Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

CLINICAL CARE CONUNDRUM

CME

Unscripted

The approach to clinical conundrums by an expert clinician is revealed through presentation of an actual patient's case in an approach typical of morning report. Similar to patient care, sequential pieces of information are provided to the clinician who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

Preethi Patel, MD[1]
Gurpreet Dhaliwal, MD[2]
Anitha Rajamanickam, MD[1]
Surafel Gebresalassie, MD[3]
Brian Harte, MD[1]

[1] Department of Hospital Medicine, Cleveland Clinic Foundation, Cleveland, Ohio.
[2] Department of Medicine, San Francisco VA Medical Center and University of California-San Francisco, San Francisco, California.
[3] Department of Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, Ohio.

A 58-year old man was admitted with generalized weakness and acute deep venous thrombosis (DVT). His past medical history included hypertension and polymyositis/dermatomyositis (PM/DM) with antisynthase syndrome, which had been diagnosed 16 months prior when his creatine kinase (CK) was greater than 12,000 U/L. At that time he also was found to have bilateral lower extremity DVT, and had been treated with warfarin for 1 year. 10 days previously, he had been discharged after a 4-day hospitalization for a polymyositis flare which was treated with methylprednisolone at 60 mg daily for 5 days. He was discharged home with daily prednisone until this follow-up a week later, where he reported weakness and bilateral edema. Lower extremity ultrasound demonstrated acute thrombus in the right common femoral vein.

This acute extensive DVT may be a consequence of recent hospitalization and a previously damaged venous system, or may reflect ongoing hypercoagulability from an unresolved condition, such as cancer. Bilateral lower extremity edema may suggest right-sided heart failure due to progressive interstitial lung disease, which occurs in a subset of patients with PM/DM. Edema may alternatively reflect biventricular heart failure, or liver or kidney disease.

Generalized weakness offers little in the way of focused differential diagnosis until it is characterized as motor weakness (eg, attributed to progression of the myopathy), a dyspnea-equivalent, or an overall sense of fatigue.

His medications included weekly methotrexate, monthly intravenous immunoglobulin (IVIG) infusions, tacrolimus, hydrochlorothiazide, and aerosolized pentamidine. He had been on varying doses of prednisone for 2 years and his present dose was 40 mg daily. He was allergic to sulfa. He was married and stopped smoking 30 years previously, and did not drink alcohol or use illicit drugs.

Various medication toxicities could account for his presentation. Methotrexate causes interstitial lung disease, and IVIG and tacrolimus may cause renal failure (and fluid overload). The heavy degree of immunosuppression renders him susceptible to a wide range of infections. Aerosolized pentamidine provides incomplete protection against *Pneumocystis jirovecii*, especially in the lung apices.

Evaluation of the status of his myositis with motor strength assessment is important. In addition associated rashes and signs of malignancy (eg, lymphadenopathy) and infection should be sought. Proximal motor weakness would suggest a myositis flare, although care must be given to exclude competing causes of myopathy, including infections, toxins, or endocrinopathies.

His temperature was 36.2°C, pulse 103 beats per minute, blood pressure 156/83 mm Hg, and respiratory rate 18 breaths per minute. He had crackles at both lung bases, and 3+ pitting edema in both lower extremities. On neurological exam his motor strength was found to be diminished at 3/5 in the lower extremities and proximal upper extremities and 4/5 in the distal upper extremities. Reflexes were uniformly at 1+/4 and his cognition was intact. Examinations of his head, skin, heart, and abdomen were normal.

The absence of elevated jugular venous pressure argues against right heart failure. He is afebrile but that is minimally reassuring given the immunosuppression. There are no clues to suggest liver or kidney dysfunction. An unrecognized occlusion of the lower abdominal venous or lymphatic system such as upward extension of the DVT into the inferior vena cava (IVC) or a pelvic obstruction of the lower extremity lymphatic vessels could be considered. It appears that his distal weakness closely mirrors his proximal weakness in distinction to most myopathies which are predominantly proximal (with some exceptions, eg, inclusion body myositis).

The white blood cell count was 26,000/μL with normal differential, hemoglobin 11.2 gm/dL, and platelet count was 191,000/μL (at recent discharge these values were 23,000, 11.9, and 274,000, respectively). Chemistries were normal except for creatinine of 1.4 mg/dL (baseline 1.2), blood urea nitrogen was 42 mg/dL, albumin 2.6 gm/dL (normal, 3.5–5.0), and CK 3,710 U/L (20–220), decreased from 6,943 U/L at recent discharge. Urine dipstick testing was positive for blood and protein; the urine sediment was unremarkable. Chest radiograph revealed normal lungs and heart.

