A 13-Year-Old Girl with Pancytopenia

Robert Listernick, MD

A 13-year-old girl was transferred from an outside hospital for evaluation of pancytopenia. Three weeks earlier, she developed abdominal and back pain associated with fatigue and decreased appetite. Her pediatrician diagnosed her as having infectious mononucleosis. She continued to have intermittent pains and tactile fevers. One week prior to admission, she developed ulcers on her buccal mucosa and her hard palate. She returned to her doctor who performed blood tests that were notable for pancytopenia, and she was then hospitalized at an outside hospital.

On review of systems, she had had 2 days of intermittent vomiting and diarrhea prior to admission as well as vague arthralgias. Her history was remarkable for her mother who has “vasculitis” treated with methotrexate and corticosteroids.

Her family history was remarkable for her father who performed blood tests that were normal for pancytopenia, and she was then hospitalized at an outside hospital.

On physical exam, she was a thin, tired-looking, pale girl. Weight and height were in the 50th percentile. She was afebrile, had a respiratory rate 20, pulse of 96, and blood pressure of 110/72 mm Hg. Her lips were chapped with dried blood. She had ulcers on the buccal membranes with erythematous bases and a raised white center bilaterally. Her lungs were clear, and a cardiac exam was normal. Her abdomen was soft without masses or organomegaly. There was neither clubbing of the extremities nor rashes.

Laboratory evaluation showed hemoglobin of 8 g/dL; white blood cell count of 1,600/mm³ with 54% neutrophils, 30% lymphocytes, 3% bands, and 1% metamyelocytes; and a platelet count of 27,000/mm³. Reticulocyte count was 1.4%. Prothrombin time (PT) was 11.5 seconds, international normalized ratio (INR) was 1.1, partial thromboplastin time (PTT) was 69.5 seconds, and d-dimer was normal. Erythrocyte sedimentation rate (ESR) was 35 mm/hour. Serum chemistries were remarkable for albumin of 3.1 g/dL, alanine aminotransferase (ALT) of 372 IU/L, and lactate dehydrogenase (LDH) of 863 IU/L. Urinalysis showed trace protein, small bilirubin, and urine protein to creatinine ratio of 0.4.

Robert Listernick, MD, moderator: She’s pancytopenic; all three cell lines are down. Is this clearly a malignancy?

Daniel Choi, MD, pediatric hematologist: Obviously that’s a reasonable initial thought. However, the relatively normal white blood count differential mitigates against leukemia, but another malignant infiltrative process is possible. If the bone marrow was working normally, we would expect a higher reticulocyte count. Still, the possible causes of pancytopenia are fairly extensive, including bone marrow failure syndromes (eg, aplastic anemia), sepsis, viral infections, autoimmune destruction of cells (eg, systemic lupus erythematosus [SLE]) and hypersplenism. Hypersplenism is unlikely given the absence of palpable splenomegaly.

Dr. Listernick: What about the elevated LDH?

Dr. Choi: That might be a clue to the presence of hemolysis or rapid destruction of cells in a malignancy process.

Jerome C. Lane, MD, pediatric nephrologist: I’d like to know if she has hematuria and if kidney function was normal. You didn’t give us the full urinalysis. Although you wouldn’t expect leukopenia, anemia and thrombocytopenia would be seen in hemolytic uremic syndrome.

Dr. Listernick: Fair enough. Kidney function and the urinalysis were normal. Further testing at the outside hospital demonstrated antinuclear antibody (ANA) of 1:1,280; anti–double-stranded DNA of 1:640; and very low C3 and C4 levels. Does she have SLE?

Michael L. Miller, MD, pediatric rheumatologist: According to well-established international consensus criteria, a patient has SLE if she has biopsy-proven lupus nephritis in combination with a positive ANA or anti–double-stranded DNA or if she meets four of 11 criteria, including one immunologic and one clinical criterion. The clinical criteria include serositis, oral ulcers, arthritis, photosensitivity, malar rash, discoid rash, or a neurologic disorder (eg, seizures, psychosis). Immunologic criteria include one or more cyto-
penias, kidney involvement, positive ANA or immunologic phenomena (anti–double-stranded DNA or other autoantibodies). She meets the diagnosis based on the presence of oral ulcers, pancytopenia, and positive ANA and double-stranded DNA.

