Palmar Petechiae in Dermatitis Herpetiformis: A Case Report and Clinical Review

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GOAL

To have a comprehensive understanding of dermatitis herpetiformis (DH)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the clinical presentation of DH.
2. Discuss the differential diagnoses for DH.
3. Identify the treatment options for DH.

CME Test on page 224.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: September 2002.

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Drs. McCleskey, Erickson, David-Bajar, and Elston report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

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Palmar petechiae or purpura is an unusual finding in dermatitis herpetiformis (DH) that occurs in children but is only rarely reported in adults. We describe a 46-year-old man with DH who presented with the classic pruritic papulovesicular eruption and associated volar finger and palmar petechiae. We discuss recent advances in the pathogenesis and treatment of DH.

Case Report

A 46-year-old man presented to our department complaining of severe pruritus associated with a rash on his elbows and knees. He also reported

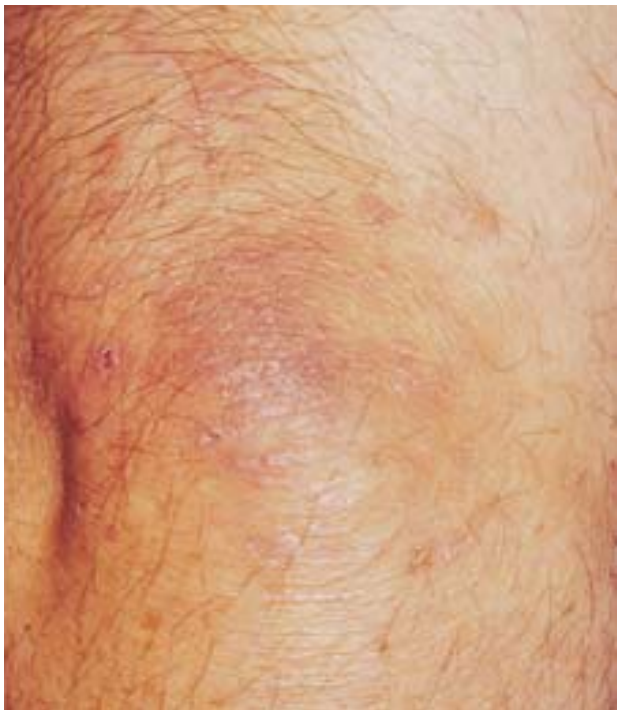

Figure 1. Erythematous papules on the extensor surfaces.

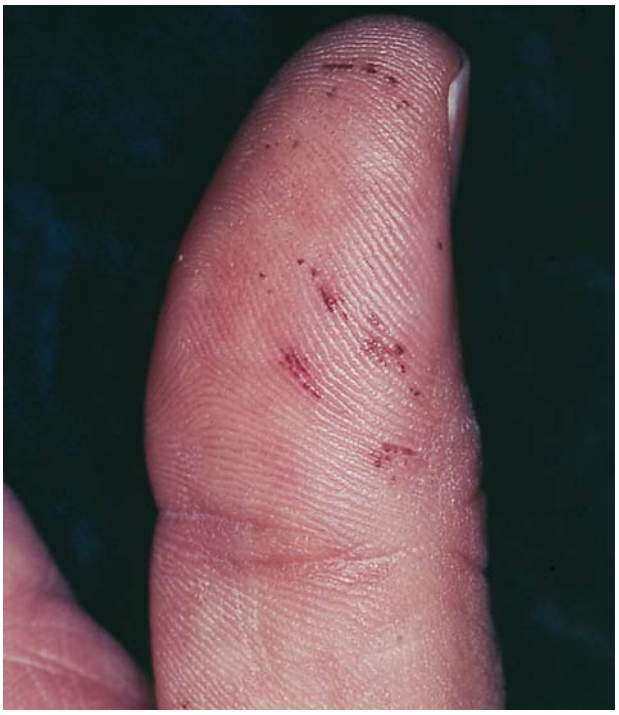

Figure 2. Volar finger petechiae following the skin lines.