2010 Society of Hospital Medicine DOI 10.1002/jhm.806
Published online in Wiley InterScience (www.interscience.wiley.com).

The white blood cell count is quite elevated, perhaps more so than could be attributed to chronic steroid use, and again raises the concern of an undiagnosed infection. The presence of heme (and protein) in the urine without cells is consistent with pigment nephropathy from the recent rhabdomyolysis.

He was admitted to the hospital. Unfractionated heparin and warfarin were started. No changes were made to his immunosuppressive regimen. Blood cultures were negative after 48 hours. Transthoracic echocardiogram showed an ejection fraction of 60%, normal valves, and right ventricular systolic pressure of 32 mm Hg (normal, 15–25 mmHg). On hospital day 3, his platelet count was 147,000/μL, and on day 5, 101,000/μL. His other laboratory values remained unchanged, and there were no new clinical developments.

A declining platelet count and extensive deep vein thrombosis suggest heparin-induced thrombocytopenia and thrombosis (HITT), especially with the greater than 50% drop in the setting of IV heparin. His platelets have continued on a downward trajectory that was evident at admission and has progressed during this hospitalization. Assuming this is not due to laboratory error or artifact such as platelet clumping, this decline could have occurred if he was sensitized to heparin during the prior hospitalization, such as for DVT prophylaxis. It is increasingly recognized that HITT can manifest even after exposure to heparin is complete, ie, posthospitalization, and there can be an immediate drop in platelet counts if an unrecognized HITT-mediated thrombosis is treated with IV heparin. Heparin should be discontinued in favor of a direct thrombin inhibitor and tests for heparin-induced platelet antibodies (HIPA) and serotonin-release assay (SRA) sent.

Antiphospholipid antibody syndrome (APLS) is associated with hypercoagulability and thrombocytopenia and is more frequent in patients with autoimmune disorders. The drug list should also be examined for associations with thrombocytopenia. The peripheral smear should be scrutinized and hemoglobin and creatinine followed to exclude thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS).

Heparin was stopped on day 5. Warfarin was continued with a therapeutic international normalized ratio (INR). Tests for antiplatelet factor 4 antibodies, HIPA, and SRA were negative. His weakness and edema improved although his CK remained between 2000 and 4000 U/L. On day 5 he developed mild hemoptysis, and a repeat chest radiograph demonstrated a new left hilar infiltrate. Computed tomography (CT) scan of the chest with contrast demonstrated a left lower lobe consolidation, scattered ground glass opacities in both lung bases, and no pulmonary embolus. He was treated with piperacillin/tazobactam and vancomycin. He remained afebrile. The same day, he erroneously received 125 mg (instead of 12.5 mg) of subcutaneous methotrexate. High-dose leucovorin was administered on days 5 and 6.

The hemoptysis resolved after 2 days. From days 5 to 9, the platelet count dropped to 80,000/μL and his hemoglobin gradually decreased to 7.3 g/dL. Anticoagulation was stopped, vitamin K administered, and an IVC filter placed. Two units of packed red blood cells (RBCs) were transfused.

In suspected HITT (which was not verified here), warfarin is typically withheld until the platelets have recovered and thrombin-inhibitor anticoagulation has reached a steady state, to avoid the transient hypercoagulability of warfarin initiation.

The unusual time course and the 3 negative tests make HITT unlikely. The continued platelet decline after stopping heparin further supports another etiology. The excess methotrexate dosing complicates interpretation of his thrombocytopenia and anemia, which can be explained by mucosal bleeding, microangiopathic hemolytic anemia (MAHA) such as disseminated intravascular coagulation or TTP-HUS, or autoimmunity (Evans syndrome). Bone marrow toxicity is also a major effect of methotrexate (in addition to elevation of liver enzymes and acute renal failure); however, there is typically a lag between administration and development of cytopenias. The antibiotics could also account for the ongoing (but not original) thrombocytopenia.

With the new pulmonary infiltrate, infections remain a primary concern and should be evaluated with sputum samples and perhaps bronchoscopy. Given the abnormal urine (even without cells), a pulmonary-renal inflammatory processes should be considered also to explain the infiltrates and hemoptysis.

