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Life-Threatening Pancytopenia and Disseminated Intravascular Coagulation Associated With Hydralazine-Induced Lupus and Vasculitis Overlap: A Comprehensive Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 52-year-old
Final Diagnosis: Pancytopenia and DIC associated with hydralazine-induced lupus and vasculitis overlap
Symptoms: Disseminated intravascular coagulation • fever • pancytopenia
Clinical Procedure: Bone marrow biopsy • hemodialysis • intubation • plasma exchange
Specialty: Critical Care Medicine • Hematology • Nephrology
Objective: Unusual clinical course
Background: This report presents a life-threatening case of pancytopenia and disseminated intravascular coagulation (DIC) related to hydralazine-associated, drug-induced lupus and drug-induced anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (DIL/DIV) overlap syndrome. Diagnostic and therapeutic challenges are discussed.
Case Report: A 52-year-old man presented with severe pancytopenia, fever, and possible pneumonia. He developed altered mental status, severe DIC with gastrointestinal bleeds requiring large amount of blood product transfusions, acute respiratory failure requiring intubation, acute kidney injury needing hemodialysis, acute liver injury, possible acute pancreatitis, and hypotension. Extensive investigations revealed no source of infection. Further work-up was consistent with hydralazine-induced DIL/DIV overlap spectrum. Hydralazine was stopped. He was treated with steroids daily and intravenous cyclophosphamide every 2 weeks (7 doses). However, pancytopenia did not improve. Therefore, on the seventh day after the second cyclophosphamide dose, a repeat bone marrow biopsy was performed to guide further therapy. He later recovered, and hemodialysis was discontinued. A total of 104 units of blood products were transfused. After discharge, steroids were tapered off and mycophenolate mofetil was given for 2 years. In August 2026 (6 years after initial presentation), he was doing well, with normal complete blood count, stable renal function, and normal urinalysis. Array genotyping revealed NAT2 diplotype *5.002/*6.002, indicating slow acetylation (poor metabolizer status).
Conclusions: This case supports, rather than proves, hydralazine-induced DIL/DIV overlap as the leading explanation for life-threatening pancytopenia with overt DIC. It highlights diagnostic and therapeutic challenges and eventual recovery after hydralazine withdrawal and immunosuppressive treatment. Salient features include the detailed autoimmune workup, severe presentation, coexistence of pancytopenia and overt DIC, and extended follow-up within a rare clinical context.
Keywords: Disseminated Intravascular Coagulation • Hydralazine • Lupus Erythematosus, Systemic • Pancytopenia • Vasculitis
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Introduction

Attempts have been made to classify hydralazine-induced systemic rheumatic syndromes as either drug-induced lupus (DIL) or drug-induced anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (DIV) [1]. However, an overlap between drug-induced lupus and drug-induced ANCA-associated vasculitis (DIL/DIV) has also been reported [1]. Here, we present a life-threatening case of pancytopenia and disseminated intravascular coagulation (DIC) associated with hydralazine-induced DIL/DIV overlap, highlighting the severe manifestations that can occur within this spectrum. The diagnostic challenges associated with drug-induced autoimmune syndromes in our patient originated from (1) the lack of similar reports during the 40 years preceding this case; (2) the anchoring bias due to incorrect medication history; (3) the multiple medicines the patient took, both long-term and in the recent past; and (4) an initially narrow differential diagnosis. The therapeutic challenge was reflected in the unresponsiveness to the initial treatment, which was likely due to the severe organ systemic injury resulting from the delayed diagnosis. A repeat bone marrow biopsy was done to guide further therapy. The other challenge was treating with immunosuppressants in the setting of severe pancytopenia and the COVID-19 pandemic. To our knowledge, this is one of the few reported cases with detailed autoimmune characterization. Other salient features of the case are the severity of presentation, coexistence of pancytopenia with overt DIC, and extended follow-up within a rare clinical context. The potential of pharmacogenetics in antihypertensive management is also discussed.

Case Report

On August 17, 2020, a 52-year-old Hispanic man was evaluated by a hematologist as an outpatient for pancytopenia and subsequently referred to the emergency department on August 19, 2020, for fever and worsening pancytopenia. His complete blood count (CBC) results were normal in June 2020 but began to decline in July 2020 (Figure 1). In the emergency department, he reported subjective fever for the past 15 days, fatigue, dizziness, rectal bleed off-and-on for 1 month, and weight loss of 13.6 kg in the past 6 months.

He had a history of primary hypertension since April 2018, when antihypertensives, including hydralazine, were started. In May 2018, he was seen by a nephrologist for chronic kidney disease stage 3A with nonnephrotic-range proteinuria, which was likely due to poorly controlled hypertension. His urinalysis showed no red blood cells (RBCs) but 2+ protein, with a urine protein/creatinine ratio of 813 mg/g. Serologies for hepatitis B and C, HIV, and ANA were all negative, with normal C3 and C4. ANCA was negative, as were anti-proteinase 3 antibody

(anti-PR3) and anti-myeloperoxidase antibody (anti-MPO) index (both < 1.0). Lisinopril was added, with subsequent good blood pressure control. His proteinuria improved and was completely resolved by October 2018. However, proteinuria reappeared, with a urine protein/creatinine ratio of 194 mg/g in January 2020, which worsened to 539 mg/g in July 2020. Nonetheless, his renal function was stable with serum creatinine (Cr) levels fluctuating between 1.7 and 2.0 mg/dL. The medication history regarding gout therapies was initially inaccurate because of a language barrier, the patient's limited ability to provide a reliable history while acutely ill, and restricted visitation policies during the COVID-19 pandemic. An initial medication history indicated that he had "always taken febuxostat that he bought from Mexico until July 2020, when his primary care physician switched him to probenecid." However, after discharge, a more accurate history was obtained from his wife and primary care physician. He had been taking febuxostat until it was switched to probenecid in March 2020. Because of sub-optimal efficacy, he resumed febuxostat in late July 2020 using leftover medication from a previous prescription. He had never obtained or taken any medications from Mexico. He also had chronic anemia attributed to chronic kidney disease and iron deficiency, and gastroesophageal reflux disease. He had been treated with amoxicillin and clarithromycin for *H. pylori* infection from August 5 through August 14, 2020. All home medications are shown in Figure 1.