Marisa Klein-Gitelman, MD, pediatric rheumatologist: By the way, everybody looks at the posterior pharynx for ulcers, but they forget to look at the hard palate, which may be their only location.

Dr. Listernick: Once the diagnosis of SLE is made, is there anything to do from the kidney viewpoint given that the urinalysis and kidney function are normal?

Dr. Lane: If the urinalysis is completely normal from the onset prior to treatment, we won’t biopsy the kidney. But if the patient develops even minimal proteinuria, hematuria, or increased urine sediment such as casts, we have a very low threshold for biopsy. We’ve seen lots of patients who have minimal urinary abnormalities but who have had florid lupus nephritis when biopsied.

Dr. Listernick: What is your first-line treatment for SLE?

Dr. Miller: Most institutions will start with intravenous “pulse steroids” at high doses. Some institutions will continue treatment with “pulses,” whereas others will transition the patient to oral medication. To be clear, I was concerned on the day of admission that this was not “run-of-the-mill” SLE.

Dr. Listernick: What was so concerning?

Dr. Miller: Although pancytopenia can certainly be a presenting sign of SLE, her hematologic abnormalities were fairly severe. The elevated LDH is not typically seen in SLE unless there is significant hemolysis. Finally, her ESR was lower than I would have expected. These abnormalities brought to mind the possibility of macrophage activation syndrome (MAS). ESR is lower than would be expected in MAS because of the interference with the liver production of cytokines.

Dr. Listernick: Your suspicion was confirmed when the following tests came back: ferritin 6,900 ng/mL (normal is 24-350 ng/mL), elevated neopterin and soluble interleukin-2 receptor, and absent natural killer cell function. What is MAS?

Dr. Miller: The hematologists call it hemophagocytic lymphohistiocytosis (HLH), which can either be a primary phenomenon due to homozygous mutations in one of several genes or secondary to any number of causes, primarily infection. The most common infection by far is with Epstein-Barr virus (EBV). Rheumatologists, who call this condition MAS, see it as a complication of several rheumatologic disorders, most commonly systemic juvenile idiopathic arthritis.

Dr. Listernick: When do you suspect the presence of MAS?

Dr. Miller: In addition to the clues I just outlined, the presence of coagulopathy, hypofibrinogenemia, severe hepatitis, hepatosplenomegaly, or neurologic dysfunction would alert me to the possibility of MAS. The primary abnormality is low natural killer cell function, which leads to unrestrained macrophage activity.

Anjali Sharathkumar, MD, pediatric hematologist: You haven’t mentioned the isolated elevated PTT!

Dr. Listernick: Should I have?

Dr. Sharathkumar: Yes, it’s an important clue. If the prothrombin time (PT) and the PTT had been abnormal, you might have thought it due to liver dysfunction or disseminated intravascular coagulation. However, in the context of a patient who clearly has SLE, one should immediately think of the possibility of the presence of a lupus anticoagulant. In order to confirm this, I would order a mixing study wherein the patient’s plasma is mixed with normal plasma. If there is a coagulation factor deficiency, the PTT should normalize; if it doesn’t normalize, an inhibitor such as lupus anticoagulant is present.

Dr. Listernick: OK, before we get to that let me give you a little more history. If you’re keeping score, she now has two sets of acronyms — SLE and MAS. She received pulse steroids as well as cyclosporine to treat the MAS. Four hours later, she developed severe unremitting abdominal pain and non-bloody, non-bilious emesis without fever or diarrhea. Her abdomen was not distended but was diffusely tender...

Panelists

Robert Listernick, MD
Moderator

Jerome C. Lane, MD
Pediatric nephrologist

Michael L. Miller, MD
Pediatric infectious disease physician

Marisa Klein-Gitelman, MD
Pediatric rheumatologist

Anjali Sharathkumar, MD
Pediatric hematologist

James S. Donaldson, MD
Pediatric radiologist

(Not pictured: Daniel Choi, MD, pediatric hematologist)

All panelists practice at The Ann and Robert H. Lurie Children’s Hospital of Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for Pediatric Annals.
without rebound tenderness or guarding. The initial CT scan of the abdomen was unremarkable. However, because of unremitting pain and the suspicion of a known complication of SLE, repeat CT scan was performed 16 hours later.

