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CASE REPORT

Perineal Cutaneous Basal Cell Carcinomas in Patients with Familial Seronegative Celiac Disease: Report of Three Cases

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ABSTRACT:

Introduction: Celiac disease (CD) is an autoimmune enteropathy due to hypersensitivity to consumed gluten. Patients can present with gastrointestinal and systemic symptoms. CD often runs in families. Studies have reported multiple subtypes of CD including at least one seronegative variant. The cutaneous manifestations of CD remain to be delineated; some cases of seropositive CD are associated with dermatitis herpetiformis.

We report three patients with a longstanding history of personal and familial seronegative CD who developed basal cell carcinoma (BCC) of the perineum.

Discussion: We report three adult patients with a diagnosed personal history of seronegative CD and a family history of CD, who presented with BCC of the perineum. The mechanism by which CD causes BCC remains to be defined. Physicians should consider evaluating patients with skin cancer located in the perineum for CD.

Keywords: Celiac, seronegative, familial, Marjolin, basal cell carcinoma, BCC

Introduction:

Celiac disease (CD) is an autoimmune enteropathy due to hypersensitivity to consumed gluten and possibly related cereal proteins. Patients can present with gastrointestinal symptoms including diarrhea and weight loss, as well as fatigue, iron-deficiency anemia, vitamin D deficiency, depression, and unexplained hypocalcemia. Gastroenterological lesions due to CD are characterized by the flattening of the small intestinal mucosa with a lymphocytic infiltrate, increased mucosal cell proliferation with crypt hyperplasia, and reduced enterocyte differentiation (1, 2). Multiple studies have shown that celiac disease has a strong hereditary component. Human leukocyte antigen (HLA)-DQ2 is present in more than 90% of patients with CD, while HLA-DQ8 is present in about 5% of patients. However, expression of HLA-DQ2 or HLA-DQ8 molecules is not sufficient since only about 1% of individuals who carry either of these alleles develop the disease (3). Furthermore, a systematic review of the prevalence of CD in generally Western European populations estimated that the prevalence of CD in first-degree relatives of patients with biopsy-proven CD can be as high as 20% (4). Another study reported that 22% of patients with CD had siblings who also had CD (5).

Although the clinical manifestations and histological changes observed among patients with Celiac disease are similar, studies have revealed multiple subtypes of CD. A disciplinary task force has suggested three subtypes of CD: classical CD (signs and symptoms of malabsorption), nonclassical CD (symptomatic but without signs of malabsorption), and subclinical CD (diagnosed in asymptomatic persons as a part of screening) (6). Patients can develop CD as children or adults, though classical CD is more associated with the pediatric population (7,6). Notably, studies have demonstrated that the adult-onset form of CD has a stronger association with other autoimmune diseases, including type 1 diabetes mellitus and Sjögren syndrome, compared to the pediatric-onset form; although both forms of the CD are associated with higher rates of autoimmune disease (8, 9). One study found that the overall burden of five autoimmune diseases (rheumatoid arthritis, juvenile rheumatoid arthritis/juvenile idiopathic arthritis, alopecia areata, insulin dependent diabetes mellitus, hypothyroidism) in CD cases was 15%, compared to the estimated population prevalence of 3–5% (9). Autoantibodies commonly associated with CD include the IgA anti-tissue transglutaminase and anti-endomysial antibodies. However, some patients with CD have a seronegative variant, which is defined as the lack of such antibodies in the presence of positive histology on duodenal biopsy samples, mild villous atrophy, and uneven brush border. Notably, the seronegative variant of CD is also associated with HLA-DQ2 and/or DQ8 (10). Regarding the pathogenesis of seronegative CD, studies have speculated that this may be due to the formation of mucosal deposits of tissue transglutaminase (tTG)/anti-tTG immuno-complexes in the GI tract, which prevent the passage of anti-tTG into the bloodstream (11).

