

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.

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Don't Just Do Something, Stand There!

A 35-year-old man presented to the emergency department of a community hospital with 3 days of nausea, vomiting, abdominal pain, and diarrhea. He had developed a sore throat, nasal congestion, and green sputum on a business trip to Las Vegas 10 days prior. He then traveled to Shanghai, China, where he developed frequent diarrhea with mucous and urgency. The stool was mustard colored without blood or melena. He became nauseated and unable to keep down food or fluids. He noted a 4-kg weight loss since the beginning of his symptoms. He had not traveled outside Shanghai or eaten exotic foods. His travel companions remained unaffected. The patient had had type I diabetes mellitus for 23 years with known retinopathy and microalbuminuria. He had hypertension and hyperlipidemia but was otherwise healthy. He was a married traveling salesman with 3 healthy children. He did not smoke or drink and reported no drug use or extramarital relations. He had no known allergies. His medications included insulin, lisinopril, atorvastatin, and valsartan. He was afebrile, his vital signs were stable and the physical examination was unremarkable.

The patient presents with gastrointestinal symptoms following a trip to China. He may have an infection that began in the respiratory system and now is causing some gastrointestinal symptoms, like *Legionella*. If he had received antibiotics, the diarrheal illness could be a complication. With his recent travel to China, typical enteric pathogens would have to be considered: enterotoxigenic *E. coli*, *Shigella*, *Salmonella*, *Campylobacter*, or perhaps *Giardia*.

He was admitted and treated with intravenous fluids and ciprofloxacin for presumed gastroenteritis. He was discharged the next day but returned 2 days later because of continued nausea and vomiting and limited oral intake. He was febrile, to 38.9°C, with chills. The results of an abdominal exam were normal. Stool studies for Salmonella, Shigella, Campylobacter, Yersinia, enterotoxigenic E. coli, Giardia, and Cryptosporidium were negative. No blood parasites were seen. The white-cell count was 3900/mm³ with a normal differential count. Hemoglobin level, platelet count, serum electrolytes and creatinine were normal. He was readmitted for intravenous fluids.

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The patient was treated for traveler's diarrhea, although this is not a typical case and is now becoming a protracted illness. Amebiasis would be a consideration, as well as typhoid or perhaps an abdominal abscess. The normal platelet count reduces the likelihood of hemolytic uremic syndrome, as does the absence of bloody diarrhea. I would evaluate for a systemic illness: check for adenopathy, do a thorough abdominal exam, and get a chest radiogram, blood cultures, and liver function tests. I am also concerned about metabolic abnormalities that could occur as a consequence of the diarrhea.

Over 3 days, oliguria developed along with urinary hesitancy, a 9-kg weight gain, and the development of marked edema. Blood pressure and heart rate remained normal, and a chest radiograph was clear. Liver function tests were normal. A urinary catheter was inserted. Urinalysis revealed a specific gravity of 1.031, protein of 100 mg/dL, and trace glucose but was otherwise negative; no casts or cells were seen in the sediment. Chemistries included sodium of 133 mmol/L, potassium of 3.9 mmol/L, and serum bicarbonate of 18.4 mmol/L. Blood and urine cultures were sterile. The creatinine increased from 1.0 mg/dL (88.4 μ mol/L) to 1.3 mg/dL (115 μ mol/L). He was transferred to a tertiary care hospital for renal consultation because of concerns of impending renal failure and for consideration of a kidney biopsy.

In a typical case of a malabsorptive diarrhea, the patient could be volume depleted, but in this case he has gained 9-kg and is grossly edematous. The chest radiograph and liver tests point to renal rather than cardiac or hepatologic causes for the edema. A glomerulonephritis may be driving the salt and water retention.

The proteinuria could be related to hemodynamics, or it could be from a glomerular lesion secondary to immune complexes. The specific gravity of 1.031 indicates the kidney is able to concentrate, and we are not seeing acute tubular necrosis. There is only minimal elevation in creatinine at this point. Quantitation or estimation of the degree of proteinuria by a protein-to-creatinine ratio would be helpful.