Haptoglobin was <20 mg/dL (normal, 37–246). The direct antiglobulin test (DAT) was negative. Serum lactate dehydrogenase (LDH) was 1657 U/L (normal, 100–220), with elevated LD4 and LD5 isoenzymes. Coagulation studies normalized after the administration of vitamin K. Anti-nuclear antibody was positive at 8.7 (normal <1.5). Tests for antineutrophil cytoplasmic antibodies were negative. No sputum could be obtained. A pathologist reviewed the blood smear and reported neutrophilic leukocytosis without left shift, and thrombocytopenia with normal platelet morphology.

Low haptoglobin in the setting of an elevated LDH is highly suggestive of hemolysis, particularly the intravascular, microangiopathic varieties. Neutrophilia may reflect infection, a primary myeloproliferative process such as chronic myeloid leukemia, steroid use, or a "reactive" bone marrow in the setting of acute illness. The negative DAT and significant immunosuppressive regimen makes immune-mediated hemolysis unlikely, although the history of autoimmunity and the small DAT false-negative rate leaves Evans syndrome as an outside possibility. Medications such as tacrolimus (causing TTP) or IVIG (given the broad spectrum of antibodies it includes) are other plausible causes of the cytopenias.

2010 Society of Hospital Medicine DOI 10.1002/jhm.806
Published online in Wiley InterScience (www.interscience.wiley.com).

At this point, I would analyze the red blood cell (RBC) morphology and check the reticulocyte count to help differentiate between hemolysis and a myelotoxin.

After transfusion, his hemoglobin remained at approximately 8.5 gm/dL and LDH remained elevated but stable. By day 12 the platelet count had fallen to 37,000/μL.

With physical therapy the patient gained strength. Antibiotics were discontinued on day 12 and a follow-up chest x-ray demonstrated no significant disease. From days 10 to 12, his creatinine rose from 1.5 to 1.9 mg/dL, although urine output remained normal.

A hematologist observed "minimal fragmentation of red cells" on the blood smear. Commenting on the thrombocytopenia, anemia, and LDH isoenzymes ("representative of skeletal/hepatic origin rather than hematologic"), and clinical improvement after treatment of a presumed pneumonia, he felt that the continued thrombocytopenia was likely due to drug toxicity, and recommended observation, treatment of renal failure, and discontinuation of tacrolimus.

The failure to increase the hemoglobin after transfusion is consistent with (but not specific for) hemolysis. In conjunction with the progressive thrombocytopenia and persistently elevated LDH, TTP remains a consideration. While TTP can be diagnosed with minimal evidence of schistocytes, the duration of this illness, now spanning almost 2 weeks without significant end organ damage—namely more pronounced renal failure, confusion, or fever—is unusual for TTP. Therefore, I think it is reasonable to withhold plasma exchange, although if the cytopenias or renal failure progress after the methotrexate, tacrolimus, and antibiotics are stopped, it may have to be undertaken empirically.

The pulmonary process remains undefined. Edema, pneumonitis (eg, aspiration), a modest pneumonia, or pulmonary hemorrhage could normalize on chest x-ray after 1 week.

Renal ultrasound was normal. Urinalysis dipstick demonstrated 3+ blood, 3+ protein, and no nitrate or leukocyte esterase. The urine sediment showed only granular casts. Fractional excretion of sodium was 6.7%. Urine protein-to-creatinine ratio was 7.5, and urine myoglobin was elevated. Serum C3 and C4 complement levels and cryoglobulins were normal. Reticulocyte count was 8.5% (normal, 0.5–3.2).

There is significant evidence for intrinsic renal failure, starting with the elevated fractional excretion. Marked proteinuria suggests glomerular damage; nephrotic syndrome could provide an explanation for the recurrent DVT. The 3+ blood without RBCs and the markedly elevated urine myoglobin suggest pigment nephropathy from both myoglobinuria and hemoglobinuria. The elevated reticulocyte count further confirms the impression of hemolysis.

2010 Society of Hospital Medicine DOI 10.1002/jhm.806
Published online in Wiley InterScience (www.interscience.wiley.com).

Nephrotic syndrome may result from a primary disease process, such as diabetes, systemic lupus erythematosus (SLE), or amyloidosis, for which there is no evidence to date, or as a consequence of indolent infection, malignancy, or drugs, all of which are reasonable possibilities.

The essential elements at this point include thrombocytopenia, kidney failure with proteinuria, and likely intravascular hemolysis. I would repeat the peripheral smear (looking for schistocytes) and discuss with the rheumatologist if any other medications could be discontinued.

A nephrology consultant diagnosed acute tubular necrosis (ATN) from a combination of insults (intravenous contrast, methotrexate, tacrolimus, and myoglobinuria). Over the next several days, his platelet count rose to approximately 60,000/μL. The patient continued to generally feel better but the creatinine steadily increased to 4.9 mg/dL.