CD is also associated with multiple types of gastrointestinal cancer, most notably non-Hodgkin lymphoma, enteropathy-associated T cell lymphoma (EATL), and small cell adenocarcinoma (12, 13). Although the mechanisms responsible for the development of malignancies are not known, it has been suggested that increased intestinal permeability to environmental carcinogens, chronic inflammation, chronic antigenic stimulation, release of proinflammatory cytokines, immune surveillance problems, and nutritional deficiencies caused by the disease may play a role (14). Several studies have investigated the prevalence of cutaneous malignancies in patients with CD. One study initially reported that patients with CD are at increased risk of developing malignant melanomas (14). However, multiple studies since then have refuted the association (15, 16). Additionally, one study reported that the standard incidence ratio (defined as the ratio of observed-to-expected cancers based on incidence figures for the whole population) of basal cell carcinoma was increased in patients with CD; however, further analysis of this finding was not conducted (16). Nevertheless, former studies have suggested that patients with inflammatory bowel disease (IBD) are at an increased risk of developing cutaneous malignancies, possibly due to immune dysfunction associated with the disease, underscoring the need for a continued investigation into the possible connection between CD and cutaneous malignancies as CD is similarly characterized by intestinal inflammation and decreased immune surveillance (17).

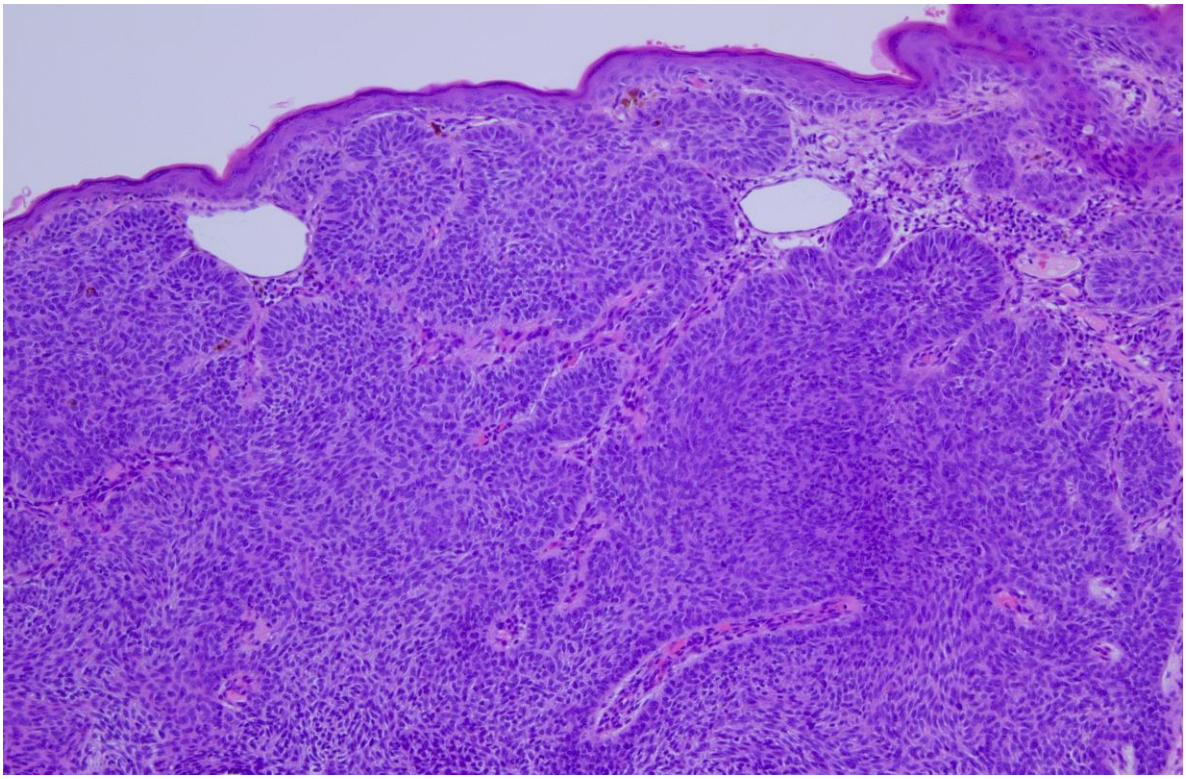
Marjolin ulcer is a rare and aggressive cutaneous malignancy with a high rate of regional metastases that arises on previously traumatized or chronically inflamed skin, most commonly in the scalp or extremities. The term is traditionally used to describe a highly aggressive squamous cell carcinoma secondary to chronic burn wounds. However, although rare, Marjolin ulcers containing basal cell carcinoma and baso-squamous cell carcinoma have also been reported (18). Interestingly, a Marjolin ulcer developed in response to chronic allergic contact dermatitis

