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Case Report

Male Infertility in Duodenitis due to Celiac Disease

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Abstract

Patients with celiac disease may present or develop extra-intestinal changes, including infertility, during the clinical course. This appears to be more common in female patients. A 36 yr-old male was investigated for infertility. In this case, diagnosis was initially delayed because of misinterpretation of the pathological label of "duodenitis". Celiac disease was eventually diagnosed after his clinical, laboratory and histological response to a strict gluten-free diet. Three years after his initial diagnosis of celiac disease, testicular atrophy with altered sperm analyses was defined. Male infertility may occur in celiac disease, even after resolution of biopsy and nutritional changes with a gluten-free diet.

Keywords: Male Infertility; Celiac Disease; Primary and Secondary Infertility; Testicular Atrophy; Duodenitis

Introduction

Celiac disease is an immune-mediated mucosal disorder of the small intestine thought to be precipitated by gluten exposure in genetically susceptible persons. Usually, celiac disease is associated with diarrhea, malabsorption and weight loss along with different extra-intestinal manifestations [1,2]. Reproductive changes have been noted [3], although systematic studies comparing both sexes have been limited. An accurate diagnosis of celiac disease followed by treatment with a strict gluten-free diet may lead to a successful pregnancy for some couples, in spite of prolonged periods of infertility prior to diagnosis.

Some have estimated that infertility may occur in up to 20% of couples in the general population. Even a definition of infertility and criteria for diagnosis of infertility may not be universally accepted. A 12 month period of inability to achieve a successful pregnancy is often considered before initiating studies to determine a cause. Since studies have suggested that celiac disease occurs in about 1 to 2% of the general population, or higher, depending on the methods of screening [4], infertility may be a potentially significant issue in couples affected by celiac disease. Here, in the present case, some of these issues are reviewed focused on "male factors" that may play a role for infertile couples.

Case Report

A 36-yr old environmental organic chemist of Indian descent presented with intermittent epigastric pain, episodic diarrhea and weight loss of 5 kg over approximately 2 years. His family physician discovered an iron deficiency anemia and a barium study of his upper gastrointestinal tract showed "duodenal inflammatory

changes" but no definite ulcer. Past history revealed only an appendectomy 20 years earlier and prior treatment with oral iron. His exam was normal, weight 63 kg. Upper endoscopy in his rural hospital revealed gastric erosions with a normal-appearing duodenum. Biopsies were interpreted to show acute and chronic "non-specific duodenitis", but on review several months later after referral, note was made of increased numbers of intraepithelial lymphocytes as absence of villi had been originally attributed to poor biopsy orientation thought to be due to sub-optimal embedding during preparation. Gastric antral mucosal biopsies revealed superficial inflammatory changes with normal gastric body mucosal biopsies. Stains for *Helicobacter pylori* were negative. He was treated with omeprazole 20 mg orally for a month. Oral iron was also discontinued. This led to complete resolution of his pain.

He was referred two months later because of recurrent and persistent diarrhea after travel to England. This was associated with a further 5 kg weight loss and did not resolve with Imodium or avoidance of milk products.

He complained of loose liquid-only non-bloody stools up to 12 daily. There was no fever or use of antibiotics. Blood studies revealed iron deficiency with a serum ferritin of 5 (normal, 22-447 ug/L) although his hemoglobin was normal 138 (normal, 135-180 g/L). Fecal bacteriology and parasite studies were negative. Peripheral blood smears for parasites, including malaria, were negative. A physical exam was normal but his weight had fallen further to 59 kg. Flexible sigmoidoscopy and rectal mucosal biopsy were normal. Blood studies revealed a normal sedimentation rate, electrolytes, liver chemistry tests, thyroid function studies, blood sugar but serum proteins were also decreased to 52 (normal, 60-80 G/L) with hypoalbuminemia of 27 (normal, 35-50 g/L).

Upper GI endoscopy appeared to be normal with no gastric erosions and normal-appearing duodenal mucosa with no scalloping. Biopsies of gastric mucosa showed superficial antral gastritis with normal gastric body mucosa. Stains for Helicobacter pylori were negative. Duodenal mucosal biopsies were severely abnormal and revealed typical changes of untreated celiac disease with loss of villi, crypt hyperplasia, increased mitotic figures and increased intra-epithelial lymphocytes (Marsh 3). A strict gluten-free diet was recommended and within 6 weeks, his bowel habit was normal, weight had increased to 63 kg and all of his blood studies had normalized, including his serum proteins (total protein, 65; and serum albumin, 36).

