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CONTINUING MEDICAL EDUCATION
ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2015, 32(4):518–521

Hematology Quiz – Case 42

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A 43-year-old male presented to the emergency department complaining of worsening generalized weakness and lightheadedness for the last two weeks and a syncopal episode lasting a few seconds while he was shopping that morning. No preceding chest pain, dyspnea, palpitations or headache were reported, also had no witnessed seizure activity. He had been fasting for 21 days prior to symptom onset "to cleanse himself" and reported weight loss of 7 kg in last two months. He had an episode of non-bloody vomiting associated with epigastric discomfort on the prior day but denied any fever, diarrhea, hematochezia, melena or any sick contacts. His medical history included chronic hepatitis B and latent syphilis treated with three penicillin weekly injections. He was not taking any medications, denied smoking, drinking alcohol or illicit drug use, had no allergies and was occupied as security guard in an urban area. He had a pet cat but denied any scratches. Family history was unremarkable apart from diabetes in his mother.

On exam, patient appeared pale and dehydrated. His temperature was 38.8 °C, heart rate 100/min, blood pressure 110/60 mmHg and saturation was 98% on room air. He had epigastric tenderness and palpable hepatomegaly but no rebound tenderness. Oral thrush was noted. Neurologic exam, cardiac and pulmonary auscultation were unremarkable but he was found to be orthostatic and also had positive stool occult blood so intravenous fluid resuscitation and intravenous PPI were initiated.

Laboratory workup revealed a white cell count of 5.39 K/μL (4.3–11) with 55% neutrophils and 37% lymphocytes, hemoglobin was 9.3 g/dL (14–18), hematocrit 28.8% (MCV 83.7 fL, MCH 27 pg, MCHC 32.3 g/dL) and platelets 191 K/μL (150–450). Serum sodium was 130 mmoL/L (136–145), potassium 4.7 mmoL/L (3.5–5.1), chloride 97 mmoL/L, bicarbonate 25 mmoL/L, BUN 24 mg/dL (7–18), creatinine 1.6 mg/dL (0.6–1.3) with a last known value of 0.7 mg/dL few months ago. PT was 12.6 sec (9.5–11.4) with INR 1.19, PTT was 26 sec (26–38) and fibrinogen was 230 mg/dL (200–400). Anion gap was elevated and lactic acid was sent that was found to be 3.4 mmoL/L (0.4–2.0). LDH was significantly elevated at 1,578 IU/L (100–190), CPK was normal. Corrected calcium was 11.1 mg/dL (8.5–10.1). Liver function tests revealed SGOT of 214 IU/L (15–37), SGPT 72 IU/L (30–65), alkaline phosphatase 239 IU/L (50–136), total bilirubin 1.06 mg/dL (0–1.0) with direct component 0.63 mg/dL (0–0.3). Total serum proteins were 8.6 g/dL (6.4–8.2) while albumin was 2.7 g/dL (3.4–5.0). Amylase and lipase were normal. Osmolar gap was normal. Peripheral smear was unremarkable, noted target cells and mild hypochromia but no schistocytes, toxic granulosis or left shift were seen. Urinalysis (UA) showed no RBC, no WBC or nitrites and no casts were reported.

Frontal and lateral chest x-ray (fig. 1) and hepatobiliary US were performed (figures 2–4).

The patient had history of chronic hepatitis B and was noted to have elevated transaminase levels in past results dating approximately 6 months prior to admission but had not followed up to primary care clinic.

He was transferred to medicine floor with initial vitals BP 106/60 and HR 99, still febrile at 101.9 F and had blood work that showed a significant hemoglobin drop from 9.3 g/dL on admission 6 hours prior, to 7.3 g/dL. Leukocyte and platelet counts had also decreased to 4.24 K/μL and 162 K/μL, respectively. MICU consult was placed as he was still orthostatic and