caused by an orthopedic implant, suggesting that prolonged allergic dermatitis can promote the development of skin cancer (19). This same study also showed that in a murine model of contact hypersensitivity, chronic allergic contact dermatitis caused by constant exposure to an allergen can promote tumorigenesis at skin sites with preexisting cancer-initiated cells (19). Furthermore, a retrospective, case-control study found that patients with a history of atopic dermatitis have an increased risk of developing squamous cell carcinoma (20).

Although the pathogenesis of Marjolin ulcer remains to be fully delineated, chronic irritation, repeated trauma, impaired immunologic reactivity of the scar tissue to tumor cells, release of toxins from the unhealthy scar, relative avascularity of the scar tissue, and lymphatic obstruction are believed to contribute to malignant transformation (21). As far as is known, no studies have reported an association between Celiac disease and Marjolin ulcer. We now report three cases of basal cell carcinoma located in the perineum of patients with familial seronegative CD suggesting that CD may predispose patients to developing skin malignancies in this region.

CASE 1: A 63-year-old Caucasian male presented with a 14 cm mass in his groin. A biopsy of the lesion revealed nodular basal cell carcinoma **(Figure 1A)**. The patient had also experienced marked gastrointestinal distress for the past decade, which worsened when he travelled away from home. Notably, his favorite dessert at home was gluten-free tapioca pudding. His HLA type, which was previously obtained for an unrelated reason, was HLA-DQ2. A diagnosis of Celiac disease was made based on a gastrointestinal (GI) biopsy of the ileum. The patient died of heart failure before receiving this diagnosis. Pedigree of case 1 is shown **(Figure 1B)**. Although the patient was never formally diagnosed with seronegative CD, family members also affected by the disease were negative for circulating anti-tissue transglutaminase antibodies. Interestingly, the age of onset decreased with successive generations.