Physical examination revealed a temperature of 38.1 °C, pulse of 88 beats/min, respiration of 16 breaths/min, blood pressure of 109/68 mm Hg, and oxygen saturation of 95% on room air. He was in moderate distress. Respirations were non-labored with mild tachypnea, and auscultation revealed basal crackles in the lungs bilaterally. There was no peripheral edema. CBC showed white blood cell count (WBC) of $0.8 \times 10^3/\mu\text{L}$, hemoglobin (Hb) level of 11.8 g/dL, hematocrit level of 34.8, mean corpuscular volume of 83.7 fL, mean corpuscular hemoglobin of 28.4 pg/cell, mean corpuscular hemoglobin concentration of 33.9 g/dL, and platelet count (Plt) of $85 \times 10^3/\mu\text{L}$. Automated and manual differential counts showed segmented neutrophils of 56%, lymphocytes of 32%, monocytes of 10%, basophils of 1%, and myelocytes of 1%, with slight ovalocytosis and polychromasia. There were no blasts on peripheral blood smear. Other blood tests revealed blood urea nitrogen (BUN) of 45 mg/dL, Cr of 2.1 mg/dL, lipase of 276 U/L (reference range, 22-51 U/L), albumin of 3.2 g/dL, alanine aminotransferase (ALT) of 40 IU/L (reference range, 4-43 IU/L), aspartate aminotransferase (AST) of 80 U/L (reference range, 9-35 U/L), total bilirubin of 0.5 mg/dL, direct bilirubin of 0.2 mg/dL, lactate dehydrogenase (LDH) of 346 U/L (reference range, 88-178 U/L), prothrombin time (PT) of 12.5 seconds (reference range, 11-13.7 seconds), and international normalized ratio (INR) of 1.0 (reference range, 0.8-1.2). Chest X-ray showed retrocardiac opacities and questionable right midlung opacities concerning for

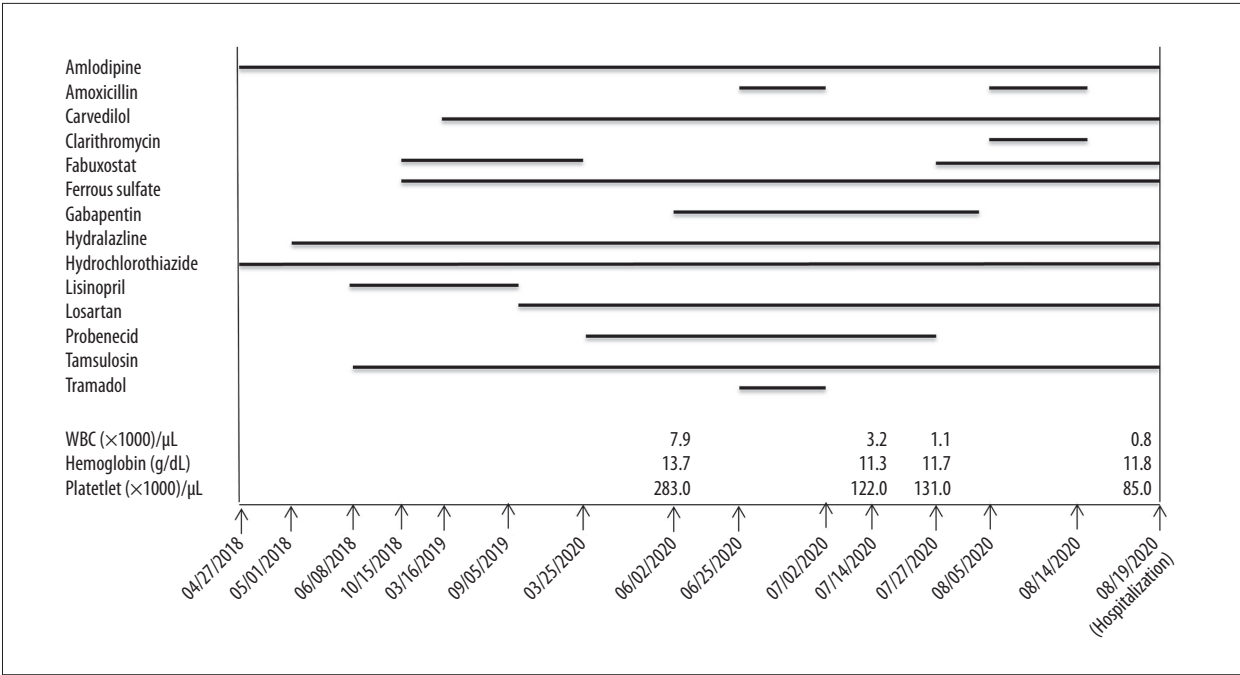


Figure 1. Medication history and complete blood count up to the day of hospital admission. (1) In the upper section of the figure, horizontal black bar denotes the period when the patient was on a specific drug. The lower section of the figure shows CBC values over time before hospitalization; (2) The X-axis (the dates) is not to scale; (3) Within a few months before the hospitalization, there were multiple drugs taken for a short period, including amoxicillin, clarithromycin, fabuxostat, gabapentin, probenecid, and tramadol.

pneumonia. Non-contrast-enhanced computed tomography (CT) of the abdomen and pelvis revealed minor stranding of the pancreaticoduodenal groove, which was likely due to acute pancreatitis, a normal appearing spleen, and moderate atelectasis of the lower lung lobes bilaterally.

Tests for pancytopenia and infections were performed. A single dose of intravenous (IV) cefepime was given in the emergency department. The patient was then admitted to the ward under hospitalists' service for febrile neutropenia and possible pneumonia. The hematologist considered aplastic anemia, potentially induced by probenecid, to be the cause of the pancytopenia. This suspicion was due to the incorrect history as mentioned above. Intravenous vancomycin and ceftriaxone were started. In the next few days, he continued to feel unwell with fatigue and fever. On hospital day 5, vancomycin was stopped for worsening renal function, while ceftriaxone was continued. However, the highest plasma vancomycin level was only 17 μg/mL. Renal function worsened, with Cr rising to 3.0 mg/dL. Intravenous fluid was started for possible hypovolemia as a cause of acute kidney injury (AKI). The prolonged course of the complicated hospitalization is shown in **Figure 2**.

By day 6, an infectious disease specialist was consulted for persistent daily fever, with a temperature of 38.9 °C and absolute neutrophil count declining from 448/μL initially to 150/

μL. The antibiotic (ceftriaxone) was changed to cefepime IV for neutropenic fever. Probenecid, gabapentin, and tramadol were discontinued as a possible cause of pancytopenia. The source of fever was unclear, and more tests were performed. Vitamin B12 and folate levels were normal. The direct Coombs test was positive for IgG but negative for C3b and C3d, suggesting warm autoimmune hemolytic anemia. The cold agglutinin screen was negative. Serum protein electrophoresis showed no paraprotein, and the serum free light chain K/L ratio was normal at 0.84. Serum IgA was 434 mg/dL (reference range, 68-378), with IgG 1869 mg/dL (reference range, 694-1618) and IgM 1237 mg/dL (reference range, 60-263). LDH was elevated, but haptoglobin remained within the reference range. ADAMTS13 activity came back normal at 68%, which ruled out thrombotic thrombocytopenic purpura. Blood test results showed no flow cytometric evidence of paroxysmal nocturnal hemoglobinuria. Bone marrow aspiration and biopsy revealed normocellular marrow at 40%, with adequate trilineage precursor cells and without evidence of malignancies. The presence of immature forms on the peripheral blood smear suggested active bone marrow compensation. Nevertheless, neutropenia worsened, prompting initiation of subcutaneous tbo-filgrastim on day 7. The cause of the pancytopenia remained unclear.