pinpoint burning on the palmar surface of his hands after which a black spot would appear in the respective location. He denied any associated diarrhea, cramping, bloating, or other gastrointestinal symptoms. Physical examination revealed many 1- to 5-mm round and oval erythematous papules with overlying excoriations distributed symmetrically over the extensor surfaces of his elbows and knees (Figure 1). Petechiae less than 1 mm were noted on the palms and volar aspect of the fingers bilaterally and seemed to follow the dermatoglyphics (Figure 2); they were more prominent over the first and second digits of each hand. There was no involvement of the soles. The patient's elbow had a single 2-mm vesicle (Figure 3). A shave biopsy specimen from perilesional skin showed strongly positive granular IgA staining at the dermal-epidermal junction (DEJ) and dermal papillae (Figure 4), with weaker C3 and fibrin staining in the same distribution; the findings are diagnostic of dermatitis herpetiformis (DH). Antigliadin IgG antibodies were positive, but antigliadin IgA antibodies and antiendomysial antibodies were negative. Results were normal for a complete blood count (CBC) and for liver, renal, and thyroid function tests, as well as for glucose-6-phosphate dehydrogenase, vitamin B_{12}, folate, and iron studies. The patient responded to 25 mg/d of dapsone and a gluten-free diet (GFD); all symptoms have since resolved.

Comment

Diagnosis and Treatment—DH is a chronic disease associated with gluten sensitivity that usually presents as an extremely pruritic papulovesicular eruption on the extensor surfaces. Its onset is typically during early adulthood to 50 years of age,[1] and its incidence is higher among Europeans than people of Asian or African descent. Male predominance is seen in adults but not in children.

The characteristic distribution is symmetrical and involves the elbows, knees, buttocks, sacrum, back, shoulders, posterior neck, and posterior hairline.[1-3] Oral mucosa and larynx involvement rarely have been reported.[4] The various morphologic presentations include pruritic erythematous papules and papulovesicles, erosions with or without crusts, urticarial papules, vesicles, and bullae. Patients sometimes note burning or itching that occurs 12 to 24 hours after the lesions present.

DH in children has a distribution similar to that of adults; however, children also may present with palmar and plantar lesions. In addition, children may exhibit red-brown macules and papules, hemorrhagic vesicles, or petechiae and purpura over the palms and volar fingers but excluding the dorsal aspect of the hands.[1,5] Often these hand lesions are asymptomatic and favor the dominant hand, suggesting a possible traumatic etiology. Soles are more rarely involved. Although this presentation of hand

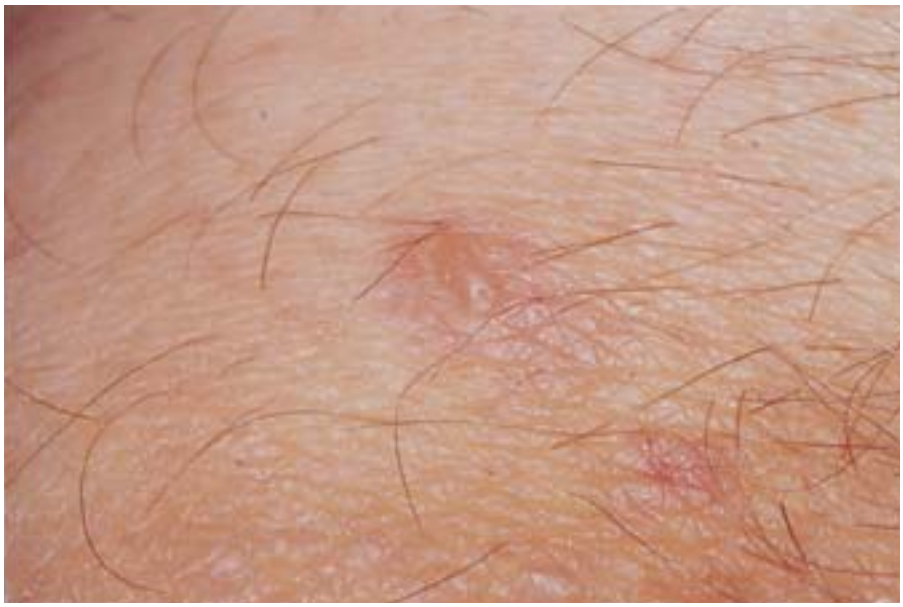

Figure 3. Single 2-mm vesicle on the elbow.