A



B

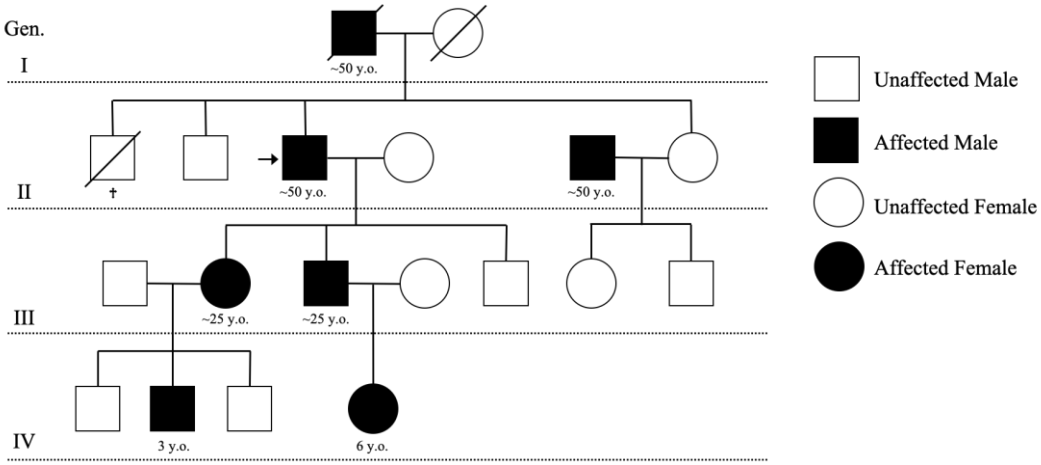
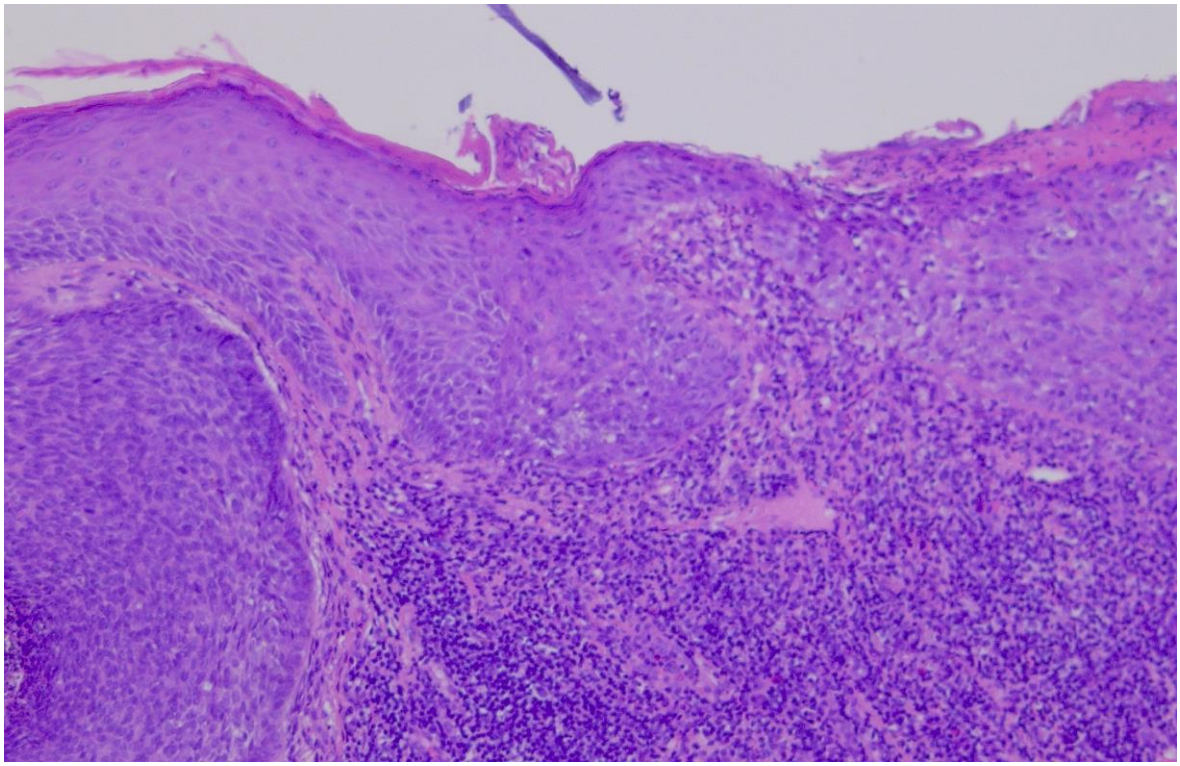


Figure 1: case 1: **(A)** Nodular basal cell carcinoma of the groin (hematoxylin & eosin, x210). **(B)** Pedigree: slashes indicate deceased members. Ages indicate age that member first presented with signs and symptoms of Celiac disease. Horizontal Arrow marks case 1 (prodrome). Generations (Gen) are indicated. Vertical arrow identifies deceased member who died of acute myelogenous leukemia at the age 27.

CASE 2: A 54-year-old female with a 12-year history of familial seronegative Celiac disease presented with a 4 cm mass on her groin. A diagnosis of nodular basal cell carcinoma with neighboring ulcer was made **(Figure 2A)**. The patient declined GI biopsy. Her HLA type was HLA-DQ2. Pedigree of case 2 is shown **(Figure 2B)**.