The workup for infections returned negative, with tests obtained at various times from day 1 through day 37. Specifically,

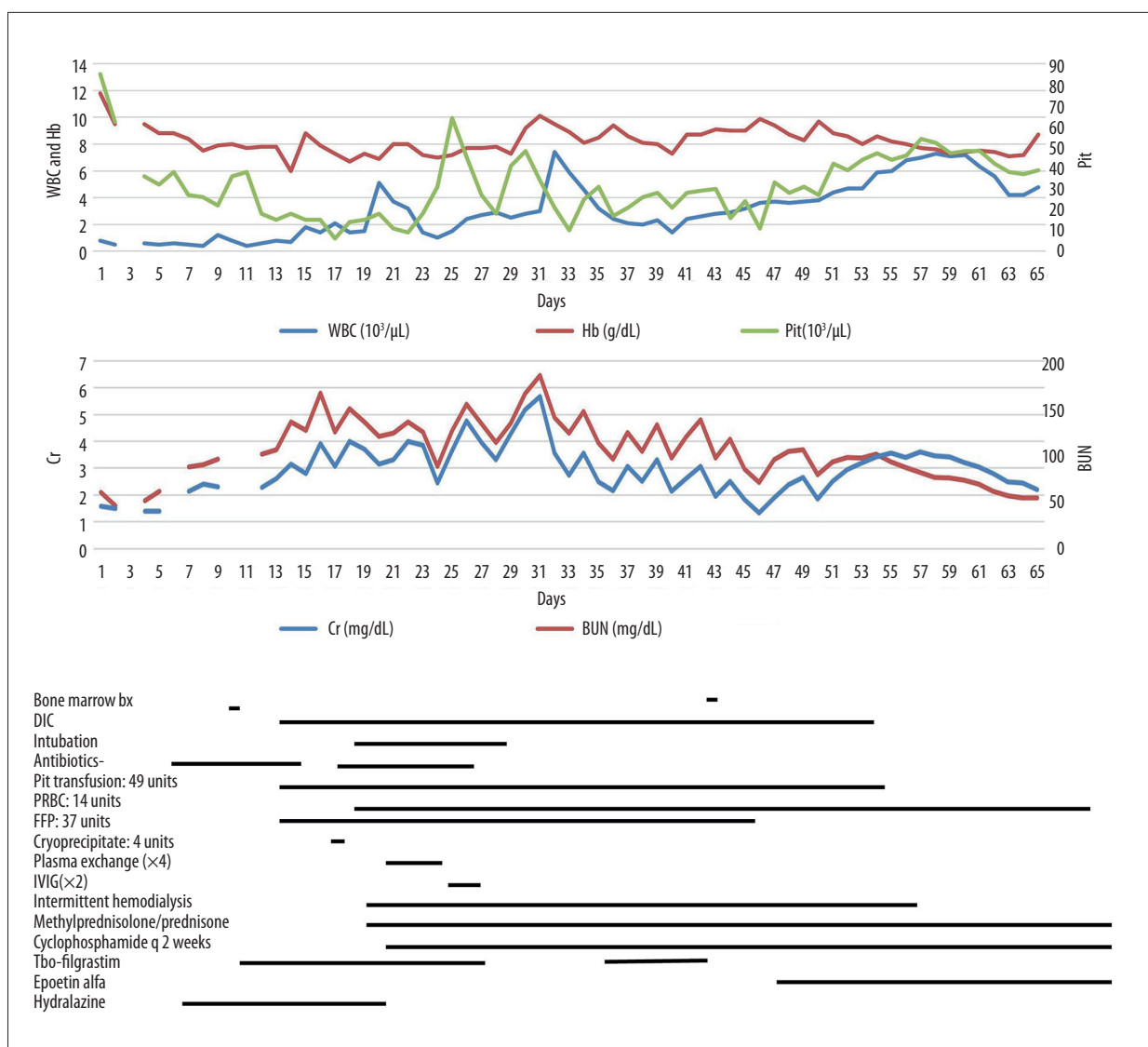


Figure 2. Clinical course during hospitalization. (1) The top section shows CBC values (WBC, Hb, and Plt) over time during hospitalization. (2) The middle section shows renal function (BUN and Cr) over time during hospitalization. (3) In the bottom section, the horizontal black bar denotes the period/date(s) when the patient was on a treatment or received intervention. Abbreviations: Bx, biopsy; BUN, blood urea nitrogen; Cr, creatinine; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; Hb, hemoglobin; IV, intravenous; IVIG, intravenous immunoglobulin; Plt, platelet count; PRBC, packed red blood cells; WBC, white blood cell count.

blood cultures (initial and repeat), urine culture, respiratory pathogen panel polymerase chain reaction with COVID-19 testing of a nasopharyngeal swab (initial and repeated twice), tracheal aspirate culture, urinary pneumococcal and Legionella antigen tests, acute hepatitis panel, rapid HIV test, syphilis test, and Coccidioides antibodies (IgM and IgG) were all negative. Of note, COVID-19 nucleic acid testing of a nasal swab was repeatedly negative (on days 6, 10, and 37). *Mycoplasma pneumoniae* IgM was within the reference range, with elevated IgG. Cytomegalovirus IgM was within the reference range, with elevated IgG, while Epstein-Barr virus IgG was elevated.

The QuantiFERON-TB Gold Plus test was indeterminate, but the PPD skin test was negative. Acid-fast bacilli smear and culture for induced sputum and tracheal aspirate, respectively, were obtained and later all came back negative.

On day 9, his mental status had worsened, and he had small amount of rectal bleeding. The DIC panel revealed a thrombin time of 19.8 seconds (reference range, 12.4-17.4 seconds), PT of 14.3 seconds (reference range, 11-13.7 seconds), INR of 1.2 (reference range, 0.8-1.2), aPTT of 45.1 seconds (reference range, 23.6-35.8 seconds), fibrinogen level of 141 mg/dL (reference

Table 1. Disseminated intravascular coagulation (DIC) panel over time*.

Laboratory value	Reference range	Day 1	Day 9	Day 10	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 22
Platelet	150-400 × 10 ³ /μL	89	22	36	18		18	15	15	6	9
Protime (PT)	11-13.7 s	12.5	14.3	14.7	16.1		19.2	19.1	15.4	13	13.4
INR	0.8-1.2	1.0	1.2	1.2	1.3		1.5	1.5	1.2	1.1	1.1
aPTT	23.6-35.8 s	44.6	45.1	43	39.8		39.5	49.3	42.5	33.3	
TT	12.4-17.4 s		19.8	20.2			20	18.8	21.8		
Fibrinogen	200-400 mg/dL		141	155	138	131	202	208	172	116	125
D-Dimer	0-243 ng/mLDDU		10 385	10 370	7141		6950	15 935	8343		
Schistocytes			Rare	Rare	Rare		Rare	Rare	Rare		
ISTH DIC score			5	5	5		6	6	5		
Fever, yes/no		Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Temperature max (°C)		38.1	37.7	37.9	38.6	38.1	39.4	37.1			
Antibiotics**		Yes	Yes	stopped	No	Yes	Yes	Yes	Yes	Yes	No
Steroids**							Yes	Yes	Yes	Yes	Yes
Hydralazine		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Stopped		

