Knowing your lab test well: Expanding the differential for elevated alkaline phosphatase

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ABSTRACT

Introduction: It is known that increased alkaline phosphatase with a distended gallbladder increases the suspicion of pancreatic malignancy. But benign etiology can be present, including a fasting state. Case Report: Our patient, a 58-year-old African–American female with a history of recurrent UTI presented to the emergency room with nausea and vomiting and loss of appetite for last five days. Physical exam was unremarkable except for dehydration. Initial laboratory test were normal including liver function tests, except for alkaline phosphatase level which was elevated to 216 (normal 35–120). She was started on intravenous fluids and antibiotics. Her symptoms improved and she tolerated a high protein and carbohydrate diet. She underwent an abdominal ultrasound of the right upper quadrant (2nd day of admission). It showed distended gallbladder and dilated common bile duct. No stones were seen and the liver was homogenous without masses. Gastroenterologist performed the EGD (3rd day of admission) which was benign. Her initial alkaline phosphatase trended down but started to rise again. The 5’ Nucleotidase was normal. An abdominal CT scan was performed (5th day of admission) showed no pancreatic mass, a contracted gallbladder and normal common bile duct. She was discharged home on oral antibiotics and a food supplement. Her follow up alkaline phosphatase was normal. Conclusion: Believe that our patient’s generalized weakness, weight loss, as well as her increased alkaline phosphatase, distended gallbladder and common bile duct dilation can be attributed to her fasting state. During this, alkaline phosphatase activity is increased. It is a component of regulatory mechanisms, by increased delivery of the enzyme to the blood and respective decrease and increase of the maximal velocities of the enzyme reactions. Studies done on rats and elephant seals showed that not only with fasting, but also with refeeding, alkaline phosphatase activity increases. Some studies have shown that fasting can cause phases of dilatation and phases of contraction of gallbladder which phases of maxima dilatation at 12 a.m. and 4 p.m., and maxima contraction at 8 a.m. and 4 p.m. Thus, we are inclined to conclude that starvation and refeeding have played role in our patient’s presentation timing is the key.

Keywords: Alkaline phosphatase, Starvation, Refeeding, Gallbladder dilatation

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INTRODUCTION

Elevated alkaline phosphatase in the setting of a distended gallbladder and dilated common bile duct increase the suspicion of benign as well as malignant conditions, including pancreatic carcinoma. We present a case with such findings without any gross underlying pathology. Could these findings also present secondary to starvation?

CASE REPORT

Our patient is a 58-year-old African–American female with a history of recurrent urinary tract infection. She presented to the emergency room with nausea, vomiting, and anorexia for the last five days. She also reported modest weight loss. Her history was significant for a recent emergency room visit for a seizure, secondary to a sub-therapeutic phenytoin level. At that time, she was also diagnosed with a urinary tract infection, and placed on an oral antibiotic regimen.

The physical exam was significant for dry mucosa and tongue, with a blood pressure of 100/62 mmHg. The exam was otherwise unremarkable. Initial laboratory examination showed hemoglobin of 12.8, and a white blood cell count of 17.8. Electrolytes, BUN, creatinine, and liver function tests were all normal, with the exception of an elevated alkaline phosphatase level (ALP) of 216 (normal 35 to 120). In the ER, intravenous fluids and intravenous antibiotics were administered. As her symptoms improved with antiemetic, she was started on a liquid diet. Her prealbumin was checked later on, and found to be 9 (Normal > 17).

Day 2: An ultrasound of the right upper quadrant of her abdomen was completed due to concerns over her elevated ALP. It showed a distended gallbladder with a dilated common bile duct of 9 mm. Stones were not visualized, and the liver was homogenous, without any masses. The gastroenterology (GI) service was consulted.

Day 3: The GI service performed an esophagogastroduodenoscopy (EGD). The study showed small esophageal ulcers and mild scarring of the distal esophagus, attributed to reflux. The study was otherwise unremarkable. During this time, there had been a downtrend in the patient’s ALP. A 5’ nucleotidase level was found to be within normal limits. Considering the improvement in laboratory and clinical findings, further invasive testing was not performed. The patient was tolerating feeds at this time and had been advanced to a high protein, and carbohydrate diet.

Day 4: The patient’s ALP levels were rising again on the fourth day. This was confirmed with a second test to rule out any laboratory errors. Accordingly, the GI service scheduled the patient for an MRI cholangiogram, and pancreaticogram to be done later on in the day. However, these tests could not be performed without clearance from the neurology service, as this patient had prior stents placed for a brain aneurism.