CASE 3: A 58-year-old Caucasian male with a 10-year history of familial seronegative Celiac disease presented with a 6 cm lesion in his groin. A diagnosis of superficial disseminating basal cell carcinoma with reactive changes was made **(Figure 3A)**. His HLA type was found to be HLA-DQ2. Pedigree of case 3 is shown **(Figure 3B)**.

A



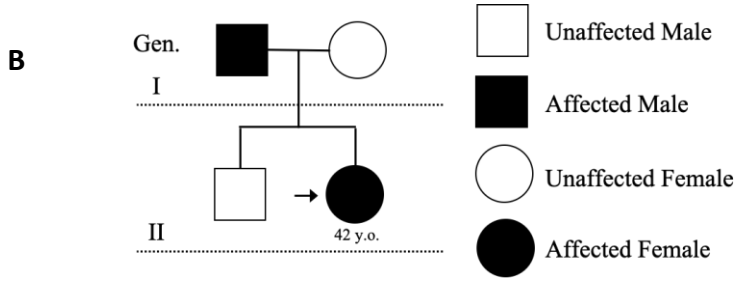
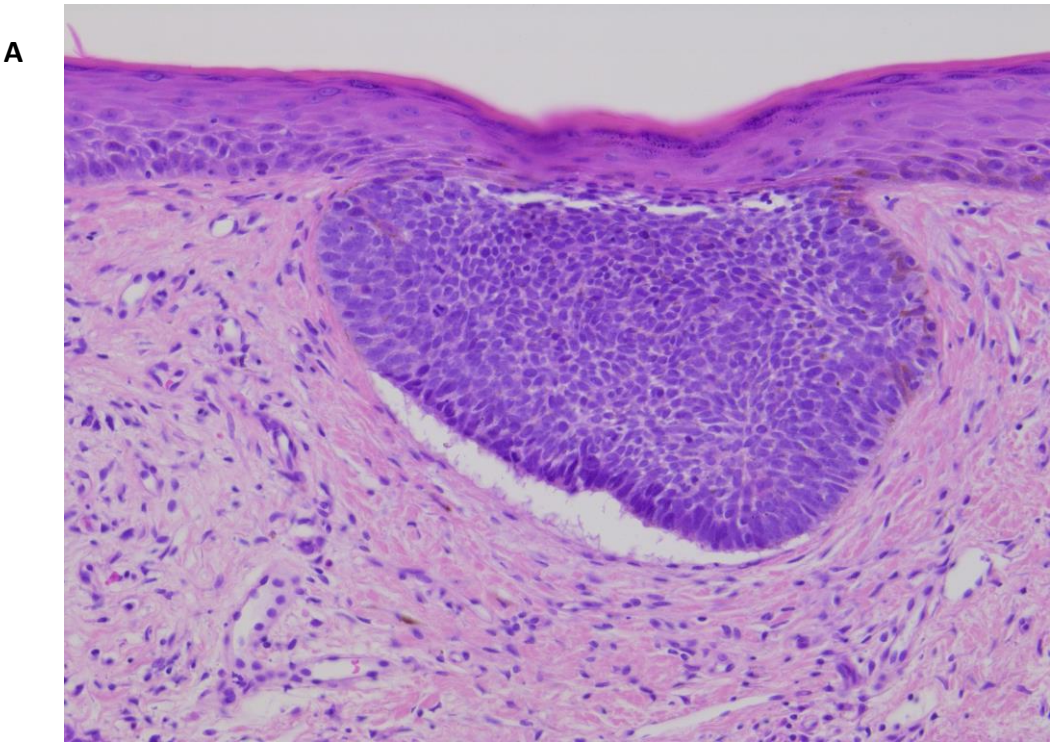


Figure 2: Case 2: **(A)** Nodular basal cell carcinoma with neighboring ulcer found in the groin (hematoxylin & eosin, x210). **(B)** Pedigree: Ages indicate age that member first presented with signs and symptoms of Celiac disease. Arrow marks case 2 (prodrome). Generations (Gen) are as indicated.



