This 15-year-old girl was transferred for evaluation of hypertension. She was well until 2 days before admission when she developed low back pain. The night before admission, she developed chest pain that felt as if “someone had punched me in the chest.” She was evaluated at an outside hospital, where her blood pressure was 231/127.

She remained hypertensive despite multiple doses of enalapril and labetalol. Review of systems was unremarkable. Her past medical history was remarkable for liver biopsy 3 years earlier that demonstrated nonalcoholic steatohepatitis. Her family history was unknown because she was adopted.

On exam, she was obese and comfortable. Pulse 80, respiratory rate 16, blood pressure 165/111. Weight was 93.6 kg, and height was in the 80th percentile. Body mass index (BMI) was 34. HEENT exam was unremarkable. Lungs were clear. Cardiac exam was normal. Abdomen was soft without masses or organomegaly. Neurologic exam was normal. Mental status was normal.

On laboratory evaluation, electrolytes were normal, BUN 16 mg/dL, and creatinine 1.1 mg/dL. Urinalysis had small occult blood, 1+ protein, 3 to 5 red blood cells, and 3 to 5 white blood cells/high-powered field. Protein/creatinine ratio was 0.2. Hemoglobin was 8.9 g/dL with MCV 69 and normal RDW. The white blood cell differential was 69% neutrophils, 21% lymphocytes, and 10% monocytes; platelet count 163,000/mm³. Ultimately, antinuclear antibodies, C3, C4, and antinuclear cytoplasmic (ANCA) antibodies were all normal. Renal ultrasound was normal.

Robert Listernick, MD, moderator: How would we have treated her if she presented to our emergency room?

Richard Cohn, MD, pediatric kidney diseases physician: She has accelerated hypertension. If she had a seizure or other signs of target organ involvement, we would call it malignant hypertension. We would send appropriate diagnostic studies and start an intravenous drip of a medication to lower her blood pressure, most commonly nicardipine. The goal is to lower blood pressure to a non-dangerous level relatively rapidly; this is best accomplished with a continuous intravenous medication that can easily be titrated.

Dr. Listernick: What would be your target blood pressure?

Dr. Cohn: Approximately 150/100 would be a reasonable target blood pressure, which should be low enough to prevent seizures.

Dr. Listernick: What would be your quick differential diagnosis on initial presentation?

Dr. Cohn: Without the data you just gave, the most likely cause of the hypertension would be parenchymal kidney disease. In a teenager, many of the vasculitides, such as lupus, would be possible culprits. I would expect that she had unknown pre-existing kidney disease that recently accelerated for unclear reasons.

Even in an obese girl, BUN16 mg/dL and creatinine 1.1 mg/dL are not normal, but obviously she does not have kidney failure. The next possibility would be renovascular hypertension. Her urine sediment was fairly “blond,” which might support this diagnosis. If renovascular hypertension were long-standing, you
might see a difference in kidney size on ultrasonography. Third, substance abuse, particularly in an adolescent, would be a possibility. Finally, she could have an undiagnosed coarctation of the aorta. I should also say that we don’t see this degree of hypertension from obesity alone.

Dr. Listernick: Her blood pressure lowered gradually to acceptable levels. At times her blood pressure was as low as 120-130/80-90. Two days later in the intensive care unit, she started complaining of blurry vision, frontal headache, and “lightheadedness.” Her mother stated the patient seemed to “have trouble getting her words out.” Computed tomography (CT) scan of the brain was performed.

Francine Kim, MD, pediatric neuroradiologist: CT scan showed multifocal regions of abnormal decreased density, most significantly a wedge-shaped area in the right parietal white matter with loss of gray-white matter differentiation. The differential diagnosis includes infarction, primary vasculitis and posterior reversible encephalopathy syndrome (PRES). PRES would be the first consideration given the clinical scenario.

Leon Epstein, MD, pediatric neurologist: Distinguishing between PRES and infarctions may be very difficult neuroradiologically. Many patients in the old literature who were said to have hypertensive infarctions on CT scans probably had PRES. PRES is a neurologic syndrome characterized by headaches, altered mental status and seizures in the setting of marked hypertension often in a patient who is receiving immunosuppressant medications. The pathophysiology is thought to be altered cerebral autoregulation. In the proper clinical setting, the classic neuroradiologic findings are white matter edema in the posterior cerebral lobes. Given the location, visual abnormalities may also occur.

Dr. Kim: Magnetic resonance imaging (MRI) will definitely help in distinguishing PRES from infarction.

Dr. Cohn: Her blood pressure was quite labile, but by controlling it at somewhat higher levels, around 150-140/90-100, her neurologic symptoms resolved. We felt that we were dealing with PRES until we saw the MRI.

Dr. Kim: The MRI revealed a large right posterior parietal-temporal cortical infarct and numerous additional small foci of watershed distribution infarcts in both cerebral hemispheres. There were also a few punctate foci of restricted diffusion in the left cerebellum. Although this was initially interpreted as “atypical” PRES, conventional angiography 2 days later demonstrated embolic occlusion of the distal branches of the right middle cerebral artery corresponding to the infarction seen on MRI. There is evidence of old and recent areas of infarction.

Dr. Listernick: What’s your clinical gestalt?

Dr. Kim: The bilateral watershed distribution infarcts appear recent and are presumably related to the rapid decrease in blood pressure in a chronically hypertensive child. The etiology of the older areas of infarction requires discussion.

Dr. Epstein: Chronic hypertension leads to changes in the cerebral vasculature, which is the hypertrophy of the vessel wall that encroaches on the vascular lumen. Subsequent rapid drops in blood pressure lead to decreased cerebral blood flow and potential damage in these watershed areas.