The hematologist's reassessment of the smear was unchanged with minimal RBC fragmentation noted. Over the next few days the hemoglobin, creatinine, and platelet count remained stable, and there were no fevers or other clinical developments. On day 21 a kidney biopsy specimen revealed evidence of thrombotic microangiopathy (TMA) and segmental glomerular necrosis, with negative immunofluorescent findings. In addition, the glomerular basement membranes were thickened and effacement of the epithelial foot processes was noted.

TTP (or other MAHA) with only a few schistocytes would be unusual at an advanced stage where organ damage has occurred, although the clinical presentation in drug-induced variety is variable. TTP is also generally a fatal disease, so relative stability over 3 weeks without definitive therapy is atypical, unless prednisone has served as a temporizing measure. The atypical features raise the possibility of a mimic or variant of TTP such as undiagnosed cancer causing DIC or a medication (eg, tacrolimus)-associated TTP syndrome.

At least 2 other conditions could account for the hemolysis, thrombocytopenia, and TMA. The positive ANA, glomerular disease, and cytopenias are compatible with SLE, although such progression on an intense immunosuppressive regimen would be unusual. The renal histology in a patient with an autoimmune diathesis warrants reconsideration of antiphospholipid antibody syndrome (APLS), especially in light of the earlier DVT.

Tests for antiphospholipid antibodies were negative. After multidisciplinary deliberation, a diagnosis of TMA due to tacrolimus-associated TTP/HUS was made. Plasmapheresis was initiated and IVIG and steroids were continued. He had a complicated hospital course and required renal replacement therapy, but with pheresis, his platelet counts and hemoglobin began to recover and he was ultimately discharged in good condition. After he was discharged, testing for ADAMTS13 (a von Willebrand factor-cleaving protease) activity was reported as 54% (normal, >66%)

Discussion

TMA in the microcirculation is the hallmark pathology of TTP-HUS but is not specific for this disease. TMA is also seen in disseminated intravascular coagulation, sepsis, cancer, malignant hypertension, human immunodeficiency virus infection, autoimmune disorders, pregnancy-related conditions, and in association with certain drugs.[1] The first pharmacological agent to be associated with TMA was mitomycin in 1971, and since then other drug associations have been described, including antiplatelet medications such as ticlopidine and clopidogrel, antibiotics such as quinine and rifampin, interferon, and immunosuppressants such as cyclosporine and tacrolimus.[2] Drug-induced variants of TTP and TMA are challenging to diagnose because the timing of onset, clinical features, and patient factors (eg, receipt of immunosuppressants) may vary widely and mimic other conditions.[2,3] TMA is a rare complication of tacrolimus and is mostly seen in renal transplant patients at a frequency of 1%. In these patients, renal dysfunction is usually the first herald of TMA and TTP; evidence of hemolysis may be absent.[3]

The clinical diagnosis of TTP has historically been based on the presence of a classic pentad: MAHA, thrombocytopenia, neurological and renal abnormalities, and fever.[4] Elevated levels of LDH and indirect bilirubin and the presence of fragmented RBCs and reticulocytes point toward active intravascular hemolysis. The DAT is usually negative. This textbook illness script—the template of a disease that is stored in a clinician's memory—is learned by physicians during training, but undergoes little modification given the limited exposure to a rare disease.

In modern practice, the pentad is rarely seen, and the characteristics of the end-organ findings may vary substantially. For instance, while neurological symptoms including seizures, coma, and transient confusion occur in 90% of cases, renal involvement is seen in about 50% and fever in only 25% of patients.[5] Although the presence of 2 or more schistocytes on the blood smear under 100× microscopy supports the diagnosis of MAHA, cases of TTP without significant schistocytosis have been reported.[6]

Furthermore, TTP is typically described as acute in onset, but in a quarter of patients the symptoms and signs last for weeks before diagnosis.[4] This variability in disease presentation coupled with the high mortality of untreated disease has changed the diagnostic and treatment thresholds for TTP. Trials and expert opinion use MAHA, thrombocytopenia, and the exclusion of alternative causes as sufficient criteria to diagnose TTP and begin treatment.[7] The measurement of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity (a von Willebrand factor-cleaving protease) for diagnostic purposes remains controversial because assay techniques are not uniform and there is insufficient correlation between levels and clinical disease.[8–10] For instance, the presence of severe ADAMTS 13 deficiency (ie, <5%) along with the presence of an ADAMTS13 inhibitor is considered to be very specific, but not sensitive, for the laboratory diagnosis of idiopathic TTP.[11] In cohort studies, the frequency of severe deficiency among patients with idiopathic TTP ranged from 18% to 100%, and the presence of severe deficiency did not predict the development of acute episodes of TTP.[9] In a registry study of 142 patients diagnosed with TTP, 81% of patients with "secondary TTP" (ie, not classified as idiopathic) had ADAMTS13 levels that were normal to subnormal (>25%), and patients with normal ADAMTS13 levels had a higher incidence of acute renal failure, similar to the findings in this patient.[10]