Note: (1) * The laboratory values might be affected by transfusion of platelets and fresh frozen plasma, which occurred daily for most of the days shown in the table. (2) ** See text for the details of antibiotics and steroids. (3) Example of ISTH DIC score calculation which was 6 (≥ 5) on day 14 indicating overt DIC: 2 (platelet) + 3 (D-dimer) + 1 (PT prolongation) + 0 (fibrinogen) = 6. (4) DIC parameters all normalized by day 49. (5) The last day of receiving transfusion of fresh frozen plasma, single donor platelets, and packed red blood cells was day 41, day 50, and day 64, respectively. Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; DDU, D-dimer units; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time; TT, thrombin time.

range, 200-400 mg/dL), D-dimer level of 10 358 DDU/mL (reference range, 0-243 DDU/mL), and rare schistocytes. The trend of the DIC panel with an International Society on Thrombosis and Haemostasis (ISTH) DIC score of 5 (and 6) was consistent with overt DIC (Table 1). Two units of fresh frozen plasma and 2 units of single donor platelets were immediately transfused. For a prolonged period, he continued to require transfusion (almost on a daily basis) of blood products for severe pancytopenia and various indications, including coffee ground aspirates from the nasogastric tube and bleeding from the lips and gums. A total of 49 units of single donor platelets, 37 units of fresh frozen plasma, 14 units of packed red blood cells, and 4 units of cryoprecipitate were transfused (Figure 2). Despite repeated transfusions, WBC reached a nadir of 0.4 × 10³/μL (day 8 and day 11), Hb of 5.8 g/dL (day 14), and Plt of 6 × 10³/μL (day 17). DIC parameters finally all normalized by day 49.

On day 10, his mental status worsened, and he could not answer questions. His temperature was 37.9°C. Cefepime was discontinued for there was no evidence of infection per infectious disease specialist recommendation.

On day 11, he remained obtunded and febrile, with a temperature of 38.5°C. Chest X-ray showed improvement of the previously noted subtle bilateral opacities. Brain magnetic resonance imaging showed no acute abnormalities. The altered mental status was considered secondary to a toxic state or medications. Ammonia was only mildly elevated at 66 μmol/L (reference range, 11-35 μmol/L). Lumbar puncture was considered but not pursued, due to profound thrombocytopenia and coagulopathy. In the next few days, his mental status had no improvement. With IV fluid given, his Cr was stabilized but without improvement.

On day 13, a nephrology consult was involved for AKI, with Cr rising to 3.53 mg/dL. He developed oliguria, and a Foley catheter was placed. Examination revealed a normal blood pressure, with respiration of 21 breaths/min while on 3 L/min oxygen via nasal cannula. He was obtunded and could not answer any questions. Wheezing and bibasilar crackles were present on auscultation. There was no peripheral edema. Serum creatine kinase was within the reference range. Urinalysis, performed 4 times from day 1 through day 13, showed protein

of 30 to 100 mg/dL, no blood to small amounts of blood, 1 to 5 RBCs/high-power field (HPF), 1 to 2 WBCs/HPF, and 0 to 1 hyaline casts/HPF, with no dysmorphic RBCs or RBC casts. The AKI was considered secondary to acute tubular necrosis due to infection (pneumonia), pancreatitis, and DIC, while glomerulonephritis could not be ruled out. However, the persistent pancytopenia was very concerning. Differential diagnosis was immediately broadened to cover autoimmune diseases, including systemic lupus erythematosus (SLE) and vasculitis, with corresponding tests obtained (Table 2). Due to persistent fever after the discontinuation of antibiotics, the infectious disease specialist was reconsulted and considered it unlikely there was an infectious process causing the patient's fever. The workup for fever was again negative, including blood culture and tracheal aspirate culture.

A few hours later, the patient developed respiratory distress and tachypnea with respiration of 36 to 40 breaths/min. Arterial blood gas results revealed metabolic acidosis with respiratory compensation. Chest X-ray showed vascular congestion and lower and mid left lung opacities. One dose of furosemide IV was given. He was intubated and moved to the ICU under intensivists' care. Broad spectrum antibiotics IV (ampicillin, cefepime, and vancomycin) were started for possible pneumonia and sepsis. The patient had bleeding from the mouth, for which transfusion of fresh frozen plasma and single donor platelets were given. The hematologist planned to start eculizumab for possible atypical hemolytic uremic syndrome, but it was held for a possible need of lumbar puncture and the concern about possible tuberculosis. However, atypical hemolytic uremic syndrome could not explain pancytopenia. Nonetheless, meningococcal vaccine was given for preparation of eculizumab administration. Treatment with rituximab was also considered; however, the clinical course later made eculizumab and rituximab unnecessary.

On day 14, he had fever with a temperature of 39.4 °C. LDH was 905 units/L (which was the highest during the hospitalization) and slowly decreased to 268 units/L by day 26. CT of the chest showed partial consolidation of the lower lobes bilaterally with air bronchograms, which might represent pneumonia. Repeat CT of the abdomen and pelvis showed no new findings. CT of the head showed no acute abnormalities. A temporary hemodialysis catheter was placed, and intermittent hemodialysis was started for uremia, metabolic acidosis, and fluid overload. Methylprednisolone 60 mg IV every 8 hours was started for concern of autoimmune process.

On day 15, fever resolved, with a temperature of 37.1 °C, and did not recur thereafter.

On day 16, autoimmune test results showed positive ANA (homogenous pattern with titer 1: 1280), reduced complements

(C3, C4), and positive P-ANCA (> 1: 640) (Table 2). At this point, DIL-DIV overlap syndrome related to hydralazine was considered as the initial cause of his pancytopenia and DIC. The cause of AKI was still considered acute tubular necrosis, but necrotizing crescentic glomerulonephritis could not be confidently ruled out. Renal biopsy could not be done, due to his being critically ill and the bleeding risk. Hydralazine was immediately discontinued. Methylprednisolone was raised to 1000 mg IV once daily for 3 days, followed by prednisone 1 mg/kg up to 80 mg by mouth once daily. Cyclophosphamide 500 mg IV every 2 weeks for 6 doses was planned and initiated (eventually, 7 doses were given). Prophylaxis for opportunistic infections was also started. From days 16 to 18, he was on norepinephrine IV for hypotension, but this was given mainly for blood pressure support during and after hemodialysis. Anti-PR3 and anti-MPO antibodies were ordered but were not done, due to an incorrect ANCA panel chosen in the ordering process. Tests were correctly done later with negative anti-PR3 and positive anti-MPO antibodies (Table 2). Tests for anti-histone antibody and lupus anticoagulants were also done and later reported as positive.

Despite normal ADAMTS13 activity, which ruled out thrombotic thrombocytopenic purpura, plasma exchange was initiated by the hematologist, who was very concerned about the persistent pancytopenia requiring continuing large-amount transfusion of blood products and considered Evans syndrome (autoimmune hemolytic anemia and immune thrombocytopenic purpura) in the differential diagnosis. Plasma exchange was stopped after a total of 4 treatments over a period of 5 days, without improvement of pancytopenia.

