratory values, clinical findings, and interventions during hospital course

Renal Function				HD begun	HD	HD	HD	HD
Blood urea nitrogen	72	89		-	-	-	-	-
Glomerular filtration ra	10		9	-	-	-	-	-
Creatinine	4.17	4.7		-	-	-	-	-
Urinalysis								
Blood								
Protein		553mg/L						
White blood cells								
Red blood cells								
Pulmonary								
Hemoptysis	Negative	Scant	Positive	Positive	Negative	Negative	Negative	Negative
Labs								
Hemoglobin	7.0	7.3	7.0	7.9	7.9	7.4	-	6.8
Hgb A1C								
Ferritin								
Interventions								
	patient readmitted, 1u PRBCs		1uPRBCs	HD begun, methylpred started		1uPRBCs	cyclophosphamide w/MESNA started	1uPRBCs, discharged on HD, prednisone taper in OP, patient dc home to care of family
				received 5x plasmapheresis during stay				

Table 3 Laboratory values, clinical symptoms, and interventions on hospital readmission

Test	Titer/unit	Reference range	Result
Anti-histone antibody	7 U	0-1	Positive
Anti-proteinase 3 (PR3) antibody	4.7 U/mL	0-3.5	Positive
Anti-myeloperoxidase (MPO) antibody	76 U/mL	0-9	Positive
Antinuclear antibody (ANA)	1: 1280 (homogeneous pattern)	<1:80	Positive
Anti-double stranded DNA (dsDNA)	15 IU/mL	< = 4.0	Positive
Perinuclear antineutrophil cytoplasmic antibody (p-ANCA)	1:640	<1:20 low	Positive
Erythrocyte Sedimentation Rate (ESR)	116 mm in 1hr	0-20	Positive
C-Reactive Protein (CRP)	21.1 mg/dL	0.0-0.5	Positive
Complement C3 (C3)	94 mg/dL	80-200	Normal
Complement C4 (C4)	25 mg/dL	10-50	Normal
Anti-cyclic citrullinated peptide (CCP) antibody	0.8 unit(s)/mL	< = 2.9	Negative
Rheumatoid factor (RF)	<15 IU/mL	0.-15	Negative
Atypical anti-neutrophilic cytoplasmic antibody	<1:20	<1:20 low	Negative
Anti-Smith antibody (Sm)	<0.2 AI	< = 0.9	Negative
Anti-ribonuclear protein (RNP) antibody index	0.3 AI	< = 0.9	Negative
Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA)	<1:20	<1:20 low	Negative
Anti-SSA antibody index (SSA)	0.3 AI	< = 0.9	Negative
Anti-SSB antibody index (SSB)	<0.2 AI	< = 0.9	Negative
Anti-Jo1 antibody index	<0.2 AI	< = 0.9	Negative
ACE levels	18 U/L	14-82	Negative
Aldolase	8.0 U/L	3.3-10.3	Negative
Anti-glomerular basement membrane (GBM) antibody	5	0-20	Negative

Table 4 Laboratory values resulted during length of hospital stay

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