CLINICAL VIGNETTE

Unusual Presentations of Celiac Disease

Jeffrey S. Goldsmith, M.D.

Case Report 1:
An otherwise well 35-year-old male presented for routine examination. He had a remote history of migraine headaches that had been infrequent and well controlled with over the counter medications. He reported regular bowel movements and no significant weight loss. He had no other complaints. His routine laboratory evaluation was remarkable for a mild elevation of alanine aminotransferase and aspartate aminotransferase of 44 and 73 U/L. Albumin and ferritin were normal and hepatitis A, B and C serologies were negative. Mitochondrial antibodies, and antinuclear antibodies were negative. Endomysial IGA levels were detected at 1:640 titer. Anti-Gliadin IGA LEVELS were present at 33.9 U/ml, and Tissue transglutaminae IGA levels were greater than 100.0 U/ml. No endoscopic procedures were performed. The patient was considered to have met criteria for celiac disease. At 6 months' follow-up on a strict gluten free diet, the patients liver functions were normal, and all antibody IGA studies previously elevated had become undetectable. Severe osteopenia of the lumbar spine was noted on his bone densitometry. Serum testosterone level was normal. At two-year follow-up, the patient's liver function remained normal. Vitamin D were low at 20ng/ml and corrected with supplementation. Repeat bone densitomety showed no significant changes.

Case Report 2:
A 90-year-old female with a past medical history of hypertension and osteoporosis was admitted to the hospital for an acute femoral neck fracture. Her only medications were lisinopril, aspirin, and occasional over the counter diphenoxylate and atropine for occasional loose bowel movements. She had not needed to use this more than twice weekly. Her admission laboratory tests included an elevated INR of 2.5. INR from a month earlier was 1.5 and 1.7 two weeks prior to admission. Her INR normalized after vitamin K. Serum albumin was normal at 4.1 g/dl six months prior to admission. One month prior to admission the serum albumin was 3.3g/dl. At the time of admission the serum albumin was 2.6 g/dl. There was no significant weight loss during this time period. During her admission, Endomysial IGA antibodies were positive at 1:320 titer. Gliadin IGA levels were 412 EU (normal range <25 EU). The patient's malabsorption syndrome was ascribed to celiac disease, and a strict glutin free diet was followed. At five month follow-up, Endomysial IGA antibodies were undetectable, and Gliadin IGA antibodies were 24 EU (normal range). Serum albumin levels were normal at 4.4gm/dl. INR remained normal. Additional deficiencies included Vitamin B12 as demonstrated by a methylmalonic acid level of 458 nmoles/L (87-318 normal range). At one year follow-up on oral supplementation of 2mg daily, the patients methylmalonic acid levels had returned to 191 nmoles/L. Vitamin D 25 hydroxy levels at the time of admission were 13 ng/ml. At one-year follow-up on supplementation her levels were 32ng/ml.

Discussion:
Celiac disease, or gluten sensitive enteropathy, is an immune mediated distructive process affecting the small intestine. Histopathologic findings include

mucosal inflammation, crypt hyperplasia, and villous atrophy.[1] Gliadin is the alcohol soluble portion of the gluten protein. It is this portion of gluten, found in wheat, rye, barley and to a lesser degree oats, that in genetically predisposed individuals will trigger the immune disorder.[2,3] Gliadin is resistant to gastric, pancreatic and intestinal brush-border membrane proteases. The 33-amino acid peptides can pass through the intestinal epithelial barrier and subsequently interact with the antigen-presenting cells of the lamina propria.[4] Patients suffering from celiac disease develop an IgA response to a smooth muscle connective tissue called endomysium. Within endomysium is a target auto antigen called tissue transglutaminase. Presence of elevated levels of endomysium and tissue transglutaminase IgA are now considered highly sensitive and specific means of diagnosing Celiac disease.[5,6] However, the incidence of IgA deficiency in patients with Celiac Disease is 1:40 as compared with 1:400 in the general population.[7,8] Therefore, to rule out selective IgA deficiency, measuring total IgA levels if markers are absent or within normal range or when clinical index of suspicion is high for celiac disease is recommended. Otherwise, the diagnosis of celiac disease is made by endoscopic biopsy of the duodenum demonstrating classic intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy and a positive response to a gluten-free diet.[4]

The incidence of celiac disease is estimated to be close to 1% of the population in both children and adults.[9,10] With the advent of serological screening, there may be both an increase in the detection rate as well as increase in the incidence of disease.[11] It has been recognized in people of European decent as well as in the Middle East, Asia, South America and North America.[4] Two alleles have been associated with celiac disease: HLA DQ2 and to a lesser degree, HLA DQ8. Up to 95% of patients with celiac disease have HLA DQ2 allele.[12] The incidence of the HLA DQ2 allele in the general population is approximated at 30-40%. This may be relevant in determining if family members should be screened with serologic testing. In the subgroup of patients where neither allele is present, there is a high negative predictive value.

The classic presentation of Celiac disease in adults is diarrhea, with associated abdominal pain or discomfort. In the last decade however, less than 50% of cases were found to have diarrhea as the main presenting symptom.[13] Less common presenting symptoms that have been found to be ascribed to celiac disease include iron deficiency anemia, osteoporosis, hypocalcemia, hypoprotenemia, elevated liver enzyme levels, dermatitis herpetiformis, as well as incidental findings due to endoscopic evaluation of gastroesophageal reflux disease.[14,15]

Management of patients such as the two described above includes adherence to a diet that is free of wheat, rye, and barley. Oats, while found to be tolerated by patients with celiac disease, remain controversial, as there is often cross contamination with other grains.[16,17] In both cases nutritional consultation was obtained. Screening studies for additional malabsorption of vitamins and minerals should be sent. These include iron, folate, B12 as well as fat soluable vitamins. Because of the higher incidence of osteoporosis in celiac disease, all patients should be screened.[18] Substitute flours may not be fortified with typical B vitamins, and as a result slow acquired deficiencies can occur even a decade after diagnosis and strict dietary adherence.[19] As a result, a multivitamin supplementation is recommended.[19]

Monitoring for response to dietary changes, as well as adherence to, may include repeat serologic screening.[20] Serum IGA antigliadin and tissue transglutaminase levels will fall in 2-3 months of adherence to a strict glutin free program. However these declines do not predict reliably the recovery

of the pathologic findings of villous atrophy in patients.[21] The European Society for Pediatric Gastroenterology and Nutrition require only clinical improvement with the diet to make the diagnosis of celiac disease.[22] Because villous atrophy can be found even after subjective response and improvement in serological markers, this requirement remains controversial. The pathologic findings can be difficult to demonstrate due to the patchy nature of the disease.[23] The findings of villous atrophy are characteristic but not specific only to celiac disease.[24] Among other diseases that have shown similar histopathology include intestinal lymphoma, Giardiasis and HIV.[24]

Use of the serologic markers is not reliable for measuring short transgressions from this strict dietary regimen.[25] In the two cases described above, histopathological diagnosis was never obtained. Biochemical abnormalities as well as demonstrably high serologic studies found on initial diagnosis were found to have completely corrected on strict gluten free diet. The patients continue on appropriate nutritional supplementation and routine health maintenance screening.

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