On day 20, the 3 antibiotics were stopped after a 7-day course was completed. On day 22, prednisone 80 mg by mouth once daily was upgraded to methylprednisolone 250 mg (a few days later, was reduced to 125 mg) IV once daily for possible autoimmune hemolytic anemia and immune thrombocytopenic purpura, which were considered due to lupus. Intravenous immunoglobulin 500 mg/kg was given daily for 2 days without improvement. On day 23, the patient self-extubated. He stayed in the ICU for a few more days due to altered mental status, which slowly improved, and he was moved back to the ward on day 26.

On day 31, the patient continued to have slight bloody oozing from the mouth. The second dose of cyclophosphamide IV was given. Overall, he was improving, but his renal function was not better. The Foley catheter was removed on day 33.

On day 38, due to persistent pancytopenia, a repeat bone marrow aspiration and biopsy was done to see if bone marrow was appropriately suppressed with immunosuppressants or if more aggressive immunosuppression would be needed. It showed

Table 2. Autoimmune test results over time.

Date		08/31 /2020	09/03 /2020	09/12 /2020	09/24 /2020	10/04 /2020	10/22 /2020	04/20 /2021	06/21/ /2021	06/08 /2023	April 2025
Hospital day		13	16	25	37	47	65				
Reference range											
ANA	< 1: 40	1: 1280			1: 1280			1: 320	< 1: 40		
C3	79-152 mg/dL		36	68	75	103	123	136			
C4	18-55 mg/dL		11	19	27	35	39	37			
Anti-dsDNA		Neg*			Neg				Neg		
Sm/RNP		Neg			Neg				Neg		
Scl-70					Neg				Neg		
SSA IgG					Neg				Neg		
SSB IgG					Neg				Neg		
Anti-Smith IgG					Neg				Neg		
P-ANCA	< 1: 20	> 1: 640			> 1: 640						
P-ANCA, atypical	< 1: 20						1: 640				
Anti-MPO	< 1.0 AI				218.5		> 8.0	2.4	2.2	1.2	1.0
Anti-PR3 index	< 1.0 AI				< 1.0		< 1.0				
Anti-histone	< 1.0 unit		13.7		5.7			1.7	1.6	< 1.0	
Anti-GBM ab		Neg									
RF		Neg			Neg				Neg		
ASO		Neg									
Cryoglobulin		Neg									
Cryofibrinogen		Neg									
Lupus anticoagulant	Not detected	Detected									
β-2- glycoprotein I IgA		Neg									
β-2- glycoprotein I IgG		Neg									
β-2- glycoprotein I IgM	< 20 SMU	109									
Cardiolipin ab IgA		Neg									
Cardiolipin ab IgG	< 14 GPL	18									
Cardiolipin ab IgM	< 12 MPL	46									

* Neg denotes values within reference range. Abbreviations: ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-GBM, anti-glomerular basement membrane antibody; anti-MPO, anti-myeloperoxidase antibody; anti-PR3, anti-proteinase 3 antibody; ASO, antistreptolysin O; C3, complement component 3; C4, complement component 4; IgA, immunoglobulin A; IgG, immunoglobulin G; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; RF, rheumatoid factor; RNP, ribonucleoprotein; Scl-70, anti-topoisomerase I antibody; Sm, Smith antigen; SSA, Sjögren syndrome-related antigen A; SSB, Sjögren syndrome-related antigen B; AI, antibody index; SMU, standardized MMP-3 units; GPL, IgG phospholipid units; MPL, IgM phospholipid units.

hypocellular marrow (10%) with decreased trilineage hematopoiesis. This demonstrated cellularity was suppressed likely because of cyclophosphamide. The extended fluorescence in situ hybridization panel showed no evidence of myelodysplastic syndrome. Therefore, the decision was made to continue the current treatment regimen.

Afterward, the patient's mental status, CBC, and renal function improved slowly, and his bleeding eventually stopped. Subcutaneous epoetin alfa was started for anemia on day 42. The third (day 45) and fourth (day 59) doses of cyclophosphamide were given as scheduled. Day 49 was the last day he received hemodialysis. Renal biopsy was planned again but was not done, due to the bleeding risk and the resolution of AKI. On day 63, methylprednisolone 125 mg IV once daily was changed to prednisone 40 mg by mouth once daily.

On day 65, the temporary hemodialysis catheter was removed. His CBC improved and remained stable, with WBC of $4.8 \times 10^3/\mu\text{L}$, Hb of 8.7 g/dL, and Plt of $39 \times 10^3/\mu\text{L}$. His renal function returned to his baseline, with BUN of 63 mg/dL and Cr of 1.9 mg/dL (**Figure 2**). He was discharged with stable vital signs. Both the anti-MPO and anti-histone antibodies declined but were still elevated (**Table 2**).

In addition, he developed acute liver injury, with a peak ALT of 163 IU/L, AST of 701 U/L, and total bilirubin of 3.6 mg/dL between days 16 and 18, which essentially normalized by day 34. Lipase was elevated at 276 U/L (reference range, 22-51 U/L) on day 1 and gradually decreased to 33 U/L by day 34. Both acute liver injury and pancreatitis were considered due to DIL-DIV overlap syndrome.

After discharge, the patient's hematologist referred him to a rheumatologist for DIL. The rheumatologist elicited a history of pain and swelling of bilateral hands, knees, and shoulders for the past 2 years. This was consistent with the patient's history of taking acetaminophen starting in October 2018. However, he now stated he rarely needed to take acetaminophen before the hospitalization. The pain started only after the hospitalization. The rheumatologist started him on subcutaneous belimumab 200 mg weekly, which he intermittently received due to insurance coverage approval and shipment issues during the COVID-19 pandemic. From May 2021 to May 2023, he received a total of 11 months' worth of weekly belimumab. He reported improvement of the symptoms with belimumab.

Prednisone was tapered off by January 2022. After the course of cyclophosphamide was completed, mycophenolate 1000 mg by mouth twice daily was started and continued until January 2023. His anti-MPO and anti-histone antibodies improved and finally normalized (**Table 2**). Urinalysis showed trace to 1+ protein up to November 2021 and then was completely normal

up to March 2026. His urine protein/creatinine ratio was 123 to 209 mg/g up to November 2022, and the most recent urine protein/creatinine was 68 mg/g (normal) in March 2026. His renal function was stable with Cr 1.96 mg/dL in July 2026. His CBC has remained normalized since February 2021, except for mild anemia, with the most recent Hb of 13.7 g/dL (normal) in December 2025. He discontinued allopurinol in February 2025 due to the absence of gout attacks. At his last office visit, in August 2026, he was doing well without requiring any pain medications. To investigate the relationship between acetylator variants and adverse effects of hydralazine, array genotyping was performed, which revealed N-acetyltransferase 2 (NAT2) diplotype *5.002/*6.002, indicating that he was a slow acetylator.

