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Sprue-Like Intestinal Disease Complicated by Inclusion Body Myositis

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Abstract A woman with long-standing weight loss and malabsorption demonstrated a severe sprue-like enteropathy. She insidiously developed persistent and progressive muscle weakness caused by inclusion body myositis, an uncommon muscle disorder. Treatment with a gluten-free diet, steroids, calcium, zinc and vitamin supplements, including empirical vitamin E resulted in weight gain, but failed to histologically improve her small intestinal mucosa or the muscle weakness which became profound. The myopathic process could reflect a co-existent autoimmune disorder, or, possibly a direct result of long-standing and superimposed nutrient deficits. An alternative explanation may be a hitherto unrecognized syndrome manifested as inclusion body myositis and a form of sprue-like enteropathy.

Keywords: *celiac disease, gluten enteropathy, small bowel ulcer, non-granulomatous ulcerative jejunitis, myopathy, inclusion body myositis*

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1. Introduction

Celiac disease is an immune-mediated small intestinal disorder that responds to a gluten-free diet [1,2]. Sometimes, a histological response to a gluten-free diet fails to occur so that the gluten-dependent nature of celiac disease cannot be documented. Although the term refractory celiac disease has been used, the term sprue-like enteropathy is a more precise label since no initial histological response to a gluten-free diet had ever been demonstrated [3]. Other systemic diseases may complicate celiac disease, including neurological diseases [4,5], often clinically characterized by muscle atrophy and muscle weakness along with a number of primary muscle disorders. These include rhabdomyolysis [6], muscular dystrophy [7] and, rarely, some inflammatory myopathies, specifically, dermatomyositis, polymyositis and inclusion body myositis [8,9,10,11].

Of these, inclusion body myositis is rarely reported with intestinal disease, but may be suspected by proximal and, sometimes, distal muscle weakness, muscle enzyme changes, neurophysiological and/or electromyographic evidence of a myopathy, and finally, failure to improve or worsening with glucocorticoids [8,10]. Pathological features in skeletal muscle biopsies are well detailed elsewhere and may provide specific diagnostic changes with light and/or electron microscopy. These are rimmed vacuoles, intranuclear and/or intracytoplasmic inclusions along with micro-tubular microfilaments in the inclusions [8]. In celiac disease, a gluten-free diet and vitamin E supplementation were anecdotally reported to also improve the muscle disease, including abnormalities detected in muscle biopsy [12]. In the present report, a patient with sprue-like intestinal disease and malabsorption developed muscle weakness due to inclusion body myositis. The muscle weakness progressively worsened despite corticosteroids, a gluten-free diet and vitamin E supplements.

2. Case Report

A 26-yr-old female was initially seen August 1959 by a surgical service in a community hospital for intermittent abdominal pain and diarrhea with 10 kg weight loss over 4 months. A focal distal jejunal stricture with ulceration was defined on a barium study of the small bowel. A localized segmental resection of an estimated 30 cm was done including the jejunal ulcer. The specimen showed inflammation with sprue-like architectural changes but no granulomata or neoplastic disease. Adjacent lymph nodes revealed reactive changes only. Further studies were not done at that time. No other specific treatment was provided.

Subsequently, she was well until 1985, except for intermittent bloating and bulky stools thought to reflect her shortened small intestine. Because of her reduced weight (42 kg), she was reviewed. Physical exam revealed her to be thin and pale, but otherwise normal. Blood studies demonstrated a low hemoglobin of 11.2 g per L, a low serum calcium of 1.77 (normal, 2.12 to 2.62 mmol per L) and a normal serum albumin. A serum carotene, however, was very low at 0.1 (normal, 1.1 to 5.6 mmol per L)

consistent with impaired absorption. Her prothrombin time was also prolonged and serum zinc level was reduced. Serum iron was reduced. Thyroid studies, transaminases, red cell folate and vitamin B12 were normal. Fecal fat was increased to 28.6 (normal, < 7 g per day). Fecal studies for bacterial agents and parasites were negative. A small bowel biopsy (duodenum) confirmed typical changes of untreated celiac disease with a severely "flattened" mucosa (i.e., crypt hyperplastic villous atrophy, Marsh 3). No infectious agents were seen. Anti-gliadin antibodies were weakly positive. She was placed on a gluten-free diet and treated with calcium, vitamin D, zinc and empirical vitamin E supplements. On a strict gluten-free diet, her weight increased to 48 kg, but her calcium studies were unchanged with a 25-hydroxy-vitamin D level of 17 (normal range, 40 to 185 nmol per L), so increased calcium and vitamin D were provided. Bone scan showed some demineralization.

