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Isotretinoin-associated Celiac Disease

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Abstract 27-yr old female marathon runner presented with profound fatigue and reduced exercise tolerance due to an iron deficiency anemia subsequent to treatment with isoretinoin for acne. Subsequent histologic and serologic studies revealed small bowel biopsies with histopathological features of celiac disease and an increased IgA tissue transglutaminase level. Isoretinoin use was terminated and after treatment with a gluten-free diet and oral iron, her symptoms resolved with normalization of her serological studies. Now, she remains completely well on a gluten-free diet alone and recently completed a full marathon.

Keywords: *Isoretinoin, retinoic acid, celiac disease, intestinal inflammation, colitis*

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1. Introduction

Celiac disease is an immune-mediated enteropathy developing in genetically prone persons [1]. Often, the clinical disorder is characterized in adults by diarrhea and weight loss, however, in some, an occult intestinal inflammatory process occurs with few or no intestinal symptoms. In some, for example, iron deficiency anemia may be the sole presenting clinical feature of adult celiac disease [2].

Many other causes for the characteristic, albeit non-specific, histopathological features of untreated celiac disease have been reported, particularly drug-induced forms of enteropathy [3]. For example, one recently reported discovery of a drug-induced small intestinal disease was olmesartan enteropathy [4]. Olmesartan has been used for treatment of hypertension as an angiotensin II receptor antagonist. In time, some patients may develop diarrhea and small intestinal biopsies show inflammatory changes virtually identical to untreated celiac disease. Discontinuation of the drug, rather than a gluten-free diet alone, usually leads to resolution of the diarrhea and histopathologic changes in the small bowel mucosa, however, the precise mechanism that leads to these clinical and pathological features is not known.

In separate literature, isotretinoin has also been thought to independently cause diffuse and extensive small intestinal inflammatory changes or a non-specific but severe pan-enteritis, even with ulceration [5]. To date, some limited case-control studies on celiac disease were not able to establish a clear relationship with isoretinoin use [6,7], similar to studies of isoretinoin in patients with inflammatory bowel disease [8,9]. The current report details a woman treated with isotretinoin for acne. Soon after initiation of the medication, she reported marked fatigue with severe iron-deficiency anemia. Subsequent studies showed features typical of adult celiac disease and cessation of the medication along with a gluten-free diet led to resolution.

2. Case Report

A 27-yr-old university student was evaluated in January 2011 from the hospital emergency ward because of fatigue developing progressively over the previous 4 months. She was a pescatarian (vegetables, fish, eggs, but no meat or poultry) from infancy, and she was sufficiently well to run full marathons, the last in July 2010. Since then, she had less energy for her usual activities, ceased running on a treadmill because of early fatigue and was having difficulty walking up hills. She was on an oral contraceptive for about 10 years with no difficulties and her menstrual periods were scant. There was no rectal bleeding or other intestinal symptoms. She estimated a 1 kg weight loss since initiation of isotretinoin 20 mg daily for acne over the past 6 months. Initial evaluation revealed that she appeared healthy with mild pallor. She was significantly anemic with a hemoglobin of 72 g per L and a mean corpuscular volume (MCV) of 74 fL. Peripheral smear revealed hypochromic and microcytic red blood cells. Her serum iron was 5 umol per L (normal, 7 to 32) with a saturation of 6% (normal, 20 to 55%) and her serum ferritin was 2 ug per L (normal, 20 to 300). Blood chemistries, including liver tests and serum albumin, were normal, but a serum tissue transglutaminase IgA antibody test was positive (45 units, normal, < 20 units). Occult blood test was negative. Endoscopic evaluation revealed scalloped duodenal mucosal folds and a duodenal biopsy showed severely abnormal architectural features of untreated celiac disease with shortened and rudimentary villi, hyperplastic crypts and increased inflammatory mucosal changes with intra-epithelial lymphocytosis (i.e., Marsh 2-3). She was treated with a gluten-free diet and iron supplements.