Discussion

This patient presented with fever, pancytopenia, and DIC requiring a large amount of transfusion of blood products repeatedly, gastrointestinal bleeds, acute respiratory failure, AKI, and hypotension. Thrombotic thrombocytopenic purpura was initially suspected but was excluded by normal ADAMTS13 activity. Pancytopenia and normal haptoglobin levels are also not characteristic features of thrombotic thrombocytopenic purpura. Similarly, atypical hemolytic uremic syndrome could not explain the pancytopenia. The original focus was on aplastic anemia, which was thought to be caused by probenecid because of the incorrect medication history. When evaluating a patient with a complex condition who has already undergone an extensive evaluation initially, there is a risk of anchoring bias. Therefore, when the nephrology consult was involved, we took a step back and reassessed all the details of the case. The differential diagnosis for pancytopenia is broad, and it can include the following categories: (1) aplastic anemia; (2) myelodysplastic syndrome and hematologic malignancies; (3) myelophthisis; (4) nutritional disorders, such as vitamin B12 and folate deficiency; (5) medication and toxin exposure; (6) peripheral destruction or sequestration of blood cells; and (7) systemic diseases, such as autoimmune disorder or chronic infection [2]. The first 4 categories were ruled out by bone marrow biopsy and blood tests. His multiple medications made the differential diagnosis very complicated. A case of ANCA-positive glomerulonephritis was associated with febuxostat in a patient who had been on the drug for 5 months, but that patient had no anemia or pancytopenia [3]. In our patient, febuxostat was restarted after several months of discontinuation, when pancytopenia was well established (**Figure 1**). Similarly, amoxicillin and clarithromycin were started after pancytopenia was found. All other medicines (except hydralazine) he took before hospitalization (**Figure 1**) were reported to be associated with cutaneous vasculitis (leukocytoclastic vasculitis) but not systemic vasculitis or ANCA positivity. Ferrous sulfate

and probenecid can cause bone marrow suppression, but our patient had no marrow suppression, based on bone marrow biopsy done at more than 1 month after pancytopenia was found. Additionally, although probenecid was stopped around the time pancytopenia was found, his condition worsened the following month. Therefore, all of these medicines, except hydralazine, were less likely the culprits. Illicit drugs can contain adulterants that cause cytopenias (eg, levamisole in cocaine), but he had no history of illicit drug use and he did not drink alcohol. The normal bone marrow biopsy findings and the presence of immature forms on the peripheral blood smear suggested active bone marrow compensation. He had no liver disease and his spleen was not enlarged. Immune thrombocytopenic purpura and autoimmune neutropenia can cause isolated low platelet and neutrophil counts, respectively, but neither of these disorders would explain a low count in all 3 cell lines. He had no history of chronic infection, prompting consideration of autoimmune disorders.

The workup for autoimmune diseases revealed a lupus and vasculitis overlap syndrome, which was most likely the cause of pancytopenia and was most likely due to hydralazine [1,4,5]. The presence of anti-histone antibody supported drug-induced autoimmune disease. His course was complicated by severe DIC, AKI, acute liver injury, possible pneumonia, hypotension, and acute respiratory failure. His AKI was likely due to acute tubular necrosis in the setting of neutropenic fever, possible pneumonia, pancreatitis, DIC, and hypotension. Necrotizing crescentic glomerulonephritis caused by MPO-specific ANCA could not be completely ruled out but was considered less likely because repeated urinalyses showed no significant number of RBCs, dysmorphic RBCs, or RBC casts. Unfortunately, because of bleeding risk, renal biopsy was not done. Without alveolar hemorrhage, his acute respiratory failure was likely due to fluid overload and/or pneumonia. Of note, the attribution of DIC and multi-organ injury (including acute liver injury and acute pancreatitis) to DIL-DIV in our patient is based on converging clinical evidence rather than definitive proof. Therefore, the causation remained unconfirmed. Nonetheless, clinicians using hydralazine and other medicines such as procainamide and propylthiouracil should be aware of the potential for the development of DIL-DIV.

Idiopathic SLE and ANCA-associated vasculitis (SLE/AAV) overlap syndrome is rare [6]. DIL/DIV overlap syndrome has also been reported [1]. While classic hydralazine-induced DIL typically presents with milder constitutional symptoms, such as arthralgia, hydralazine-induced DIV often manifests with severe multi-organ involvement, including crescentic glomerulonephritis, alveolar hemorrhage, and systemic vasculitis [1,4,5]. Our patient had elements of both DIL and DIV, as manifested by high ANA and ANCA titers as well as the presence of anti-histone and anti-MPO antibodies [1,7]. Although there was

no evidence of alveolar hemorrhage or crescentic glomerulonephritis, the severe pancytopenia, which persisted long after normalization of complements but which slowly improved with the gradual decline of anti-MPO, in the setting of aggressive immunosuppressive treatment, supported that this case best fit into a DIL/DIV spectrum. The main differential diagnosis of DIL/DIV is idiopathic SLE/AAV. There is a significant overlap in clinical features and autoantibodies in both diseases; therefore, long-term follow-up is mandatory. Compared with other cases of hydralazine-induced pancytopenia, our case is characterized by a long-term follow-up (Table 3) [4,5,8-12]. With treatment, the patient recovered well (including from AKI) and had no recurrence of lupus/vasculitis over 6 years since his initial presentation, supporting DIL/DIV.

Hypotheses for how hydralazine induces autoimmunity include (1) its binding to MPO leading to neutrophil apoptosis resulting in the production of multiple antibodies, (2) reversal of epigenic silencing of MPO and PR3 leading to increased expression of neutrophil autoantigens, and (3) a breakdown of central tolerance by drug metabolites in slow acetylators of hydralazine [1]. These are all potential contributors to increased antigen presentation and production of antibodies against MPO, histone, and dsDNA, which may be seen in hydralazine-associated DIL and DIV [1]. Hydralazine-induced DIL was thought to occur only in slow acetylators. However, some cases, although rare, have been described in rapid acetylators, who were also patients with atypical clinical features [13,14]. In our patient, hydralazine was started at a dose of 25 mg by mouth twice daily in April 2018, raised to 50 mg by mouth 3 times daily in June 2018, and raised again to 50 mg 4 times daily in October 2018. He was maintained on this same dose until his presentation to hospital in August 2020, with a cumulative dose of 153 000 mg. The score of the Naranjo scale was calculated as 5, placing hydralazine in the probable category of causality. The duration and dose of hydralazine fell within the range of a review study that reported a duration of 12 months to 48 months (mean: 23.1 months) and cumulative dose of 36 000 to 324 000 mg (mean: 145 181 mg) [1]. Previous studies were on acetylator phenotypes. Of late, genotyping studies have emerged [14,15]. Array genotyping revealed NAT2 diplotypes *5.002/*6.002, indicating that our patient was a slow acetylator, which might have predisposed him to developing DIL/DIV.

