FEATURE ARTICLE

CE 1.0 Contact Hour

Cutaneous Manifestations of Celiac Disease

Xin Zheng, Sneha Shaha, and Talha Khawar

ABSTRACT: Celiac disease is a systemic immune-mediated enteropathy that is primarily characterized by its gastrointestinal symptoms with significant extraintestinal manifestations. A multidisciplinary approach is often required to appropriately recognize and manage the disease. Dermatology providers play an important role in the early recognition and diagnosis of this disease especially in those individuals who initially present with prominent cutaneous manifestations. This review article focuses on the cutaneous manifestations of celiac disease with the aim to increase awareness of this disease among dermatology providers to facilitate an early diagnosis and referral to appropriate specialty providers.

Key words: Celiac Disease, Dermatitis Herpetiformis, Autoimmune Disease

Celiac disease (CD) is a chronic immune-mediated condition that is triggered by gluten ingestion in genetically predisposed individuals. It can present with a wide array of signs and symptoms (Leffler et al., 2015). It is generally seen in people of northern European ancestry, although individuals of other ethnicities with the correct genetic predisposition can still develop the disease. HLA-DQ2 and HLA-DQ8 are the genetic alleles associated with the disease and are present in 90%–95% and 5%–10% of cases, respectively (Leffler et al., 2015). CD has a prevalence ranging from 0.5% to 1% and is more commonly seen in women. Disease prevalence has been increasing in the Western countries, which may be because of wider detection. The prevalence is higher in first-degree relatives as well as other at-risk groups such as those with Down syndrome, Type I diabetes, or Immunoglobulin A deficiency (Caio et al., 2019).

Several studies and reports have shown that the extraintestinal manifestations of CD are much more prevalent than traditional gut-related manifestations (Castillo et al., 2015; Leffler et al., 2015). This review aims to delineate the most common dermatologic manifestation of CD.

Xin Zheng, DO, MS, *Department of Medicine, Loma Linda University, Loma Linda, CA.*
Sneha Shaha, DO, *Department of Medicine, Loma Linda University, Loma Linda, CA.*
Talha Khawar, MD, *Division of Rheumatology, Department of Medicine, Loma Linda University School of Medicine, Loma Linda, CA.*

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Correspondence concerning this article should be addressed to Talha Khawar, MD, Division of Rheumatology, Department of Medicine, Loma Linda University School of Medicine, 11234 Anderson St., Loma Linda, CA 92354. E-mail: talha.khawar@va.gov

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MANIFESTATIONS

The most notable dermatologic manifestation of CD is dermatitis herpetiformis (DH). This was first reported by Dr. Luis Duhring, a dermatologist, in 1884 (Duhring, 1884). Although DH is associated with several other autoimmune diseases, it is present in more than 90% of cases of CD (Plotnikova & Miller, 2013). This is because both DH and CD share the same genetic susceptibility with HLA-DQ2 and HLA-DQ8 alleles (Zone, 2005). DH is characterized by grouped pruritic papules and vesicles on an erythematous base with crusting or excoriations. These are primarily located symmetrically on extensor surfaces such as the elbows, knees, buttocks, or lower back (Figure 1; Leffler et al., 2015; Plotnikova & Miller, 2013). These lesions can be present intermittently in small areas or widespread throughout the body such that the excoriations may be the only finding during a physical examination. Thus, it is important to review a history of chronic pruritic lesions in these patients (Leffler et al., 2015). DH is thought to occur because of an antibody-mediated process. Individuals with active CD produce antibodies against the endogenous protein tissue transglutaminase 2 (TG2) found in the intestine. A closely related antibody against epidermal transglutaminase 3 (TG3) that is mainly found in the skin is seen in almost all patients with DH. These skin antibodies are thought to have much higher affinity to TG3 than intestinal antibody does against TG2. This may explain why in a significant number of patients skin manifestations appear before or regardless of the intestinal manifestations

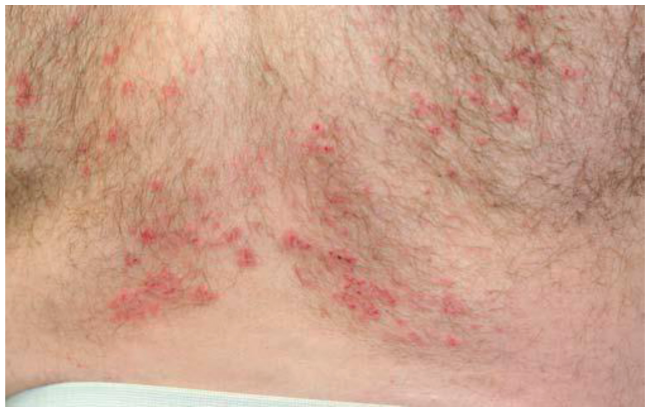

FIGURE 1. Symmetric excoriated papules located on the lower back (Plotnikova & Miller, 2013).