Dr. Cohn: Confusing the picture at this time, we learned that her blood pressure had been normal 3 months earlier in her physician’s office; she did not have long-term hypertension.

Dr. Kim: The angiogram showed filling defects in multiple vessels. Although we couldn’t distinguish between thrombi and emboli, this was an unexpected finding. Vasculitis is also on the differential diagnosis, but there’s no evidence of vasculitis in any of the other blood vessels.

Robert Liem, MD, pediatric hematologist: In terms of immediate treatment of her strokes, there’s a dearth of data in children. Still, we generally recommend anticoagulation until the possibilities of vertebral dissection or cardiac emboli are excluded. The reluctance about anticoagulation in the acute setting has to do with weighing the risks of bleeding against its potential benefits. We don’t even know whether anticoagulation...
with heparin in the acute setting helps. After looking for causes of hypercoagulability, we examine all the identified risk factors and make a decision as to whether to provide chronic anticoagulation.

**Dr. Epstein:** Anticoagulating a child who has an arterial dissection makes sense because the intima of the blood vessel is abnormally exposed. I’d be more concerned about anticoagulation in a child whose blood pressure is labile, who might be at high risk for evolving into a hemorrhagic stroke if the blood pressure changed rapidly again.

**Dr. Listernick:** I don’t believe she received any anticoagulation initially.

**Dr. Cohn:** We believed that she had PRES up until the time that the angiogram was performed.

**Dr. Liem:** We certainly wouldn’t have recommended anticoagulation if we thought she had PRES. Once the abnormalities on the angiogram were identified, I would have performed an echocardiogram immediately.

**Dr. Listernick:** Before we discuss the echocardiogram, what would have been the hypercoagulable evaluation?

**Dr. Liem:** We would certainly want to examine the genetic hypercoagulable factors, including factor V Leiden, prothrombin gene mutation, methylenetetrahydrofolate reductase, and proteins C and S, as well as autoantibodies that are implicated in thrombosis such as anticardiolipin and antiphospholipid antibodies.

**Dr. Listernick:** Transthoracic echocardiography was difficult to interpret because of her obesity. However, transesophageal echocardiography revealed two discrete mitral valve vegetations as well as a patent foramen ovale. The left ventricular mass was not hypertrophied, suggesting that her hypertension was not long-standing. Multiple blood cultures were sterile. However, testing was positive for antibodies to beta-2-microglobulin, virtually diagnostic of antiphospholipid syndrome.

**Michael Miller, MD, pediatric rheumatologist:** Antiphospholipid syndrome (APS) is characterized by recurrent arterial or venous thromboses, as well as recurrent fetal loss in women. It can be seen in association with other rheumatologic conditions (eg, lupus), infections such as hepatitis C, or as an isolated condition.

**Dr. Listernick:** What do you see clinically?

**Dr. Miller:** APS should be considered when a child has an unexplained venous or arterial thrombosis; culture-negative cardiac valvular vegetation; stroke; digital ischemia; or “idiopathic” pulmonary hypertension.

**Dr. Listernick:** How do you make the diagnosis?

**Maurice O’Gorman, PhD, clinical pathologist:** We used to perform a large panel of anti-phospholipid autoantibodies using a “homebrew” assay system.” The previous assay measured IgG, IgM, and IgA specific for five different phospholipid...
ids, as well as anticardiolipin (ie, 18 different tests). This homebrew test has been replaced by an assay that measures antibodies specific for a phospholipid consensus panel. The new assay measures IgG and IgM antibodies specific for beta-2-microglobulin and cardiolipin only.

Dr. Liem: I should point out that the reason APS was suspected, even before the results of the echocardiogram, was the fact that she was positive for lupus anticoagulant. Although the specificity of this test is poor and lupus anticoagulant may be found in 10% of the population, its presence in this specific clinical setting greatly raises its significance. By convention, we can’t definitively diagnosis APS unless these autoantibodies persist for at least 12 weeks.

Stanford T. Shulman, MD, pediatric infectious disease physician: Given that the mitral valve is an unusual location for primary thrombus, consideration needs to be given to the possibility of culture-negative endocarditis, even though she didn’t have fever.

Dr. Listernick: Treatment for APS?

Dr. Liem: We usually recommend unfractionated heparin if the patient will be having further invasive interventions because it can be stopped abruptly and the partial thromboplastin time will return to normal rather quickly. She was not scheduled for any more procedures, so we used enoxaparin. In general, we would recommend at least 6 months of anticoagulation, if not longer, if the autoantibodies persist.

Dr. Listernick: What about anti-platelet therapy?

Dr. Liem: We believe that adequate anticoagulation is better achieved with heparin rather than with anti-platelet agents.

Dr. Listernick: I know that she was started on a course of corticosteroids.

Dr. Miller: There was long discussion about its use. Many rheumatologists reserve use of immunosuppression for patients who have catastrophic APS who have multiple organ involvement.

Dr. Listernick: I still don’t understand why she was hypertensive.

Dr. Cohn: It was confusing, but one possible explanation would be the presence of multiple small renal arterial thromboses leading to renovascular hypertension.

Dr. Listernick: Thank you, everybody.

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### Key Learning Points

1. A reasonable initial treatment of accelerated hypertension is continuous infusion of an easily titratable intravenously infused medication, such as nicardipine.
2. Posterior reversible encephalopathy syndrome (PRES) is a neurologic syndrome characterized by headaches, altered mental status, and seizures in the setting of marked hypertension. It is seen often in patients who are receiving immunosuppressant medications.
3. Antiphospholipid syndrome (APS) is characterized by recurrent arterial or venous thromboses, as well as recurrent fetal loss in women. It can be seen in association with rheumatologic conditions (eg, lupus); infections, such as hepatitis C; or as an isolated condition.