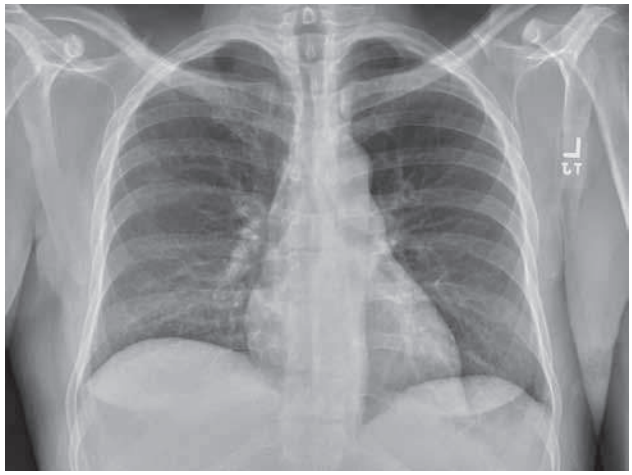

Figure 1

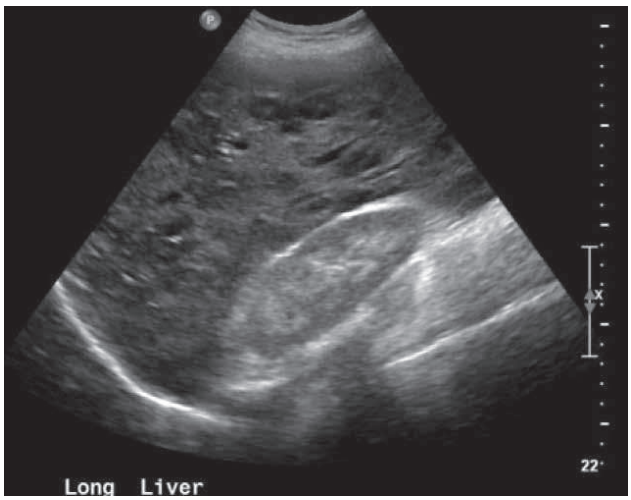

Figure 2

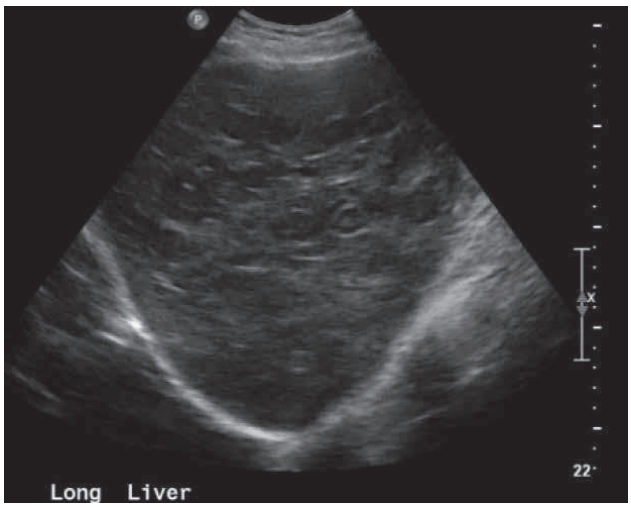

Figure 3

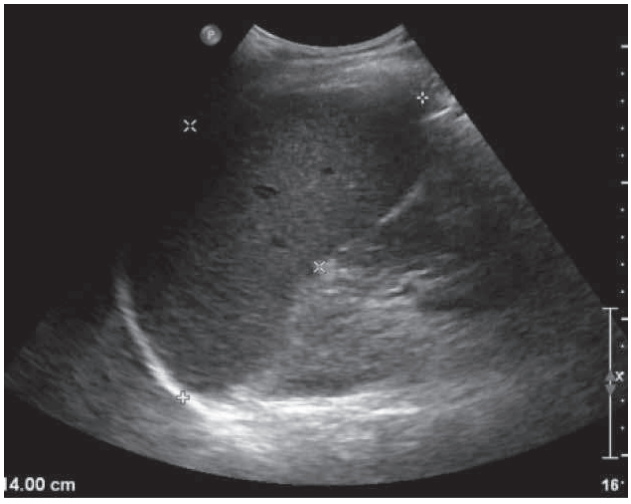

Figure 4

the patient was accepted. Reticulocyte count was 1.6% with absolute number of 45,000/μL and reticulocyte production index of 0.1%. Haptoglobin was 220 mg/dL (30–200), repeat creatinine was 1.2 mg/dL and BUN 20 mg/dL, sodium and potassium were normal, chloride had increased to 109 mmoL/L and bicarbonate decreased to 22 mmoL/L. Anion gap was 13 with a lactate of 2.6 mmoL/L. Repeat LDH was 1,442 IU/L and γGT was 170 IU/L. Iron was 31 μg/dL (42–146), TIBC 192 μg/mL (250–450) with transferrin saturation being 16%, ferritin 1,318 ng/mL (22–322), B_{12} 712 pg/mL (200–700), folate 21.5 ng/mL (4.1–22). Hemoglobin electrophoresis showed HbA 63%, HbF 2.5%, HbA_2 4% and HbS 30.5%.