Untreated TTP has a mortality rate of greater than 90%, but with plasma exchange, survival has improved dramatically.[4,7] Glucocorticoids are often used in addition to plasma exchange, based on case series and reports.[9] The addition of cryoprecipitate or fresh frozen plasma to plasmapheresis has not been shown to be beneficial, but rituximab, an anti CD-20 monoclonal antibody, has shown promise in a small prospective study.[12,13]

TTP is a rare disorder with a classic description but substantial variation in clinical presentation. In this case, the background autoimmune myopathy, immunosuppression, coincident acute DVT, unexplained infiltrates, complex medication regimen, and nephrotic range proteinuria (attributed to focal segmental glomerular sclerosis based on the limited evidence available from the biopsy) led the clinicians to ascribe the patient's thrombocytopenia and renal injury to more common conditions and created a challenging environment for the diagnosis of TTP. TTP is a complex disorder and the simplified understanding of the disease and its time course prevented a prompt match between the patient's clinical course and his diagnosis. The combination of a rare condition with inherent variability arising in the setting of medical complexity challenges the processes of problem representation and "scripting the answer" for even the most seasoned clinician.

Key Teaching Points

- The classically described pentad of TTP is seldom seen, and the findings of otherwise unexplained MAHA and thrombocytopenia should prompt consideration of TTP.
- TTP may be acute and idiopathic, or be secondary to drugs, infections, or other conditions. Medication-induced TTP may present with a wide range of clinical findings.
- Therapeutic plasma exchange may be life-saving in cases of TTP, and when appropriate, should be initiated promptly based on clinical suspicion and without waiting to perform tissue biopsy.

Address for correspondence and reprint requests:
Preethi Patel, MD, Desk M2, 9500, Euclid Ave., Cleveland, OH 44195; Telephone: 216-444-0933; Fax: 216-444-8530;

2010 Society of Hospital Medicine DOI 10.1002/jhm.806
Published online in Wiley InterScience (www.interscience.wiley.com).

E-mail: patelp3@ccf.org Received 8 September 2009; revision received 25 January 2010; accepted 13 May 2010.

References

1. Remuzzi G, Ruggenenti P, Bertani T. Thrombotic microangiopathies. In: Tischer CC, Brenner BM, eds. *Renal Pathology.* 2nd ed. Philadelphia, PA: JB Lippincott; 1994:1154–1184.
2. Pisoni R, Ruggenenti P, Remuzzi G. Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Saf.* 2001;24(7): 491–501.
3. Trimarchi H, Truong L, Brennan S, Gonzalez JM, Suki WN. FK 506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation*. 1999;67(4):539–544.
4. Amorosi EL, Ultmann JE. Thrombotic Thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine (Baltimore)*. 1966;45: 139–159.
5. Sarode R, Gottschall JL, Aster RH, McFarland JG. Thrombotic thrombocytopenic purpura; early and late responders. *Am J Hematol*. 1997;54: 102–107.
6. Sarode R. Atypical presentations of thrombotic thrombocytopenic purpura: a review. *J Clin Apheresis*. 2009;24(1) 47–52.
7. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med*. 1991;325:393–397.
8. Terrell DR, Williams LA, Vesely SK, Lammle B, Hovinga JA, George JN. The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS13deficiency. *J Thromb Haemost*. 2005;3:1432–1436.
9. George JN. Thrombotic thrombocytopenic purpura. *N Engl J Med*. 2006; 354:1927–1935.
10. Vessely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. 2003;102:60–68.
11. Lammle B, Hovinga JAK, Alberio L. Thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2005;3:1663–1675.
12. Micheal M, Elliot EJ, Craig JC, et al. Interventions for hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: a systematic review of randomized controlled trials. *Am J Kidney Dis*. 2009;53:259–272.
13. Fakhouri F, Vernant JP, Veyradier A, et al.: Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient TTP: A study of 11 cases. *Blood*. 2005;105:1932–1937.

 DOI 10.1002/jhm.806
Published online in Wiley InterScience (www.interscience.wiley.com).