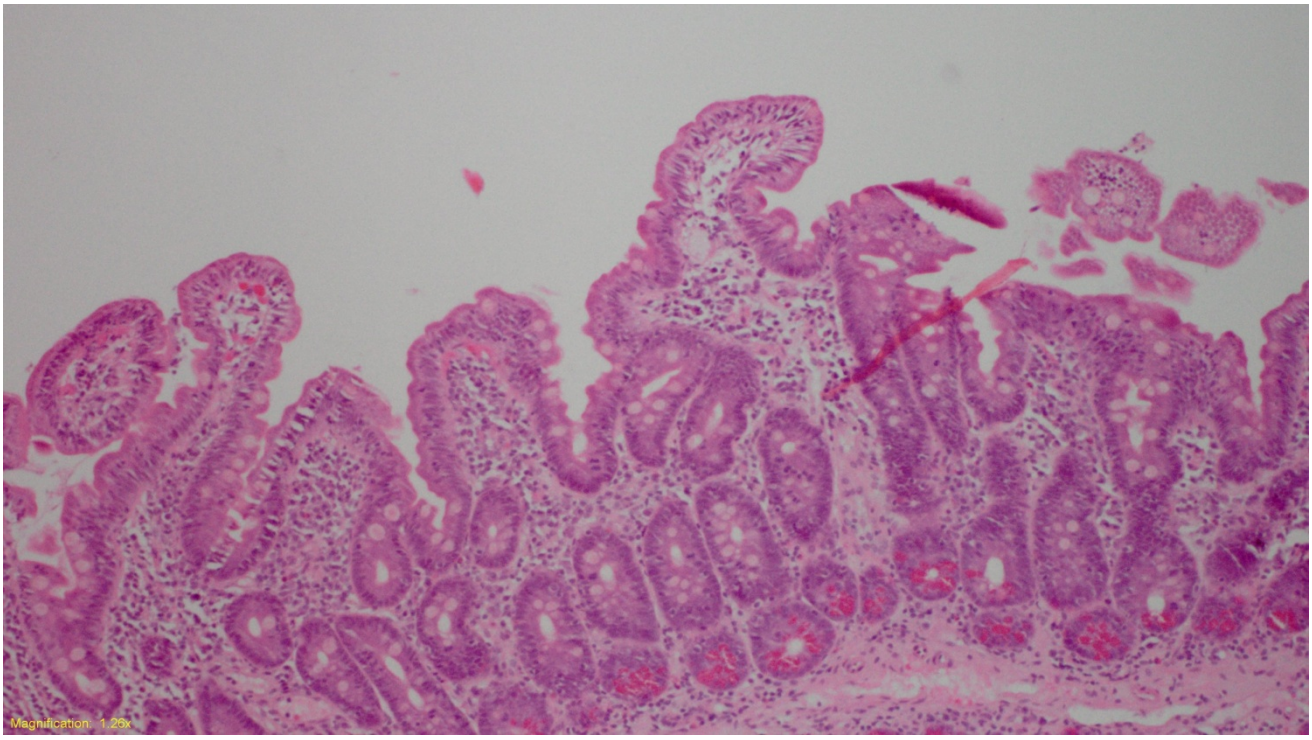

Figure 1. Duodenal biopsy showing poorly formed villi and focal areas of increased crypt lengthening with increased inflammatory cells. Hematoxylin and eosin, X 10