Searching the PubMed database using “pancytopenia” and “hydralazine” as keywords revealed only 7 cases in the English literature, as summarized in Table 3 [4,5,8-12]. Interestingly, 3 cases were from before 1981 [8-10] and 4 cases were reported after 2022 [4,5,11,12]. Of note, our case was treated in 2020 and therefore appeared to be one of the few cases with detailed autoimmune characterization. Most of the cases recovered after cessation of hydralazine. In addition to our

Table 3. The reported cases of pancytopenia caused by hydralazine.

Author, patient characteristics	Interval* and dose**	Presentation	Nadir value in each cell line	Autoimmune tests	Treatment
Kaufman 1953, [8] 44-year-old female Hospitalized	7 months; 400 mg/day	Ecchymosis, chills, splenomegaly	WBC $1.95 \times 10^3/\mu\text{L}$, Hb 9.5 g/dL, Plt $48 \times 10^3/\mu\text{L}$ Bone marrow biopsy showed hypocellularity and normal megakaryocytes	Not done	Hydralazine stopped; 500 mL of whole blood was transfused; 2.5 weeks later pancytopenia resolved
Evans 1955, [9] 43-year-old female Hospitalized	12 months; 400 mg/day	Fever, sore throat, swelling of cervical lymph nodes. Initially suspected as mumps.	WBC $1.9 \times 10^3/\mu\text{L}$, Hb 9.0 g/dL, Plt $110 \times 10^3/\mu\text{L}$	Not done	Hydralazine stopped. Penicillin given. Pancytopenia much improved in 3 weeks and resolved in 2 months
Stewart 1981, [10] 63-year-old male Hospitalized	10 days; 200 mg/day	Fever, obstructive jaundice; mild bicytopenia	WBC $3.6 \times 10^3/\mu\text{L}$, Hb 11.8 g/dL, Plt $231 \times 10^3/\mu\text{L}$ Liver biopsy showed intrahepatic cholestasis	Not done	Hydralazine stopped; fever resolved within 24 hours; 2 weeks later pancytopenia and liver abnormalities all resolved
Our current case 2026. (Presented and treated in 2020, with long-term follow-up) 52-year-old male Hospitalized	28 months; 200 mg/day. See text for details	Fever, weight loss, DIC, gastrointestinal bleed, acute kidney injury, acute respiratory failure, acute liver injury, acute pancreatitis. Also found to be a slow acetylator	WBC $0.4 \times 10^3/\mu\text{L}$, Hb 5.8 g/dL, Plt $6.0 \times 10^3/\mu\text{L}$ in the setting of repeated transfusions. Bone marrow biopsy showed normocellularity	ANA 1: 1280 (reference range [RR] < 1: 40), anti-histone 13.7 U (RR < 1), anti-dsDNA negative, P-ANCA > 1: 640 (RR < 1: 20), anti-MPO index > 218 (RR < 1.0), anti-PR3 index < 1.0 (RR < 1), low C3 and C4	Hydralazine stopped. Antibiotics, hemodialysis, intubation, large-amount transfusion, steroids with tapering, cyclophosphamide IV, plasmapheresis, intravenous immunoglobulin, followed by mycophenolate and belimumab. Recovered well and no relapse (see text)
Brar 2022, [11] 73-year-old male Clinic visit	3 years; 150 mg/day	Fever, weight loss, moderate right pleural effusion	WBC $4 \times 10^3/\mu\text{L}$, Hb 9.9 g/dL, Plt $83 \times 10^3/\mu\text{L}$	ANA 1: 1280 (RR < 1: 40), anti-histone 1.6 (RR < 1), anti-dsDNA negative.	Hydralazine stopped. 2 months later all symptoms resolved
Shah 2023, [4] 51-year-old female Hospitalized	13 months; 80 mg/day	Palpable purpura	WBC $1.9 \times 10^3/\mu\text{L}$, Hb 7.8 g/dL, Plt $113 \times 10^3/\mu\text{L}$ Bone marrow biopsy showed no malignancy. Skin biopsy showed leukocytoclastic vasculitis	ANA 1: 1280 (RR < 1: 40); anti-histone 3.3 U (RR < 1), anti-dsDNA 16 IU/mL (RR < 4), ANCA 1: 640 (< 1: 20), anti-MPO 1.6 AI (RR < 0.9), anti-PR3 790 AI (RR < 1), low C3 and C4	Hydralazine stopped. Treated with steroids (tapered over 5 months), mycophenolate mofetil and outpatient rituximab. Rashes improved and no relapse, but length of follow-up not reported

Table 3 continued. The reported cases of pancytopenia caused by hydralazine.

Author, patient characteristics	Interval* and dose**	Presentation	Nadir value in each cell line	Autoimmune tests	Treatment
Jerome 2024, [12] 76-year-old female Hospitalized	About 2 years; 200 mg/day	Syncope, fever, weight loss, small bilateral pleural effusion and small pericardial effusion	WBC $1.1 \times 10^3/\mu\text{L}$, Hb 7.5 g/dL, Plt (not reported). Bone marrow biopsy showed normocellularity and active trilineage hematopoiesis	Anti-histone positive (4 HU), anti-dsDNA positive (1: 40), C3 low (45 mg/dL), C4 normal, lupus anticoagulant positive	Hydralazine stopped. All cell lines improved the next day and patient was subsequently discharged. Follow-up was not reported
Ibrahim, 2025, [5] 77-year-old female Hospitalized	1.5 months ago dose raised to 300 mg/day	Fatigue, acute kidney injury, hemoptysis	WBC $1.78 \times 10^3/\mu\text{L}$, Hb 6.8 g/dL, Plt $122 \times 10^3/\mu\text{L}$. Renal biopsy showed chronic pauci-immune crescentic glomerulonephritis	ANA < 1: 40, anti-histone 5.3 U (RR < 0.9), anti-dsDNA 986 IU/mL (RR < 200), P-ANCA > 1: 12850 (RR < 1: 20), C-ANCA 1: 40 (RR < 1: 20), Anti-MPO 128 CU (RR < 20), anti-PR3 69 CU (RR < 20), low C3 and normal C4	PRBC transfused, tranexamic acid, high-dose steroids, plasmapheresis $\times 5$, rituximab and hemodialysis. Discharged to outpatient hemodialysis with steroid taper and rituximab. Follow-up was not reported

* Interval denotes the period from the start of hydralazine to the presentation of pancytopenia. ** Dose denotes total daily dose of hydralazine. Abbreviations: AI, antibody index; AKI, acute kidney injury; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-MPO, anti-myeloperoxidase antibody; anti-PR3, anti-proteinase 3 antibody; C3, complement component 3; C4, complement component 4; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; DIC, disseminated intravascular coagulation; Hb, hemoglobin; HU, histone units; IV, intravenous; MPO, myeloperoxidase; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; Plt, platelet count; PRBC, packed red blood cells; RR, reference range; U, units; WBC, white blood cell count.

case, only 2 of the other cases required immunosuppressants [4,5]. Compared with the cases in the literature, our patient had more severe pancytopenia and required a large amount of blood product transfusion (104 units in total) (Table 3).