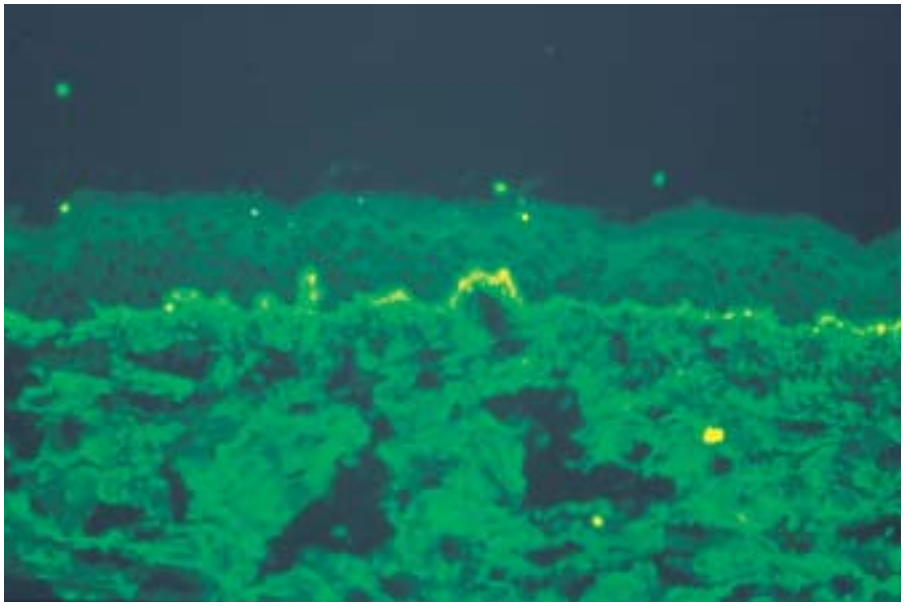

Figure 4. Granular IgA deposits at dermal papillae on direct immunofluorescence (original magnification ×200).

lesions is more common in children, it has been reported in 10 adults.[6-9] Despite early description as pseudopurpura,[8] the purpura seen in DH had been shown histologically to have both extravasated erythrocytes[6,9,10] and papillary neutrophilic microabscesses,[6,8-11] the latter being typical histological findings in DH.

The differential diagnosis of DH lesions includes linear IgA disease (LAD), erythema multiforme, pemphigoid gestationis, bullous pemphigoid, pemphigus vulgaris, pityriasis lichenoides et varioliformis acuta, transient acantholytic dermatosis, papular urticaria, scabies, insect bites, neurotic excoriations, bullous impetigo, and atopic dermatitis.[1,2] LAD deserves mention because some older classifications grouped it with DH because of the presence of IgA. Childhood LAD (also known as chronic bullous dermatosis of childhood) is characterized by large bullae in rosettes that may cluster in the genital and perineal distribution and is not associated with gluten-sensitive enteropathy (GSE). Adult LAD is similar but typically occurs in the seventh decade and may involve mucous membranes, as well as skin.

Histopathology of early DH lesions reveals a neutrophilic infiltrate in the dermal papillary tips (microabscesses) with variable eosinophilia and subepidermal vesicles with neutrophil cellular debris and fibrin.[2,3,12] The vesicle expands to involve

several adjacent papillae. The histopathologic differential diagnosis of early DH lesions includes LAD, bullous lupus erythematosus, epidermolysis bullosa acquisita, and bullous pemphigoid. LAD, bullous lupus erythematosus, and epidermolysis bullosa acquisita tend toward a more continuous array of neutrophils at the DEJ. Bullous pemphigoid tends toward a more eosinophil-rich infiltrate. Later lesions may resemble any of the inflammatory subepidermal blistering diseases, including bullous pemphigoid, bullous drug reactions, erythema multiforme, and pemphigoid gestationis.