In 1988, she was first seen in our hospital neuromuscular unit. She had developed poor balance, especially with walking. She required support or a shopping cart in stores to prevent falls. There was no family history of neurological or neuromuscular disease. Exam revealed proximal muscle weakness while electro-physiologic studies suggested a diffuse neuromuscular disorder. A CT contrast scan revealed some minimal cerebellar vermis atrophy but no focal lesion. No diarrhea was present and her weight had increased to 50 kg. Biopsies of the duodenum, however, were severely abnormal with no evidence of histological improvement, so the gluten-free diet treatment was continued. A muscle biopsy of the biceps brachia for both light and electron microscopy was done. Changes consistent with inclusion body myositis were seen, including inclusions within and adjacent to muscle fibers. Inclusions were variable in size along with osmiophilic granules. Membranous whorls were also present within inclusions and adjacent to the nucleus. Compression, distortion and disruption of the normal myofibrillar pattern was also present. She was treated with added prednisone, but muscle weakness worsened.

She was first referred to our intestinal diseases service in 1990 still on a gluten-free diet, supplemental vitamins including D and E, calcium, zinc and prednisone. Prior to review, muscle weakness had progressed and was profound. Diarrhea had resolved and her weight was 50 kg. Laboratory studies revealed a normal hemogram with a hemoglobin of 131 (normal, 120-160 g per L), calcium 2.07 (normal, 2.15-2.64 mmol per L) and carotene 0.4 (normal, 1.0-4.0 umol per L). Albumin, prothrombin time, iron studies including ferritin, red cell folate and vitamin B12 were all normal. Repeat duodenal biopsies were not improved with persistent severe histological changes, specifically, continuing crypt hyperplasia and villous atrophy, but her gluten-free diet was continued in a long-term care facility. Over the next 3 years, she gradually deteriorated with recurrent weight loss, progressive muscle weakness and dementia.

3. Discussion

Celiac disease may be complicated by several other systemic disorders [1]. These may include neurologic diseases [2] that may secondarily cause muscle weakness and atrophy [2] as well as primary myopathic processes that may even be the presenting clinical feature of underlying or occult celiac disease. These include inclusion body myositis [8,10,12], an uncommon inflammatory myopathy, observed in the present patient and characterized largely by progressive skeletal muscle disease reflected in progressive weakness. This patient presented with difficulties walking attributed to proximal muscle weakness, myopathic changes on physiologic studies and muscle biopsy features demonstrated using light and electron microscopy to be characteristic of inclusion body myositis.

Her muscle disorder developed in the setting of long-standing intestinal disease, likely present for decades after an initial presentation with a focal jejunal ulcer requiring surgical resection. Limited intestinal symptoms appeared to persist for years before her small intestinal mucosal disease was treated. In spite of a strict gluten-free diet (and later, prednisone for her muscle disease), she had persistent and difficult to manage nutritional deficits, notably iron, zinc, calcium as well as evidence for severely impaired absorption of dietary fat and fat soluble vitamins, specifically vitamin A, vitamin D and vitamin K depletion. Although her weight had improved along with some laboratory blood tests, biopsies remained abnormal despite a strict gluten-free diet. This may have reflected a histologically "slow-to-respond" form of celiac disease or another, as yet, hitherto undescribed or unidentified sprue-like enteropathy associated with this uncommon, but distinctive form of myopathy, inclusion body myositis.

Our patient's small intestinal biopsies did not appear to histologically respond to a gluten-free diet, despite more than 5 years of treatment after her initial biopsies. This is unusual for celiac disease since the vast majority should respond within a period of 1-2 years [13]. Without a response to a gluten-free diet, it was not possible to unequivocally diagnose this patient with celiac disease, a known gluten-dependent disorder. Treatment with concomitantly administered steroids for her muscle disease also appeared to have no effect. For some, such a scenario might be lead to the label of "refractory" or "non-responsive" celiac disease. Indeed, it is conceivable that her long-standing and untreated intestinal disease with multiple nutritional deficits might predispose to a "treatment-resistant" form of celiac disease. Alternatively, celiac disease may not have been present at all. This so-called "wastebasket" group of patients with biopsy changes that mimic untreated celiac disease have more precisely been defined as "unclassified sprue" or "sprue-like intestinal disease" [14]. A number of different or heterogeneous causes have been identified that may histologically look like celiac disease [14]. Infectious agents are particularly notorious [14] along with a number of novel pharmaceutical agents, such as olmesartan [15].

Temporally, the intestinal disorder pre-dated (by decades) the clinical appearance of the myopathy. Because of its inflammatory nature defined pathologically by muscle biopsy, it is likely in this case that inclusion body myositis represented another extra-intestinal autoimmune manifestation of an intestinal disease. Indeed, immune mechanisms have been previously suspected by others [16,17,18,19] to play a role in inclusion body myositis.

Alternatively, long-standing macronutrient and micronutrient deficiencies caused by a severe and extensive pan-malabsorptive process could conceivably cause the development of an insidious and progressive myopathic process leading to ongoing and profound muscle weakness. In a prior report [12], a myopathic process, similar to inclusion body myositis, has been described in celiac disease attributed to vitamin E deficiency along with its reversal with vitamin E. Unfortunately, our patient with sprue-like intestinal disease was also empirically treated with prolonged vitamin E, but her weakness was not reversible as she continued to progress with worsening weakness, and eventually, dementia.

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