Further workup was sent, with results reported the next day. Hepatitis B surface and core antibodies were positive, surface antigen and core IgM were negative. Hepatitis C antibody was negative. Hepatitis A IgM antibody was negative. AFP was 1.5 ng/mL (0–10) and CEA was 0.5 ng/mL (<5). Two more sets of bacterial blood cultures were sent and preliminary report results were negative. The patient received one packed RBC transfusion. The patient's hemoglobin went to 8.7 g/dL after transfusion and remained stable. No melena was documented. He continued having fever spikes up to 39 °C twice daily, with no specific pattern. He denied any night sweating or fever episodes in the days prior to admission. Fungal and mycobacterial cultures, *Histoplasma* urine antigen, cryptococcal antigen, *Aspergillus* antigen, coccidioides serology, *Bartonella* serology, *Toxoplasma* serology, *Entamoeba* serology, *Echinococcus* serology and EBV and CMV IgM were sent as per ID recommendations and were negative. PPD was placed. Syphilis IgG were reactive, but RPR was negative. No antibiotics were given as patient appeared to tolerate fever well and all blood cultures had been negative. Echocardiogram had normal ejection fraction and did not show any vegetations.

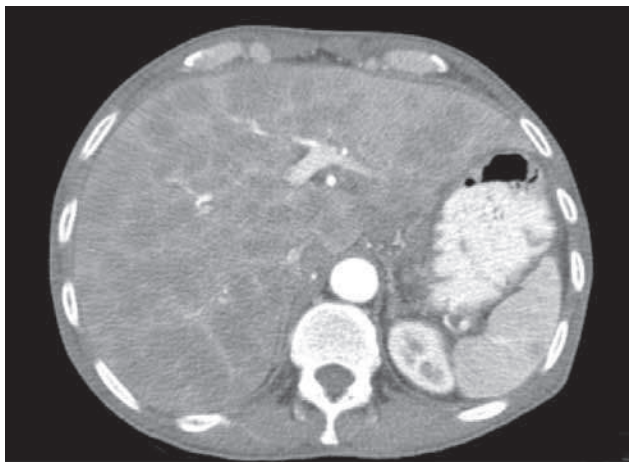

Figure 5

Contrast abdomen and pelvis computed tomography (CT) was performed (figures 5, 6) and confirmed diffuse low attenuation lesions throughout the liver parenchyma and splenomegaly. Stomach wall thickening was seen and also enlarged and highly vascular periportal lymph nodes. An enlarged lymph node in the left diaphragmatic crus was seen. No retroperitoneal lymphadenopathy was noted. Pancreas, gallbladder, adrenals and kidneys were unremarkable. Contrast chest CT did not show any hilar, mediastinal or axillary lymphadenopathy and was negative for any pulmonary findings.

Brain CT with contrast was unremarkable.

Esophagogastroduodenoscopy was performed and revealed small distal esophageal varices and diffuse granular abnormal gastric mucosa with thick folds. Multiple biopsies were performed. Duodenal mucosa was unremarkable. No evidence of bleeding. Biopsy results came back a week later and were consistent with chronic active gastritis, while *Helicobacter pylori* was negative.

CT-guided liver biopsy was done on the third day of the hospitalization without complications. Preliminary report was malignant neoplasm with cellular features suggestive of large cell lymphoma, mucin was negative. Immunochemistry was send out, with result favoring DLBCL, CD20+, CD10+, BCL-6 positive, BCL-2 negative, CD23 negative, cyclin D1 negative, pan-cytokeratin negative. 60–70% of atypical lymphoid cells were Ki-67 positive. The sample contained infrequent small T-cells positive for CD3 and CD5. *In situ* hybridization for EBV was negative.

At that time HIV antibody report came back positive and absolute CD4 count was 32. The PPD had 0 mm induration. Patient was started on atovaquone and weekly azithromycin prophylaxis.