Three months later, he weighed 72 kg. Repeat endoscopy was normal along with gastric biopsies. Further duodenal biopsies showed normalized architecture with only minimal inflammatory changes including a slight increase in intra-epithelial lymphocytes consistent with a positive gluten-free diet response [12]. After 2 years, his physical exam appeared to be normal with a weight increase to over 80 kg. Blood studies were all normal including his serum iron and albumin.

Three years later, he was referred by his family physician to a urologist and endocrinologist to address an independent concern that celiac disease might be causing infertility. He had remained on his gluten-free diet.

His weight was stable. The couple already had a 7 yr old daughter following an initial healthy and uneventful pregnancy. He was a non-smoker, non-drinker and denied use of hot tubs, steam baths or saunas. He did not use marijuana, other drugs or prescription medications. There was no history of significant childhood infections, including mumps. He was now managing his own environmental firm, worked in an office role only and denied exposure to chemicals, toxins or heat. Investigations of his wife had already excluded factors associated with female infertility. His physical exam, however, demonstrated a small right testicle, confirmed with urological evaluation. His prostate exam was normal.

Scrotal ultrasound showed a left-sided varicocele and right testicular atrophy. Three different sperm analyses revealed low to normal volumes with ranges from 0.8-2.8 ml (normal > 1.5 ml), motility ranging from 10% to 58% (normal, 32%), sperm counts under 6 million/ml (normal > 15 million/ml) and normal sperm morphology ranging from 12% to 17% (normal > 4% normal forms). Hormone studies, including thyroid studies and serum gonadotrophins were normal, except for a marginally elevated serum FSH. It was believed that infertility was not due to his celiac disease and treatment of his varicocele by embolization or ligation was offered for consideration if the infertility persisted over more than a year.

Discussion

Celiac disease is an immune-mediated small intestinal mucosal disorder that may be triggered by ingestion of gluten in genetically susceptible persons [1,2]. Although it usually causes diarrhea, malabsorption and weight loss, atypical presentations may occur

often associated with different extra-intestinal changes, including skin and other diseases, such as dermatitis herpetiformis. Diagnosis is usually straightforward but is generally based on small intestinal mucosal biopsy that demonstrates the characteristic features of untreated celiac disease. Screening serological studies may be helpful. In addition, since many other causes of sprue-like intestinal disease may occur [13], improvement with a strict gluten-free diet is critical. In this patient, convincing clinical changes occurred with resolution of his diarrhea and dramatic weight gain. In addition, blood studies normalized and repeated biopsies of his small intestine returned to normal. Here, diagnosis was delayed for about 2 months because his initial biopsies done in a rural hospital were poorly oriented. This issue has been previously noted [14] and the current case demonstrates the need for care in biopsy processing and recognition of preparation-related artifacts during histological evaluation so that over- and under-interpretation does not lead to misdiagnosis. In this situation, external review of biopsy material or re-biopsy may be useful.

Other associated non-intestinal disorders may occur in celiac disease that may lead to infertility including pancreatic insufficiency with diabetes and "autoimmune" islet cell changes [5,6] as well as other endocrine disorders [7], including "autoimmune" thyroid, parathyroid, adrenal and pituitary disease [8-10] along with ovarian failure in females [11]. In the present case with apparent secondary male infertility, testicular atrophy was suspected that caused his altered sperm analysis. In this case, sperm analyses produced variable, but definitely abnormal results. Clearly, celiac disease may impact male fertility through several possible mechanisms, including impaired nutrition due to malabsorption. Here, however, previous changes associated with his celiac disease were no longer evident. Indeed, his weight was stable and all blood and intestinal biopsy studies were completely normal on a gluten-free diet.

In conclusion, male infertility may occur in biopsy-defined celiac disease. In some cases, this may reflect an associated autoimmune endocrine disorder, however, in the present case infertility was independent of the healed intestinal disease.

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