A further workup should include additional blood cultures and a CT scan of the lungs and abdomen to look for occult infection. Is he unfortunate enough to have developed a malignancy? Is

this a connective tissue disease? Reexamination of the urine sediment is important to evaluate for glomerulonephritis.

The patient reported ongoing nausea and vomiting, but his diarrhea resolved. He was tachypneic, with a respiratory rate of 26 breaths/minute and an oxygen saturation of 98% breathing ambient air. His temperature was 37.1°C, heart rate 84 beats/minute, and blood pressure 120/65 mm Hg. His mucous membranes were moist, and his jugular venous pressure was 6 cm. No lymphadenopathy was present. The heart and lungs were normal. The abdomen was soft, nontender, and without organomegaly, masses, or shifting dullness; bowel sounds were hypoactive. Severe edema of his legs, sacrum, hands, arms, and orbits was noted. His right hand and wrist were painful with limited mobility and small joint effusions of the wrist and metacarpophalangeal joints, but without erythema or warmth. Small petechiae were noted on his eyelids; skin examination was otherwise unremarkable. He had been given ciprofloxacin, phenergan, calcium carbonate, and pantoprazole prior to transfer. Stool was negative for occult blood.

His lungs are clear, but it is possible to have early pulmonary congestion with normal breath sounds. As he is normotensive and has a normal JVP, I would not give further intravenous fluid. Unless he has evidence of symptomatic pulmonary edema, I would not give diuretics but would simply observe his course. At this point I would ultrasound his kidneys to make sure there is no obstruction. The proteinuria could be a result of underlying diabetic glomerulopathy that may predispose to fluid retention.

He has significant oliguria but only a mild rise in creatinine. As the referring physicians requested a biopsy, we should consider it. A decision to biopsy the kidney would rest on the degree of proteinuria and the "activity" of the sediment. For example, if red blood cell casts or dysmorphic red cells were present, postinfectious glomerulonephritis or IgA nephropathy would be more likely. However, if the proteinuria is in the non-nephrotic range and the sediment is nonreactive, the yield of a biopsy would be low.

His right hand and wrist are painful with limited mobility. This could be a sequela of endocarditis, although the absence of a murmur and negative

blood cultures make it unlikely. He could have an infectious arthritis, although this usually presents more dramatically. He could have gout or pseudogout, which could be determined by joint aspiration. Finally, could this be iatrogenic? A drug reaction could explain some of the features, including rash, fever, joint symptoms, and renal abnormalities.

Repeat urinalysis revealed protein of more than 300 mg/dL, hematuria (1+), mucous, renal tubular epithelial cells, renal tubular epithelial cell casts, and granular casts. Eosinophiluria was absent. Laboratory evaluation revealed a hemoglobin level of 10.7 g/dL (decreased from 13 g/dL on initial presentation), white-cell count of 7300/mm³, platelet count of 337,000/mm³, serum creatinine of 1.2 mg/dL (106 μmol/L), blood urea nitrogen of 23 mg/dL (8.2 μmol/L), total serum protein of 6.3 g/dL (normal range, 6.3-8.7), and albumin of 2.7 g/dL (normal range, 3.2-5.2). Other liver tests and serum electrolytes were normal.

This degree of proteinuria is significant, but it is unclear whether this is related to the underlying disease process or his advancing diabetes. He has some hematuria, but that could be from the urinary catheter. It would be helpful to know if the red blood cells are dysmorphic, which would point to a glomerulonephritis. He has renal cells, renal cell casts, and granular casts, which are nonspecific. He has a mild anemia, which is unexplained, but could relate to phlebotomy or overhydration. The hypoalbuminemia may be a result of renal losses or a catabolic state.