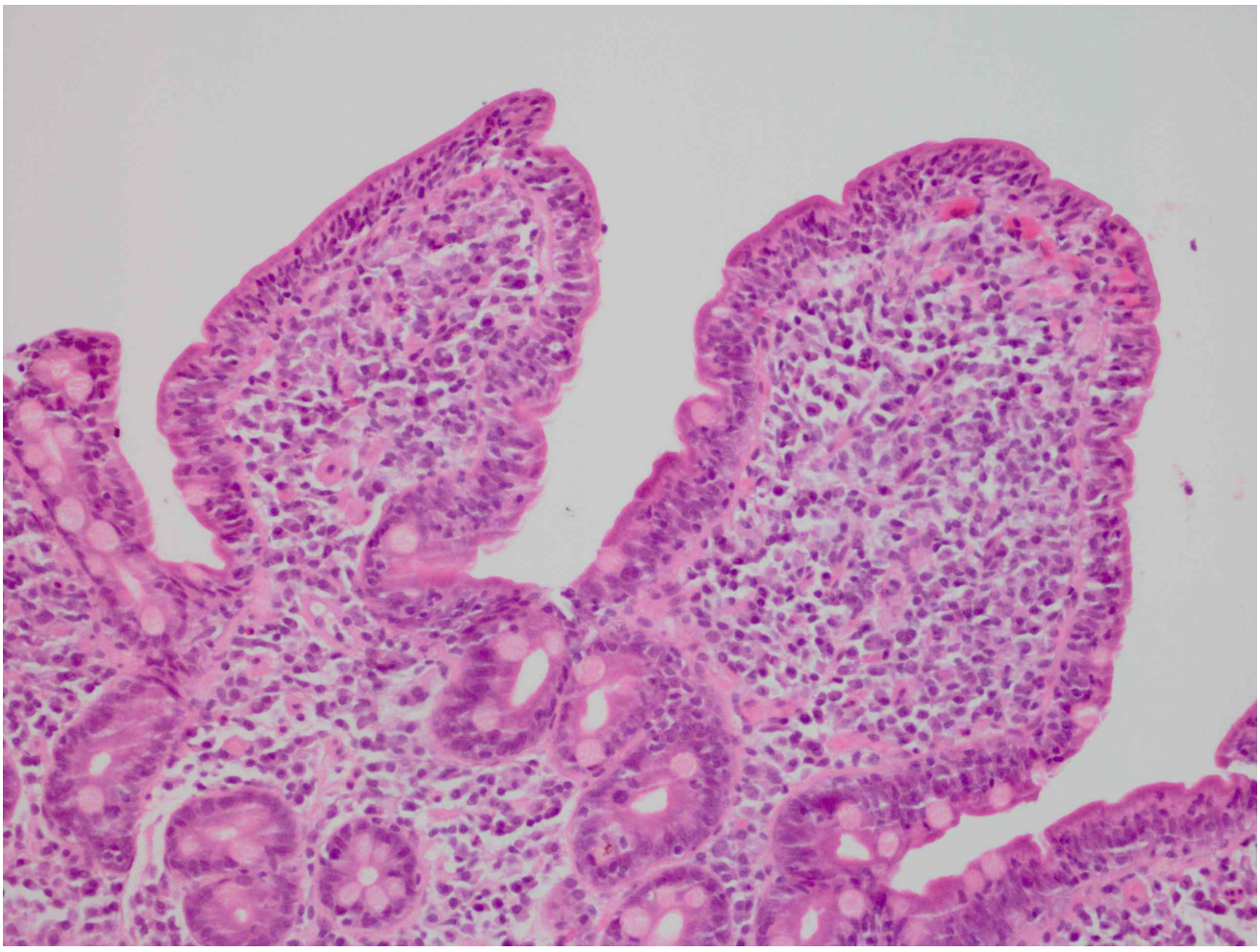

Figure 2. Duodenal biopsy showing marked inflammatory change with increased lamina propria inflammatory cells along with increased numbers of intra-epithelial lymphocytes. Hematoxylin and eosin, X 20