Day 5: We chose to forego the MRI studies altogether and proceed with an abdominal CT scan on the fifth day, in hopes of finding an etiology for the elevated ALP. The CT scan visualized a pancreas that was free of any masses. The gallbladder was contracted, and the common bile duct could not be visualized. The study as a whole was unremarkable.

Day 6: The patient felt well, and her prealbumin level had risen to 14 from 9. ALP levels demonstrated a second downtrend. Considering that the work up was negative, and her symptoms had resolved, the patient was discharged home on oral antibiotics for her urinary tract infection, and a nutrition supplement.

One month later, she followed up in the clinic. She was doing well without any complaints and her ALP level was rechecked and was found to be within normal limits.

DISCUSSION

There are three isoenzymes of alkaline phosphatase (ALP). Two different genes code for ALP of intestinal and placental origin (during the third trimester). A third gene codes for ALP synthesized by multiple organs including the liver, bones, and kidneys. The 5’ nucleotidase may be helpful in delineating which isotope is elevated in the serum, as this test may be abnormal in cases of liver pathology.

The 5’ nucleotidase test in our patient was within normal limits. However, the results of this test should be interpreted cautiously. This test is better used for ruling in hepatic pathology rather than ruling it out (the specificity is better than its sensitivity) [1]. Additionally, our patient presented with gastrointestinal complaints. A process involving the liver could not be completely ruled out.

The initial ultrasound showed a distended gallbladder, and dilated common bile duct but failed to demonstrate cholelithiasis. Additionally, the patient did not have clinical signs or laboratory results consistent with jaundice. As such, an acute obstructive process (e.g. cholecholithiasis) was less likely to be the cause. The subsequent workup, including and EGD and abdominal CT scan failed to show any gross obstructive or inflammatory etiologies responsible for the dilated CBD. The negative workup ultimately led us to conclude that this patient’s chief complaints of nausea, vomiting, and anorexia were most likely secondary to her UTI.

It could be argued that this isolated elevation in ALP may have been related to phenytoin use [2]. However, we must recall that the patient’s ALP level fluctuated throughout the hospital stay, and the gallbladder was, indeed, distended upon admission.

Studies done in animals may suggest a possible etiology for the elevated ALP. Recall that due to the nausea, vomiting and loss of appetite, our patient had not eaten for the last five days. Studies in animals have shown that starvation has been associated with changes in serum ALP activity. While one study demonstrated a decrease in serum ALP activity in fasting rats, two other
studies showed increased in fasting seal pups and female monkeys [3–5]. One study also showed increased serum ALP activity upon refeeding fasting rats [6]. Fasting and refeeding have also been associated with disturbances of ALP activity (increases as well as decreases) in histological sections of the intestine, liver and fat of different animals [7–9].

A study done in Sweden, examined metabolic abnormalities in teenage girls (mean age 15 years) with eating disorders [10]. ALP was among the tests performed in 251 subjects. When adjusted for their age, most of the ALP levels were either lower than the reference range, or marginally normal. One possible conclusion of this study could be that the fasting state affected the ALP levels only slightly (and in the opposite direction from which we observed in our patient). However, to make that conclusion, we must assume that these patients were necessarily in a starvation state when they were evaluated. In reality, they may or may not have had a regimen of regular, but small meals as part of their eating disorders. Our patient did not have a long-term history of malnutrition, or eating disorders; she presented with an acute episode of starvation.

We believe our patient’s elevated ALP and distended gallbladder could be attributed to her state of starvation. Note that some time after initiation of a regular diet, her ALP level took a down trending course. The subsequent transient rise in ALP might be due to refeeding. Also the gallbladder was initially dilated due to her fasting state and with refeeding the gallbladder was contracted [11].

**CONCLUSION**

When a patient presents with elevated ALP activity and a distended gall bladder, the clinician must consider several etiologies in the differential diagnosis. The biggest concern is always the obstructing lesion. Our patient had these abnormalities in the background of a negative clinical work up, including abdominal CT scan. Considering that these findings were isolated in regards to workup and combining the clinical picture, they proved to be transient as our patient was slowly started on a normal diet, we are inclined to conclude that starvation and refeeding have played role in our patient’s presentation.

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**Author Contributions**

Sachin Kumar Amruthal Jain – Involved in substantial contributions to conception and design, acquisition of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published

Kashyap Patel – Involved in substantial contributions to conception and design, acquisition of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published

Yousif Ismail – Involved in substantial contributions to conception and design, acquisition of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published

**REFERENCES**