The common causes of DIC include sepsis, trauma, malignancy, fulminant hepatic failure, obstetric complications, and intravascular hemolysis due to transfusion reaction. Laboratory abnormalities usually begin to improve within a few days after the inciting trigger is terminated. The mortality rate ranges from 40% to 80% in patients with severe sepsis, trauma, or burns. DIC rarely occurs in patients with SLE [16]. The pathogenesis is not clear and may be related to vasculitis or antiphospholipid antibodies [16]. Only 1 factor, infection, was found to have predictive significance for the development of acute DIC in patients with SLE [17]. Our patient, to our knowledge, was among the first cases of hydralazine-associated DIC. He had persistent spiking fever, and his mental status progressively worsened despite 10 days of antibiotics. DIC developed

at day 9 of antibiotic treatment. Repeated workups for infection were all unrevealing, and the infectious disease specialist repeatedly stated that the fever was not caused by infection. Two days after re-starting antibiotics and 1 day after starting methylprednisolone, the fever resolved. It was surprising that fever resolved on day 15, while he was on antibiotics for most of the days for that 15-day period (Table 1). His slow clinical improvement was concomitant with the improvement of autoimmune markers along with the administration of immunosuppressants (Tables 1, 2). These suggest that the steroids played a role in his defervescence and improvement of DIC, which might support DIL-DIV as a factor in causing DIC, although infection cannot be absolutely ruled out as an element as well. A fatal case of DIC was attributed to idiopathic SLE in a 65-year-old woman receiving hydralazine, despite no prior history of SLE [16]. However, given the patient's autoimmune antibody profile and exposure to hydralazine, hydralazine-induced DIL/DIV with DIC may also have been a possible diagnosis. The authors did not consider hydralazine as

a potential cause [16]. That case apparently did not have infection. Searching PubMed using “hydralazine” and “DIC” as keywords revealed only 1 case of hydralazine-associated DIC, which was published in 2021, one year after our patient’s presentation in 2020 [18]. That patient was treated with high-dose steroids, plasmapheresis, and rituximab. She survived but was not doing well at discharge due to her underlying cirrhosis.

Our patient’s sepsis-like presentation raised the possibility of an underlying infection. However, vasculitis can cause systemic inflammatory response syndrome, mimicking sepsis. A case series reported 3 critically ill cases of ANCA-associated pulmonary renal syndrome [19]. Case 1 had true septic shock due to infection with respiratory microbiology tests being repetitively positive despite antimicrobial therapy. He also received immunosuppressants but died from multi-organ failure. Case 2 was initially started on antibiotics but deteriorated with respiratory failure, diffuse alveolar hemorrhage, and hypotension, requiring intubation and vasopressors. Case 3 was started on antibiotics, but she developed fever, worsening respiratory status, and diffuse alveolar hemorrhage. In both of the latter 2 cases, microbiology tests were negative and the patients improved with immunosuppressants, which was similar to the clinical course of our patient. SARS-CoV-2 infection and vaccination have been shown to increase the risk for autoimmune diseases. There are case reports of ANCA-positive vasculitis associated with SARS-CoV-2 infection [20]. However, there was no evidence of recent or current SARS-CoV-2 infection in our patient. His COVID-19 test was repeatedly negative, and his family did not contract SARS-CoV-2 infection during that period. Therefore, his illness was less likely due to SARS-CoV-2 infection. Further, COVID-19 vaccination did not play a role in our patient, because his illness presented 4 months before the COVID vaccines first became available.

As shown above, the recent cases were reported only after the year 2022, and thus there were no similar cases of severe pancytopenia that we could cite as references to guide us in diagnosis and treatment in 2020. In the setting of severe, persistent pancytopenia and AKI, we decided to treat with immunosuppressants, as is done for other patients with severe ANCA-associated vasculitis. However, after treatment with high-dose steroids and 2 doses of intravenous cyclophosphamide, neither the patient’s blood counts nor renal function improved. At this point, we faced an important question: Was the bone marrow adequately suppressed? If not, should the immunosuppressive regimen be changed or escalated? Therefore, a repeat bone marrow biopsy was done, showing the bone marrow was suppressed, which was consistent with the effect of cyclophosphamide. This boosted our confidence to continue the same treatment, with eventual recovery of all blood cell counts and renal function. However, the repeat bone marrow biopsy in our patient may not be generalizable to other patients.

Fortunately, he did not contract SARS-CoV-2 infection during the prolonged hospitalization while COVID-19 was widespread and he was treated with aggressive immunosuppressants.

The application of pharmacogenetics to antihypertensive agent selection and dosing remains an emerging field [14]. The hydralazine and NAT2 drug-enzyme pair is an attractive candidate that can be used to implement genotype-guided therapy. Hydralazine undergoes metabolism by the NAT2 enzyme. NAT2 is highly polymorphic, as approximately 50% of individuals in the general population are slow acetylators [14]. A review of 29 studies revealed a significant link between NAT2 genotype and acetylator phenotype (assayed by enzyme activity), with an overall concordance between genotype and phenotype of 92% [14]. There is also an association in all of the following: (1) between genotype and systemic hydralazine concentration; (2) between phenotype and systemic hydralazine concentration; (3) between genotype and blood pressure; (4) between phenotype and blood pressure; (5) between genotype and toxicity; and (6) between phenotype and toxicity [14]. An individual’s NAT2 genotype or phenotype can predict the antihypertensive efficacy of hydralazine [14]. Greater hydralazine exposure, due to either higher doses of hydralazine or a slow acetylator phenotype, increases the risk of DIL [13,14]. In a genotype study, 4 of 169 patients developed hydralazine-related adverse effects resulting in drug withdrawal, 3 of whom were slow acetylators (including 1 with DIL) [15]. To our knowledge, our patient was the second case of a genotyped slow acetylator associated with DIL. Additional studies are warranted to confirm the association between NAT2 activity and hydralazine-induced DIL [14]. Slow acetylators (ie, poor metabolizers) are predicted to have increased hydralazine levels, which can lead to increased efficacy and adverse effects. Caution should be exercised in slow acetylators with total daily hydralazine doses of 200 mg or more [14]. On the other hand, intermediate or fast acetylators may be allowed a total dose of up to 300 mg daily [14]. However, these are hypothesis-generating observations only. Broader utility, causality, and management recommendations require confirmation in larger studies. As part of an upcoming trial called the GUARDD-US study (NCT04191824), approximately 6000 individuals will be genotyped for NAT2, including those with resistant hypertension being prescribed hydralazine. This pragmatic study will help clarify the relationship between NAT2 genotype, blood pressure, and adverse events in a real-world setting [14].

Conclusions

This case supports, rather than proves, hydralazine-induced DIL/DIV overlap spectrum as the leading explanation for life-threatening pancytopenia with overt DIC. It characterizes the diagnostic and therapeutic challenges and eventual recovery

after hydralazine withdrawal and immunosuppressive treatment. The salient points of the case are the detailed autoimmune workup, severity of presentation, coexistence of pancytopenia and overt DIC, and extended follow-up within a rare clinical context.

Institution Where Work Was Done

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Patient Permission/Consent Declaration

The patient gave written informed consent for publication of his clinical details. There are no identifying images in this article.

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