A bone marrow aspiration and biopsy was done on day 5 of hospitalization. Results came back two weeks later showing mildly hypercellular marrow (60–70%) with trilineage hematopoiesis, mature myeloid and erythroid precursors with mildly decreased M: E ratio, atypical megakaryocytes (focal cluster formation), 30% CD138+ plasma cells without definite light chain restriction by *in situ* hybridization, adequate iron stores, mild reticular fibrosis. A single lymphoid aggregate was noted composed of variably sized lymphoid cells with mature chromation. A few larger lymphocytes were noted in this aggregate. Immunohistochemistry showed that this aggregate contained CD3+ T-cells and CD20+ B-cells. Few cells in the aggregate and also throughout the core biopsy were PAX-5 positive. BCL-6 and CD10 were mostly negative. Scattered cells were positive for cyclin D1. CD34 did not show increased blasts. MPO stained some myeloid cells.

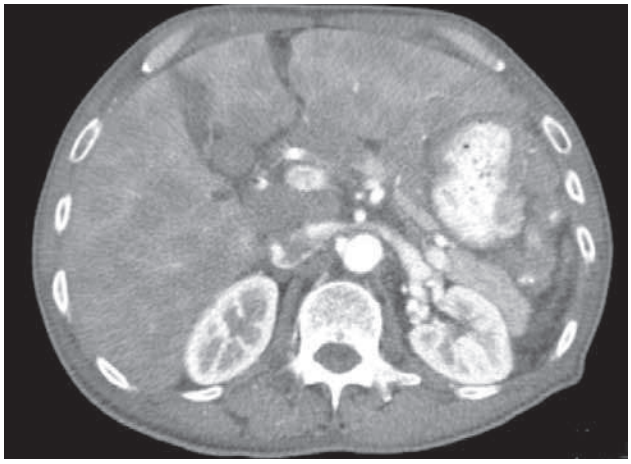

Figure 6

The patient had lumbar puncture to complete workup that showed two lymphocytes/μL, normal glucose, and normal protein. No evidence on malignancy, lymphocytes noted were small as per cytology report. CSF VDRL was negative. He was started on highly active antiretroviral therapies (HAART) regimen and transferred to another facility for chemotherapy.

Comment

The initial imaging findings were concerning for fungal infection, especially in immunocompromised setting suggested by the oral thrush, but also for metastatic malignancy. Markedly thick and edematous gallbladder can be attributed to hepatitis or cirrhosis but in proper clinical settings can also represent acalculous cholecystitis or gallbladder carcinoma. Epigastric tenderness, fever and elevated liver function tests with normal CPK denote liver injury that appeared to be mostly hepatocellular and less of biliary origin. Alcoholic hepatitis can be suggested by these results given the transaminase ratio and the elevated ALP while viral hepatitis reactivation is also in the differential but less likely. However, that level of LDH cannot only be explained by hepatic necrosis comparing the level of transaminase elevation. Elevated LDH with low hemoglobin and acute kidney injury raise concern for microangiopathic hemolytic anemia but the peripheral smear did not show any schistocytes, also fibrinogen and platelet count were normal and at patient's baseline. The patient is noted to have elevated total proteins and hypoalbuminemia, findings consistent with inflammatory state with a broad differential, from infectious to autoimmune or malignancy-associated.

The hemoglobin drop in the repeat CBC is concerning for ongoing bleeding but the downtrending lactate after patient was given fluids shows improving hemodynamic status and all cell lines noted to be decreased, suggesting hemodilution after resuscitation. Creatinine normalized and haptoglobin was not low arguing against microangiopathy. Anemia workup was consistent with sickle cell

trait pattern and chronic disease with poor marrow response. The patient had mildly decreased bicarbonate and elevated chloride, consistent with non-anion gap metabolic acidosis after the 0.9% normal saline (NS) resuscitation boluses.

The low attenuation liver lesions and the lymphadenopathy noted in the CT entertained the diagnosis of visceral malignancy with liver metastasis.

HIV infection is well associated with DLBCL and Burkitt lymphoma, while Hodgkin lymphoma in immunosuppressed patients is strongly associated with EBV. The level of the patient's LDH suggested a highly malignant lymphoma, arguing against Hodgkin. Burkitt was also less likely as biopsy showed large lymphoid cells, Ki-67 was less than 95% and BCL-6 was positive, even though overlapping cases have been described. Cyclin D1 which is positive in 95% of mantle cell lymphomas was found negative. Also poorly differentiated carcinoma was less likely as cytokeratin was negative.

The bone marrow immunochemistry shows that the aggregate is a mixture of B-cells and T-cells but a definite diagnosis of marrow infiltration could not be established. Increased plasma cells in HIV patient marrow biopsy have been noted in literature.

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