(Sárdy et al., 2002). Therefore, serologic testing for TG2 and TG3 can also be beneficial in diagnosing DH.

Other less common cutaneous manifestations of CD with variable association include linear IgA bullous dermatosis, urticaria, cutaneous vasculitis, hereditary angioneurotic edema, cutaneous vasculitis, erythema nodosum, necrolytic migratory erythema, vitiligo disease, Bechet's disease, oral lichen planus, and dermatomyositis. In addition, certain dermatologic diseases are also thought to be associated with CD. These can include psoriasis, eczema, alopecia areata, and aphthous stomatitis (Abenavoli et al., 2006).

CLUES TO HELP DIAGNOSE CD

CD can also be characterized by nondermatologic presentations, which would be helpful to consider across all medical subspecialties in accurately diagnosing the disease. These can occur across multiple organ systems and can be divided into two main groups: sequalae of chronic inflammation and manifestations of malabsorption from the disease process. More common extraintestinal manifestations include iron deficiency anemia, osteoporosis, arthritis, peripheral neuropathy, and hepatitis. Hyposplenism, acute and chronic pancreatitis, infertility, aphthous ulcers, dental enamel defects, and gluten ataxia have been less commonly reported as with varying frequency. Clinicians need to be vigilant of pediatric extraintestinal manifestations such as short stature and delayed puberty (Leffler et al., 2015). These conditions when present in the appropriate clinical setting should raise the possibility of CD (Caio et al., 2019).

DIAGNOSTIC WORKUP

Diagnosing CD is usually made in the presence of mucosal changes seen on duodenal biopsy in combination of positive serologic testing. Serologic testing is done for IgA antibodies against tissue transglutaminase, endomysium, and IgG against deaminated gliadin peptide (Rubio-Tapia et al., 2013). In addition, serologic testing for TG2 and TG3 can also be beneficial in diagnosing DH.

In addition to clinical presentation, history, and serologic testing, other diagnostic testing such as tissue pathology from skin biopsy and direct immunofluorescence (DIF) microscopy can also help differentiate DH from other causes. The initial approach in the dermatology clinic setting involves obtaining two types of skin biopsies—one lesional for routine hemotoxylin-and-eosin staining and a perilesional for DIF. A diagnosis is made from the hemotoxylin-and-eosin staining showing neutrophilic infiltrate within the dermal papillae or subepidermal vesiculation or blisters with collections of neutrophils, eosinophils, and fibrin (Figure 2). DIF is currently considered the gold standard and confirms the DH diagnosis. DIF typically shows granular Immunoglobulin A deposits within the dermal papillae (Plotnikova & Miller, 2013; Zone, 2005). For DIF, it is important that the biopsy is taken from normal-appearing skin adjacent to a lesion, because studies had shown lesional skin biopsies are more likely to yield false-negative findings (Zone et al., 1996).

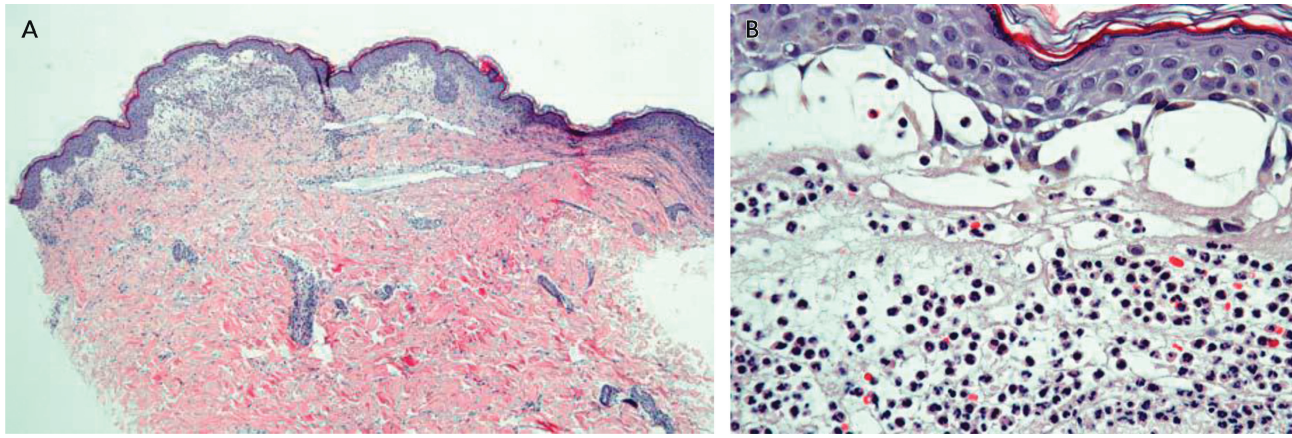

FIGURE 2. (A) Light microscopy at lower power magnification showing subepidermal bullae accentuated within dermal papillae (Plotnikova & Miller, 2013). (B) Light microscopy at high power magnification showing subepidermal bullae with numerous neutrophils (Plotnikova & Miller, 2013).