A renal ultrasonogram was normal, apart from evidence of bilateral pleural effusions. Antinuclear antibody and rheumatoid factor test results were negative, as were those for hepatitis A, hepatitis B surface antigen, and hepatitis C antibodies. Anti-streptolysin O and antideoxyribonuclease B titers were normal. Total complement Ch50 was low at 29 U/mL (normal range, 30-75) as was complement factor C3 at 67 mg/dL (normal range, 90-180). Complement factor C4 was normal. Serum and urine electrophoresis revealed no monoclonal protein spike. Vitamin B12 and serum folate were normal, serum ferritin was 584 ng/mL (normal range, 30-400), iron serum was 29 μg/dL (normal range, 45-160), transferrin saturation was 16%, and total iron-binding capacity was 164

μg/dL (normal range, 250-450). The reticulocyte count was 2.9% with an absolute reticulocyte count of 102/cm³ and a reticulocyte production index of 0.96 (normal range, 1.0-2.0).

It is reassuring that his urinary tract ultrasound is normal. In addition to edema, he has bilateral effusions, which are probably transudative, related to fluid overload. The urinalysis does not suggest a rapidly progressive glomerulonephritis, but autoimmune disease is still in the differential.

He has a mild complement C3 deficiency. In nephrology we think of lupus, infective endocarditis, cryoglobulinemia, and specific glomerular lesions such as membranoproliferative glomerulonephritis and postinfectious glomerulonephritis as being associated with the development of circulating immune complexes that may lead to low complement levels. There is no evidence of a paraprotein, but testing for cryoglobulins should be considered. Cryoglobulins are associated with hepatitis C but may be induced by a variety of infections. Acting like immune complexes, they can lead to low complement levels and could cause some of this patient's symptoms. However, this whole illness seems most likely to be secondary to infection. The normal anti-streptolysin O and antideoxyribonuclease B titers make streptococcal disease unlikely, but another bacterial infection could cause postinfectious glomerulonephritis.

Over the course of his 5-day hospital stay, the patient received furosemide with increased urine output and normalization of his serum creatinine to its baseline level of 1.0 mg/dL (88.4 μmol/L). Proteinuria resolved to 44 mg/dL. A kidney biopsy was not performed. The parvovirus IgG index, checked because of anemia and oligoarthralgias, was 3.67 (normal 0-1.10), and the IgM index was 8.13 (normal 0-1.10), suggesting recent infection. The patient was discharged after 5 days. His edema had resolved on discharge; he continued to be nauseated but was able to eat and drink normally. Six months after his hospitalization, his symptoms had completely resolved.

Parvovirus! It could cause the pulmonary infection and the gastroenteric symptoms. Parvovirus usually causes more anemia than nausea and vomiting. We see it occasionally in our transplant patients. The underlying diabetic nephropathy may have made him more symptomatic with a superimposed glomerulonephritis. The most important pedagogic

point is that he did well with a very conservative approach, and the possible iatrogenic consequences of a kidney biopsy, had it been performed, were avoided.

COMMENTARY

Parvovirus B19 is endemic, with as many as 80% of adults showing serologic evidence of past infection. Although most adults with detectable B19-specific IgG do not recall having had specific symptoms, a number of syndromes have been associated with acute infection.^{1,2} Parvovirus B19 should be included in the differential for postinfectious glomerulonephritis, especially if a patient presents with marked edema with preserved renal function.

Human parvovirus B19, a member of the erythrovirus genus, is a nonenveloped single-stranded DNA virus that propagates in erythroid progenitor cells, arresting erythropoiesis.³ The cellular receptor for the virus is globoside (erythrocyte P antigen), a neutral glycosphingolipid densely present on erythroid cells and also found on hepatocytes, nephrons, and bowel mucosa.^{3,4}

The most common clinical presentation of parvovirus B19 in children is erythema infectiosum, or fifth disease.³ In adults, the infection is known to cause symmetric polyarthropathy, rash, malaise, coryza, headache, and gastrointestinal symptoms (nausea, abdominal pain) and may mimic systemic lupus erythematosus.^{1,3} In patients with sickle cell anemia or other chronic hemolytic disorders, parvovirus B19 can cause a transient aplastic crisis.³ Immunosuppressed patients (eg, organ transplant recipients, patients with certain cancers or advanced AIDS) may develop chronic infection and anemia because of an inability to mount an immune response to clear viremia. Mild anemia or pancytopenia is frequently observed in normal infected hosts.