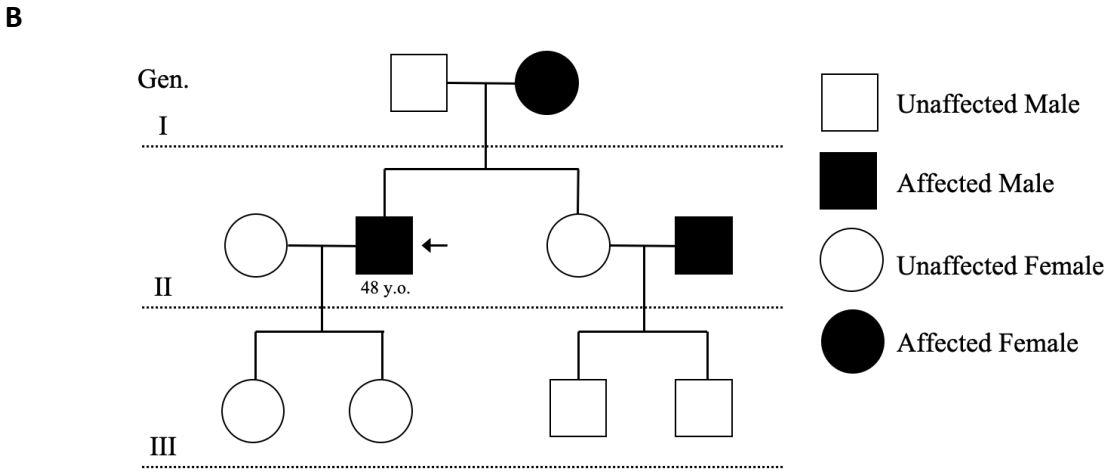


Figure 3: Case 3: **(A)** Superficial disseminatied basal cell carcinoma with surrounding reactive changes found in the groin (hematoxylin & eosin, x310). **(B)** Pedigree: Ages indicate age that member first presented with signs and symptoms of Celiac disease. Arrow marks case 3 (prodrome). Generations (Gen) are as indicated.

Discussion:

We report three middle-aged adult patients with a history of Celiac disease, all with HLA-DQ2 haplotypes and a family history of CD, who presented with basal cell carcinoma of the groin. The mechanism by which CD causes basal cell carcinoma remains to be defined. Previous studies have reported the cutaneous manifestations of CD. One case report described a 49-year-old woman who presented with a 10-year history of anogenital pruritis. Skin biopsy from the affected skin showed acanthosis of the keratinized skin, focal parakeratosis, and mild to moderate chronic inflammation of the superficial dermis with occasional eosinophils and neutrophils in the epidermis and a clinical diagnosis of lichen simplex chronicus. Additionally, serum tissue transglutaminase antibodies were found to be elevated and subsequent duodenal biopsy revealed villous atrophy consistent with CD. One year following treatment with a gluten-free diet, her pruritus had resolved, and examination of her perineum and vulva revealed normal skin (22). Another report described three girls with known CD who presented with pruritus in the perivaginal and perianal areas, consistent with a diagnosis of lichen sclerosus et atrophicans (LSA). Interestingly, treatment with a gluten-free diet did not appear to change the course of the LSA (23). These studies suggest that CD can manifest as inflammation in the anogenital region in the form of lichen simplex chronicus or LSA. Notably, it has been reported that squamous cell carcinoma can arise from both lichen simplex chronicus and LSA (24, 25). These studies provide a pathway by which CD may contribute to the development of skin malignancies such as basal cell carcinoma by promoting chronic inflammation of the perineum inducing Marjolin ulcer formation. However, other yet to be defined pathways may also exist. Based on our findings, physicians should consider testing patients with skin cancer located in the perineum for Celiac disease.

Note added in processing: While this paper was in processing, a shorter version, without images or pedigrees, was published in the British Journal of Dermatology.[26]

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