CLINICAL VIGNETTE

Nutritional Deficiencies and Metabolic Bone Disease in Primary Biliary Cholangitis

Rauz A. Eshraghi, MD and Sonya Heitmann, MD

Introduction

Primary biliary cholangitis (previously called primary biliary cirrhosis or PBC) is a progressive degenerative disease of the intrahepatic bile ducts. Over time biliary duct destruction leads to cholestasis and eventually liver fibrosis and cirrhosis. Other complications of PBC include hepatocellular carcinoma, malabsorption, and metabolic bone diseases.[1, 2] Since bile acids are essential for proper absorption of fats and vitamins, patients can develop deficiencies specifically in fat soluble vitamins (A, D, E and K). Osteopenia, osteoporosis and rarely osteomalacia are also known sequalae of PBC.

In the United States, PBC is the most common cause of cholestatic hepatic disease. It is rare with a prevalence estimated to be between 2 to 40 cases per 100,000 persons.[1] Women are more commonly afflicted than men with the peak age of diagnosis of 40s to 50s.[2] Though the pathogenesis is not entirely understood, it is hypothesized to be a T-cell mediated autoimmune process triggered by environmental factors. Geographic studies indicates higher prevalence in Northern Europe and in North America interestingly specifically in the mid-western United States, suggesting an underlying genetic predisposition.[3]

More than 50% of patients are asymptomatic at the time of diagnosis.[2] Diagnosis is often made while undergoing the routine evaluation for abnormal liver function tests. Symptoms in early stages of PBC commonly include fatigue and pruritus and, less frequently, upper abdominal pain, depressed mood, memory deficits and trouble with concentration. As the disease progresses malabsorption and metabolic bone diseases can be seen.

Case Report

A 50-year-old postmenopausal Caucasian woman presented to establish care with a new primary care physician. Her medical history was notable for hypothyroidism and a history of carotid artery dissection with subsequent left cerebrovascular accident approximately 6 years prior. During that hospitalization she noted significant pruritus and was found to have elevated liver enzymes. Further workup revealed positive anti-mitochondrial antibodies (AMA). A liver biopsy confirmed PBC. She was treated with ursodeoxycholic acid and rifampin. Symptoms were initially stable however her clinical course was complicated by bleeding esophageal varices requiring multiple blood transfusions and endoscopic band ligation. Due to disease progression, she was listed for liver transplant. She now presented with complaints of occasional abdominal bloating and significant chronic low back pain.

Her back pain was insidious in onset with no preceding injury or trauma. She described it as a severe, constant ache which was exacerbated with reclining. It was midline with radiation to the buttocks and groin. She denied neurologic symptoms including numbness, weakness or tingling. She had no bowel or urinary incontinence. She had been given tramadol and gabapentin for pain, both of which provided minimal relief. Approximately one week prior to her visit, her pain had acutely worsened. She denied any trauma and had no fever or worsened malaise.

Her musculoskeletal exam was notable for bony tenderness to palpation over the lumbar spine at L3 and L4. There was no paraspinous muscle spasm or pain. Straight leg test on the right elicited pain down the ipsilateral leg. Hip exam revealed normal range of motion. Neurologic exam including strength and reflexes were normal. Imaging with x-ray of the hip and lumbar spine revealed a new L4 compression fracture as well as the suggestion of osteopenia.

She was treated with oxycodone, as nonsteroidal anti-inflammatory medications and acetaminophen were avoided given her liver disease. A bone density scan was obtained and revealed severe osteoporosis in the left femoral neck, left hip, right femoral neck and right total hip with T-scores of -3.2, -2.9, -4.0, and -3.7, respectively and osteopenia with a T-score of -2.1 in the spine (L1-L4).

Labs showed a Vitamin D, 25-Hydroxy level of 5 ng/mL (normal 30-80), Vitamin D 1,25-DiOH of 6pg/mL (normal 15 - 75 pg/mL), Vitamin E of 4.7mg/mL (normal 5.6 - 22.0 mg/L) and Vitamin A <0.1mg/mL (normal 0.3 - 0.9 mg/L). Vitamin K level was normal.

She was started on calcium daily and Vitamin D2 50,000IU weekly. Given her history of esophageal varices, bisphosphonates were contraindicated and she was referred to rheumatology for further management of her osteoporosis.

She was treated with Vitamin A and Vitamin E. Repeat labs 8 weeks later showed a Vitamin D, 25-Hydroxy level of 9 ng/mL, Vitamin E of 17.5mg/mL and Vitamin A of <0.1mg/mL. Her Vitamin D2 dose was increased to be taken every other day. The Vitamin A dose was increased. She underwent liver trans-

plantation 6 weeks later. Subsequent labs 8 weeks after liver transplant showed a Vitamin D 25-OH of 16. Vitamin A, E and K were in the normal range.

Discussion

Metabolic bone diseases including osteoporosis and osteomalacia are seen in a variety of liver diseases. In PBC, almost all patients have osteopenia and up to 52 percent of patients have osteoporosis.[4] The etiology of osteoporosis in PBC is still unclear but likely multifactorial. It was previously believed that Vitamin D malabsorption was a significant contributor to osteoporosis. However this theory has come under question as Vitamin D, repletion has not been shown to reverse bone disease.

An additional consideration is that PBC predominately affects perimenopausal and postmenopausal women who are already at risk for osteoporosis.

Screening for osteoporosis in PBC should occur at the time of diagnosis with surveillance every 2 to 4 years as well as prior to liver transplantation, in those with fragility fractures, and in patients with advanced disease.[4] Treatment is similar to management in the general population including calcium and vitamin D supplementation and avoidance of alcohol, tobacco, caffeine and corticosteroids. Regular weight-bearing exercise should be encouraged. Medications are also used although, bisphosphonates are avoided in patients with history of esophageal varices.

With respect to malabsorption, patients with PBC can develop deficiencies in fat soluble vitamins including Vitamin A, D, E and K. These levels should be tested annually.[1]

Conclusion

Primary biliary cholangitis is classically seen in middle aged women and often found incidentally in the workup of abnormal liver function tests. Common symptoms include fatigue and pruritus. Disease progression can cause malabsorption of fat soluble vitamins. Additionally, metabolic bone disease including osteoporosis and osteomalacia are common complications. Continued surveillance and management of these complications are essential in the management of PBC.

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