James S. Donaldson, MD, pediatric radiologist: Review of the initial CT scan was unrevealing. However, on the repeat CT scan, there is a large wedge defect in the liver that is so big it almost looks like a traumatic laceration. There’s no history of trauma. In addition, there are multiple smaller defects within the liver unrelated to the large one. Putting the information together, she appears to have a large liver infarction probably with multiple smaller ones within the liver parenchyma. When we looked closely at the vasculature, we couldn’t find any evidence of thrombi. There’s no evidence of bowel ischemia; the mesenteric vasculature is normal.

Dr. Listerick: Would a CT angiogram provide us with more information?

Dr. Donaldson: We obtained very good arterial and venous phases with the conventional CT scan. For a CT angiogram, we give a timed arterial bolus of contrast that would give slightly better arterial resolution, but we wouldn’t obtain the venous phase. A conventional angiogram would provide a better look at microvascular disease. We should see an arterial thrombus on a conventional CT scan, but we might easily miss small abnormalities seen in patients with vasculitis.

Dr. Klein-Gitelman: When we saw these findings, we ordered a brain MRI to ensure that there were no embolic or thrombotic lesions. It was normal.

Dr. Listerick: She continued to have severe abdominal pain despite some interventions that were undertaken. In addition, several small discoid red lesions on her ears enlarged and became purpuric and edematous. CT angiography of the abdomen was performed 24 hours after the previous study.

Dr. Donaldson: There were no arterial abnormalities. The venous phase demonstrates multiple well-demarcated infarctions in the liver. There are no infarctions in the spleen or kidneys. However, the left kidney now has a dilated pelvis and delayed nephrogram with hemorrhage around the perinephric space.

Dr. Listerick: To bring it full circle, the lupus anticoagulant and antiphospholipid panel were both abnormal. She now can be given her third acronym in addition to SLE and MAS: catastrophic antiphospholipid syndrome (CAPS).

Dr. Sharathkumar: The initial PTT gave us a clue to the presence of lupus anticoagulant. Contrary to its name, these children are at risk for developing thrombosis. Although the multiorgan dysfunction generally is driven by thrombotic microangiopathy, as in this patient, large vessel thrombosis may occur.

Dr. Klein-Gitelman: The presence of lupus anticoagulant or antiphospholipid antibodies is not sufficient to label an individual as having antiphospholipid syndrome. The child needs to have suffered a thrombotic event. If three different organs are involved in less than 1 week, the diagnosis of CAPS is applicable. Although CAPS can occur in the setting of SLE or another vasculitic syndrome, as many as 50% of the patients do not have an underlying autoimmune disease.

Dr. Listerick: Treatment?

Dr. Klein-Gitelman: This condition has a mortality of 50%, so it needs to be treated aggressively. She also had a Coombs’ positive hemolytic anemia related to her SLE that complicated transfusion therapy. Immediate anticoagulation is the mainstay of treatment.

Dr. Sharathkumar: Her treatment was quite complicated. Despite the very high PTT, immediate heparinization was necessary, although we worried about the development of heparin-induced thrombocytopenia that would exacerbate her already low platelet count. Given the necrotic lesions on her ears, we also worried about the possibility of a condition that would exacerbate the ongoing thrombosis. Sometimes these patients will develop antibodies to protein C or protein S that can increase the hypercoagulability; these were not present.

Dr. Klein-Gitelman: Additional measures in the treatment of CAPS are intravenous corticosteroids to suppress the immune responses as well as plasmapheresis, which hopefully removes the offending antiphospholipid antibodies. After two cycles of plasmapheresis, she was remarkably improved. She was actually discharged from the hospital several days ago receiving anticoagulation as well as treatment for the MAS and CAPS.

Dr. Listerick: Thank you, everyone.