Case Presentation: Mr. J, an 88 year-old man found on the floor, complaining of generalized weakness

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Mr. J is 88-years old, with a medical history of bladder cancer, status-post resection with a neo-bladder, right ureteral stent and chronic renal insufficiency. He was brought to a local emergency department after his son found him on the floor. The patient said that earlier in the day, he was getting up from a chair, felt weak, and slid to the ground. He could not get up. Review of systems was positive for having chills during the past few days; decreased appetite, with 6-pound weight loss over the last month; and bloody urostomy output over the past 36 hours and was otherwise negative.

Medical History

He was diagnosed with bladder cancer in January 2006. Cystoscopic pathology showed grade III papillary urothelial carcinoma invading the lamina propria and muscularis. He underwent 6 courses of BCG intravesical treatment. Repeat pathology in May 2006 showed muscle invasive disease. In July 2006, Mr. J underwent radical cysto-prostatectomy and ileal loop diversion. He was not treated with chemotherapy or radiation, and subsequent CT scans showed no metastatic disease. Other medical history included chronic renal failure, with a baseline creatinine of approximately 2.5 mg/dl, hypertension; diet-controlled diabetes mellitus II; hypercholesterolemia, bilateral deep venous thromboses diagnosed in April 2007 (on warfarin); right ureteral stent secondary to obstruction caused by the bladder cancer; peripheral vascular disease; and Gleason 3 Prostate cancer.

Medications

Warfarin 3 mg daily, amlodipine 10 mg daily, atorvastatin 10 mg daily, mirtazepine 30 mg at bedtime, pantoprazole 40 mg daily and pentoxyfylline 400 mg twice daily. He had no known drug allergies.

Social History

Mr. J was a retired engineer. He was in the military approximately 60 years ago, but had no known exposure to harmful substances. He smoked a pipe for several years, but quit 10-15 years ago. He drank alcohol rarely, and never used illicit substances. Prior to his diagnosis of bladder cancer, he had been active and lived alone. Subsequently, he lived with his son. His health and functional status had gradually declined over the last year, with several hospitalizations and short stays in skilled nursing facilities (SNF)s for rehabilitation.

Physical Exam

The patient was thin, slightly diaphoretic, tired-appearing, but pleasant with a gentle smile. His temperature was 100.9°F, blood pressure was 148/64 (not orthostatic), heart rate was 64, respirations were 16, and his pulse oximetry was 97% on room air. Head and neck exam was significant for temporal wasting and dense arcus senilis. Lung and cardiac exams were normal. His abdomen was soft, non-tender, non-distended, and there were no palpable organs. He had a left lower quadrant ostomy, with a pink stoma and blood-tinged urine in the ostomy bag. He had no lower extremity or scrotal edema. He was alert with intact cognition, and neurological examination was normal, although gait was not assessed.

Labs

WBC 13.4; 94% polys, no bands. Hgb 10.3, platelets 279. Chem 7 revealed sodium of 141, potassium 4.8, bicarbonate 23, BUN 0.5, and creatinine of 5.9. CK was 582, troponin <0.15, PT 43.2, INR 4.90, AST 50, ALT 67, alkaline phosphatase (ALP) 507, T Bili 1.3, D Bili 0.5, Albumin 2.5, Protein 7.4, Lactate 1.3. U/A showed 2+ blood, 600 protein, 3+ LE, 13RBC, 2WBC. EKG showed NSR @ 64, 1st degree heart block (unchanged)

Imaging studies: Chest X-ray & CT of the head were normal. CT of the abdomen and pelvis showed an obstructing 6mm stone in the distal left ureter with extensive inflammatory stranding and hydroureter. The liver had a nodular contour.

Hospital Course

Mr. J was admitted with a diagnosis of acute on chronic renal failure secondary to an obstructing stone. He was seen by a urologist, and underwent percutaneous drainage of his left kidney and had nephrostomy tubes placed bilaterally. He received a 7-day course of piperacillin/tazobactam for treatment of pyelonephritis. His liver enzymes continued to rise. ALP 527, AST 91, ALT 97, T Bili 4.4, D Bili 3.9 after several days. An ultrasound showed coarsened echotexture but no focal lesions. There was no evidence of ductal dilatation, no stones and a negative sonographic Murphy's sign.

What is the Differential Diagnosis of Asymptomatic Elevated bilirubin?

Elevation of direct bilirubin is divided into three major categories: extrahepatic cholestasis (or biliary obstruction), intrahepatic cholestasis, and hepatocellular injury.
Once the above possibilities were ruled out, drug-induced hepatotoxicity (also known as drug-induced liver injury, or DILI) was raised as a possible etiology for the elevated liver tests. DILI encompasses a spectrum of clinical disease, ranging from mild biochemical abnormalities to acute liver failure. It is a clinical diagnosis based on history, probability of suspected medication as a cause of liver injury, and exclusion of other causes. The incidence is difficult to determine, and thought to be under-diagnosed.

The definition of liver injury is twice the upper limit of normal levels of ALT or conjugated bilirubin, or a combined increase in levels of AST, ALP, and total bilirubin, with at least one being more than twice the upper level of normal. Elevations in serum enzyme levels (ALT, AST, ALP) indicate liver injury. Increases in both total and conjugated bilirubin, decreased platelet count, or abnormal coagulation studies are indicators of overall liver function. Clinical patterns of DILI include hepatocellular, cholestatic, and a mixed pattern. There are also immunoallergic, autoimmune, and steato-hepatitis drug reactions.

The patient's medications were reviewed to identify possible causes of DILI. While in the hospital, he had been on piperacillin/tazobactam, an antibiotic known to cause a cholestatic drug reaction, but he had already completed his 7-day course. He had been taking atorvastatin for over 5 years. He had been taking mirtazapine for the last 6 months.

A literature review revealed 2 reports of patients with hepatic injury secondary to mirtazapine; a 54-year-old woman on mirtazapine for 3 years, and a 49-year-old woman on mirtazapine for 1 year. Both patients developed elevated liver tests and prolonged jaundice. After they stopped mirtazapine, their liver tests returned to normal after a few months. Both atorvastatin, and mirtazapine were stopped. The patient's liver studies began to decline, and he was discharged to a SNF with a plan for ureteral stone removal once his liver studies normalized.

Six days after discharge, the patient was readmitted because of abnormal lab values, weakness and anorexia. He felt some chills, but denied fever, nausea, vomiting or abdominal pain. In the ED, his vital signs were normal. His physical exam was notable for jaundice and scleral icterus, but no abdominal pain or distention. His urostomy bag contained dark urine.

His labs showed WBC 7.9, hgb 104, platelets 265. His chem 7 revealed CO2 19, BUN 40, and a creatinine of 3. His INR was 1.2. UA showed 1+ bili, 2+ blood, 30 protein, 3+ LE, WBC >180, and RBC 32. AST was 102, ALT 116, ALP 205 (482 on discharge); T Bili was 8.2 (3.4), D Bili 5.2 (2.2), showed high-grade transitional cell carcinoma.

FINAL DIAGNOSIS
Metastatic bladder cancer to the liver with resulting cholestasis

RESOLUTION OF CASE
The patient’s oncologist felt that because of the patient's poor performance status, chemotherapy was not an option. The patient was discharged to Steere House, and expired two weeks later under hospice care.

REFERENCES
7. Alpert Medical School of Brown University.

Disclosure of Financial Interests
The authors have no financial interests to disclose.