TREATMENT

Management of patients with CD and its associated skin manifestations requires a multidisciplinary approach.

The American College of Gastroenterology strongly recommends strict lifetime adherence to a gluten-free diet (Rubio-Tapia et al., 2013). Patients with CD should be referred to a dietitian with expertise in treating such conditions and complications from nutritional deficiencies.

Although a gluten-free diet has been shown to be effective for both DH and CD, response to this diet can take months or years if used as a sole treatment. In contrast, dapsone, a synthetic sulfone, has a much faster response interval, leading to a resolution of DH usually within days (Plotnikova & Miller, 2013). Unfortunately, dapsone therapy has known adverse reactions inherent to the medication and has no benefit on the gastrointestinal symptoms of CD. Dapsone therapy is known to be associated with multiple adverse effects including hemolysis, methemoglobinemia, agranulocytosis, and a dapsone hypersensitivity reaction. Individuals with glucose-6-phosphate dehydrogenase deficiency are more prone to severe hemolytic anemia if they take dapsone. Therefore, a glucose-6-phosphate dehydrogenase screening is indicated before the start of this medication. It is important to closely monitor patients while on dapsone with laboratory testing. Before starting therapy as well as during the therapy, typical blood work includes complete blood count, liver function tests, and kidney function tests.

Therefore, the most commonly used first-line therapy for patients with CD presenting with skin manifestations includes elimination of gluten from the patient's diet and also a prescription of dapsone therapy. With clinical improvement of cutaneous manifestations, dapsone therapy can be slowly tapered, with the ultimate goal to manage CD with only gluten-free dietary modifications. Most patients can maintain remission of symptoms with only dietary therapy, and 10%–15% of these patients may even remain symptom-free after the discontinuation of both treatments (Paek et al., 2011).

CONCLUSION

CD is a multisystem autoimmune disease with various extraintestinal manifestations. Proper recognition of disease presentation requires a collaborative approach between dermatologists, rheumatologists, and gastroenterologists. Although varied cutaneous manifestations of CD can be seen, DH is by far the most common dermatologic manifestation. ■

REFERENCES

Abenavoli, L., Proietti, I., Leggio, L., Ferrulli, A., Vonghia, L., Capizzi, R., Rotoli, M., Amerio, P. L., Gasbarrini, G., & Addolorato, G. (2006). Cutaneous manifestations in celiac disease. *World Journal of Gastroenterology*, *12*(6), 843–852. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4066147/

Caio, G., Umberto, V., Sapone, A., Leffler, D., Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: A comprehensive current review. *BioMed Central Medicine*, *17*(142), 1–20. https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-019-1380-z

Castillo, N., Theethira, T., & Leffler, D. (2015). The present and the future in the diagnosis and management of celiac disease. *Gastroenterology Report (Oxford Academic)*, *3*(1), 3–11. https://pubmed.ncbi.nlm.nih.gov/25326000/

Duhring, L. (1884). Dermatitis herpetiformis. *Journal of the American Medical Association*, *3*, 225–228.

Leffler, D., Green, P., & Fasano, A. (2015). Extraintestinal manifestations of coeliac disease. *Nature Reviews Gastroenterology & Hepatology*, *12*(10), 561–571. https://pubmed.ncbi.nlm.nih.gov/26260366/

Paek, S., Steinberg, S., & Katz, S. (2011). Remission in dermatitis herpetiformis: A cohort study. *Archives of Dermatology*, *147*(3), 301–305. https://pubmed.ncbi.nlm.nih.gov/21079050/

Plotnikova, N., & Miller, J. (2013). Dermatitis herpetiformis. *Skin Therapy Letter*, *18*(3), 1–3. https://pubmed.ncbi.nlm.nih.gov/23674144/

Rubio-Tapia, A., Hill, I., Kelly, C., Calderwood, A., & Murray, J., ACG (2013). American College of Gastroenterology clinical guidelines: Diagnosis and management of celiac disease. *The American Journal of Gastroenterology*, *108*(5), 656–677. https://pubmed.ncbi.nlm.nih.gov/23609613/

Sárdy, M., Kárpáti, S., Merkl, B., Paulsson, M., & Smyth, N. (2002). Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. *Journal of Experimental Medicine*, *195*(6), 747–757. https://pubmed.ncbi.nlm.nih.gov/11901200/

Zone, J. (2005). Skin manifestations of celiac disease. *Gastroenterology*, *128*(4, Suppl. 1), S87–S91. https://pubmed.ncbi.nlm.nih.gov/15825132/

Zone, J., Meyer, L., & Petersen, M. (1996). Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. *Archives of Dermatology*, *132*(8), 912–918. https://pubmed.ncbi.nlm.nih.gov/8712841/