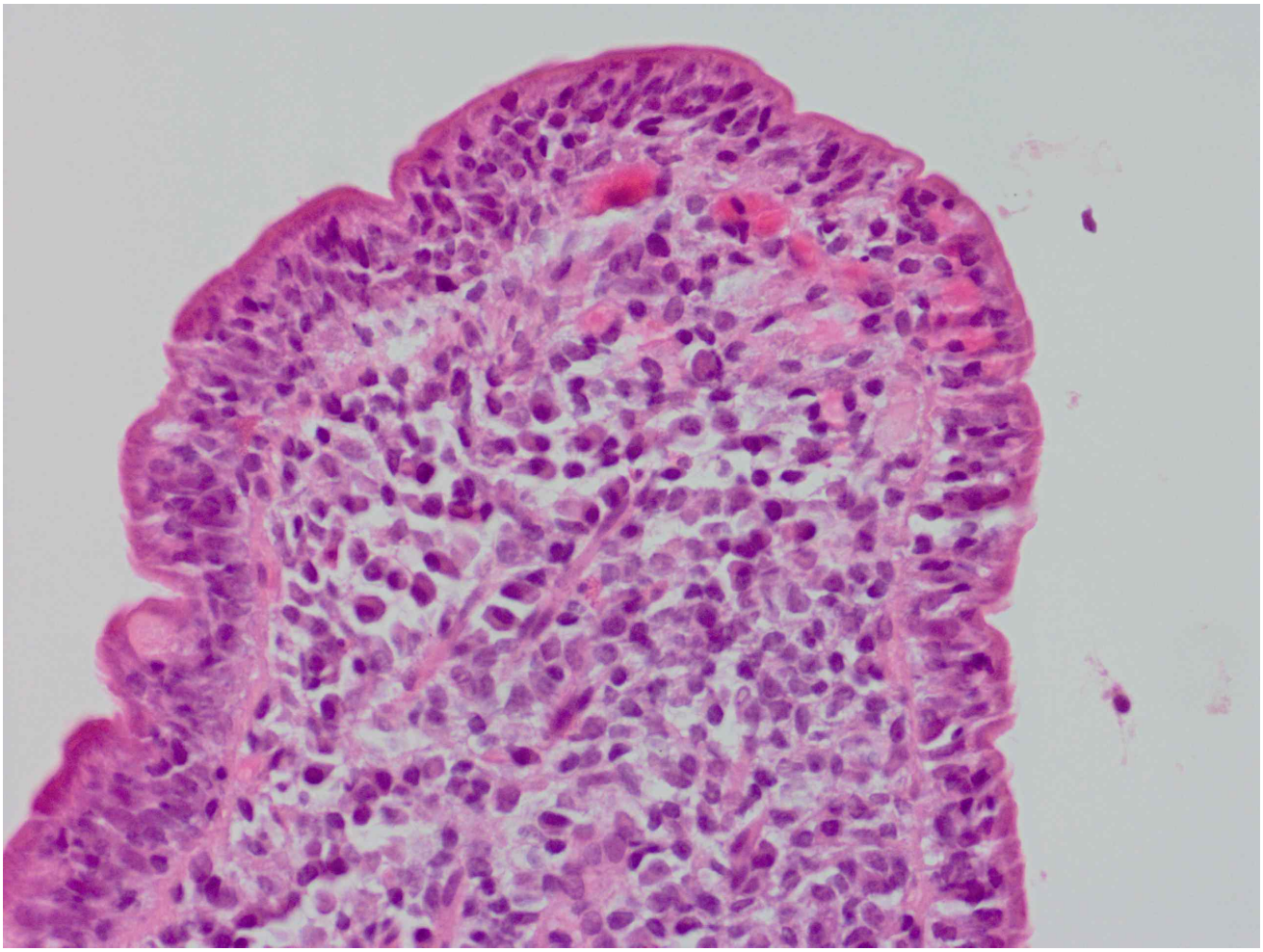

Figure 3. Duodenal biopsy at high power showing inflammatory changes with increased numbers of intra-epithelial lymphocytes. Hematoxylin and eosin, X 40

The use of isoretinoin was terminated. By July 2011, she appeared perfectly healthy with resolution of her fatigue and iron deficiency anemia. Her IgA tissue transglutaminase assay was also normal at 8 units. In February 2016, she was clinically well and had resumed her marathon running. Her hemoglobin was 130 g per L, serum ferritin 75 ug per L and IgA tissue transglutaminase assay 9 units. She now actively trained and recently completed a full marathon.

3. Discussion

Isotretinoin was initially linked to small and large intestinal inflammatory disease, in particular, a non-specific pan-enteritis [5]. In some, a severe colonic ulcerative inflammatory process was described, specifically labeled as ulcerative colitis, leading some to not only consider his drug as a cause of colitis, but alternatively, a factor that could lead or predispose to development of ulcerative colitis.

In the present patient, severe iron deficiency anemia, marked fatigue and impaired exercise tolerance led to eventual definition of underlying adult celiac disease. Diagnosis of celiac disease after presentation with even an isolated iron deficiency anemia is not unusual [2].

After onset of treatment with isoretinoin for acne, she concomitantly developed profound and severe symptoms suggesting that isoretinoin either directly caused celiac disease, or more likely uncovered or precipitated clinical features of occult celiac disease. Interestingly, biopsy changes were accompanied by elevated tissue transglutaminase levels, typical of the serological changes of adult celiac disease. Clinical recovery and resolution of her iron deficiency state along with abnormal serological changes occurred completely with iron and a gluten-free diet allowing her to return to her pre-illness exercise level with only a gluten-free diet.

As suggested by earlier reports, most patients with acne treated with the drug, isoretinoin, have no difficulties tolerating this medication [6,7], however these population-based studies should not dissuade clinicians from considering this medication in the ever-growing list of drugs that may cause or precipitate onset of celiac disease.

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