INTRODUCTION

Dermatitis herpetiformis (DH) is a chronic, recurring skin disease and presents with pruritic papulovesicles mainly on extremities and buttocks [1]. It usually is associated with celiac disease although non-celiac gluten sensitivity syndrome has been reported to cause DH [2]. This dermatitis usually responds to a gluten free (GF) diet but when this fails the only treatment option is long-term dapsone [3]. Patients with DH and celiac disease share three features: same histocompatibility antigens, presence of circulating IgA against transglutaminase autoantigens and clinical remission on a GF diet. Both diseases exhibit tissue transglutaminase-specific autoantibodies in the small bowel mucosa where B-lymphocytes are first activated [1]. Dapsone-dependent GF diet-refractory DH was present in 7/403 (1.7%) patients in a recent study [3]. Dermal IgA was present in 5/6 GF diet-refractory vs. 3/16 GF diet-controlled DH patients. Duodenal mucosal IgA was absent in all 5 GF diet-refractory and in 7/8 controls patients which suggests that the IgA is being produced elsewhere in the body. We hypothesize that gluten-associated antigens produce long-lasting memory B-cells in the reticuloendothelial system and this causes autoantibodies and persistent DH. We theorize that gluten-associated antigens activate long-lasting memory B-lymphocyte cells that produce autoimmune antibodies and this may perpetuate dermatitis herpetiformis. Endorphins produced via up-regulation by low dose naltrexone may reduce this B-cell activity.

CASE DESCRIPTION

A 37 years old Caucasian woman with a past medical history of chronic joint pain from Ehlers-Danlos syndrome had a 2 year history of a pruritic vesicular rash with underlying erythema on the extensor surfaces of her knees and elbows and the dorsal surface of her neck. She also had 2 year history of postprandial bloating. An allergist diagnosed celiac disease by an abnormal tTG antibody level although duodenal biopsies were not obtained. A GF diet was initiated and the abdominal bloating resolved. Vesicles on the knees and elbows (Figure 1A) disappeared but the erythema persisted. The neck rash and itching continued (Figure 1B). Expert review (MS) of the photographs determined that the rashes were characteristic for DH.
Figure 1A. Dermatitis herpetiformis on elbow prior to the gluten free diet.

Figure 1B. Persistent dermatitis herpetiformis on the left posterior neck despite adherence to the gluten free diet.

The patient had general concerns about her disease and was evaluated by a gastroenterologist (LW). Duodenal biopsies and the tTG level were normal. Owing to prior experience with LDN giving pain relief to Ehlers-Danlos syndrome patients [5] and with the Internet-based observations that DH is responsive to LDN, naltrexone was prescribed. Dosing started at 1 mg/day/per os and was increased by 1 mg every 4 days to get to 4.5 mg/day. After 2 weeks, the patient reported improvement in neck irritation and resolution of the redness on her knees and elbows. At the 2 month visit, the lesions had nearly resolved and at the 3 month visit there was complete resolution. The patient has continued LDN for over 2 years without recurrence of DH and has noted improvement in Ehlers-Danlos syndrome joint pain.

DISCUSSION

Chronic relapsing pruritis and papulovesicles are the hallmarks of DH [1]. The diagnosis can be confirmed by histology and immunofluorescence showing granular IgA deposits in peri-lesional skin [1], as well as detection of autoantibodies against transglutaminase. Celiac disease is the primary cause of DH and is an autoimmune disorder related to recognition of peptides by HLA molecules, post-translational modifications required for optimal peptide binding, and immune mechanisms which lead to tissue damage [1,6]. B-cells are responsible for autoantibody production in celiac disease [7]. Autoimmune disorders such as diabetes and thyroiditis may appear after celiac disease has been diagnosed and treated with a GF diet [6,7]. Adherence to the diet may have no effect on the progression of these disorders suggesting other factors are involved [7].

CONCLUSION

This case report demonstrated that GF diet refractory DH could be placed into remission with LDN. Randomized controlled trials showed that low dose naltrexone is effective in other inflammatory diseases including Crohn’s disease and fibromyalgia [8,9]. We theorize that gluten-associated antigens produce long-lasting memory B-cells that lead to continued autoantibody production and refractory DH. Endogenous opioid peptides (e.g. enkephalins and endorphins) are present in the gastrointestinal tract and endocrine cells and help modulate immune responses including B-cell production [4,10-12]. Up-regulation of tissue met-enkephelin and opioid receptors can be induced by a rebound effect from administration of short-acting, low dose naltrexone (LDN) [13]. The endorphin met-enkephelin B-cell activity as has been demonstrated in cell culture studies [4]. Reduction of IgA production by
abnormal memory B-cells produced in the thymus \cite{14} may be the mechanism whereby LDN is effective in reducing autoimmune diseases including DH.

**REFERENCES**