The syndrome of renal involvement in parvovirus B19 includes the typical features of fever, a maculopapular or reticular erythematous rash on the face or extremities, and polyarthritides, accompanied by oliguria that leads to systemic edema. Mild pancytopenia, proteinuria, hematuria, and hypocomplementemia are often present. Creatinine is usually normal or near normal. These symptoms typically appear 1-2 weeks after the initial viral syndrome.^{5,6} With supportive care, most recover spontaneously, although chronic kidney disease has been reported.^{7,8}

Published kidney biopsy findings of parvovirus

B19 show endocapillary or mesangial proliferative glomerulonephritis with subendothelial electron-dense deposits and granular deposition of C3, IgG, or IgM along the capillary walls and mesangium. These lesions suggest immune complex deposition and are consistent with postinfectious glomerulonephritis.^{5,9,10} Indeed, increased levels of circulating immune complexes have been seen during acute parvovirus B19 infection.^{6,9} It is likely that the protracted symptoms our patient experienced resulted from the formation, circulation, and deposition of immune complexes. The presence of globoside in the kidneys and bowel also raises the possibility of direct infection of these organs.

Postinfectious glomerulonephritis is often thought to be synonymous with poststreptococcal glomerulonephritis. However, viruses, including hepatitis B and C viruses, human immunodeficiency virus, cytomegalovirus, hantavirus, and parvovirus B19 may cause postinfectious glomerulonephritis. As with poststreptococcal glomerulonephritis, glomerular disease associated with viral infection appears to be mediated by the immune complexes. The pathogenic series of events leading to glomerular injury includes formation of circulating immune complexes with subsequent deposition in the glomerulus, or formation of in situ antigen-antibody reactions.¹¹ Immune complexes in the glomerulus lead to activation of the complement cascade, which in turn leads to hypocomplementemia, as the complement cascade is activated faster than the synthesis of new complement proteins.¹² Histologically, a number of different renal lesions may be seen in postviral glomerulonephritis, including membranous, membranoproliferative, and mesangial glomerulonephritis, as well as focal segmental glomerulosclerosis.

Our patient presented with symptoms compatible with but not specific for parvovirus B19. Using a pattern recognition approach to diagnosis, our discussant correctly identified the disease pattern as a postinfectious glomerulonephritis but was unable to identify the correct pathogen, as bacterial infections were the main focus of concern, and viruses, parvovirus B19 in particular, were not considered. The clinical pattern of arthralgia, gastrointestinal symptoms, fever combined with anemia or pancytopenia, and hypocomplementemia is typical of the clues for parvovirus B19. Although renal involvement is unusual, the presence of oliguria, hematuria, and edema with minimal creatinine elevation is typical of parvovirus renal disease.

An essential part of clinical judgment is care-

fully determining which of a patient's often myriad complaints must be considered part of the disease process. Common and nonspecific signs and symptoms often fall off the clinician's radar screen. In this instance, several of the hallmark features of parvovirus B19 disease were dismissed by our discussant as due to the patient's previous medical conditions or hospital-related interventions. Anemia (due to interruption of erythropoiesis by parvovirus B19 replication) was attributed to hydration or phlebotomy, fluid retention was attributed to advancing diabetes, and hematuria was attributed to a urinary catheter. It is important to evaluate the entire clinical picture prior to excluding potential clues to the diagnosis. Another reasonable approach would have been to choose a less general sign or symptom to narrow the possible diagnoses. For example, had the wrist arthralgia been more central in the discussant's thoughts, parvovirus B19 might have appeared on the differential.

Finally, the discussant wrestled with the decision to perform a renal biopsy for a definitive diagnosis versus the potential complications of the procedure. In this case, it was possible to achieve a clinical diagnosis, support it with serologic evidence, and thus avoid the need for biopsy. The current medical climate emphasizes the importance of reaching a definitive diagnosis as rapidly as possible. There are pressures to act quickly and utilize technology that may add both cost and risk. This case emphasizes the value of clinical reasoning and patience, which led to a correct diagnosis and a favorable outcome without the need for invasive procedures. Clinical acumen must occasionally include avoiding the temptation to perform the next test and merely standing at the patient's bedside instead.

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