Direct immunofluorescence (DIF) of perilesional skin should be performed by taking a 3- or 4-mm punch biopsy within 1 cm of a lesion and either placing it in the immunofluorescence transport medium or immediately freezing it. Lesional skin should not be used because DIF results are negative in 80% of lesions.[13] Granular IgA deposition along the DEJ with prominence at the dermal tips is the hallmark of DH, but a granular IgA pattern along the entire DEJ may occur as well. This must be differentiated from the smooth linear IgA pattern seen in LAD. Granular IgA in uninvolved skin is the most reliable criterion[3] for DH and is the basis for most study inclusion criteria.

Immunoelectron microscopy is not performed routinely in DH; however, it should be noted that the IgA deposits seen in early studies of DH seem to bind to microfibrillar components of elastin fibers in the papillary dermis and below the basal lamina.[3,13] There are reports of colocalization with fibrillin and hexabrachion.[13] A tendency toward vertical streaking of the granular deposits may reflect this distribution.

DH clearly is associated with increased incidences of other autoimmune diseases, including celiac disease (CD), rheumatoid arthritis, diabetes mellitus (usually insulin dependent), and hyperthyroidism or hypothyroidism.[14] There may be an increased incidence of IgA nephropathy, primary biliary cirrhosis, chronic active hepatitis, splenic atrophy, Addison disease, AIDS-related complex, dermatomyositis, polymyositis, Raynaud phenomenon, Sjögren syndrome, lupus erythematosus, ulcerative colitis, and vitiligo. The association with other autoimmune diseases may be due in large part to the human leukocyte antigen (HLA) haplotypes that appear most often in DH, including HLA-B8, HLA-DR3, and HLA-DQw2.[2,15,16] The extended haplotype associated with HLA-DQw2c (HLA-B8, HLA-SC01, HLA-DR3, HLA-DQw2) appears in 75% of patients with DH.[16]

Patients with DH and CD are at increased risk of associated malignancies, most notably lymphoma in both diseases[2,17-19] and oral, pharyngeal, and esophageal carcinoma in CD.[17] The most common associated malignancy is non-Hodgkin's lymphoma of the gastrointestinal tract,[19,20] which has been referred to as enteropathy-associated T-cell lymphoma. Lymphomas have not been reported in association with DH in childhood.[1]

CD is a gluten-sensitive enteropathy characterized by malabsorption and atrophy of the small intestine associated with dietary gluten. Patients often complain of diarrhea, cramps, and bloating. The pathologic hallmarks revealed by results of jejunal biopsies are jejunal villous blunting, elongation of intestinal crypts, flattening of surface epithelial cells, reduction of microvillous formations, and lymphohistiocytic infiltrate in the lamina propria.[15] CD is diagnosed by the finding of villous atrophy and 2 of the following 3 serum antibodies: antiendomysium IgA antibodies (AEA), antireticulin IgA antibodies (ARA), or antigliadin IgA antibodies (AGA).[13] Twenty percent to 30% of patients with CD also have DH.

Fifty percent to 90% of patients with DH exhibit the same findings on jejunal biopsies as patients with CD,[2,3,21] even though only 10% to 30% of patients with DH have gastrointestinal symptoms at presentation. Upon gluten loading, 100% of DH patients will show the above microscopic findings of GSE,[2,15] suggesting that CD and DH share a common pathogenesis.

Removal of dietary gluten reverses mucosal atrophy, symptoms, and titers of serum AEA, ARA, and AGA in both CD and DH.[13,22-25] A strict GFD will dissipate the rash and cutaneous IgA deposits over time.[23] These changes correlate directly with the strictness of the diet. Ermacora et al[21] and Leonard et al[23] each conclusively demonstrated that gluten induces DH in susceptible individuals. They both showed that a strict GFD cured their patients of clinical, serologic, and microscopic signs and symptoms of disease, but that upon gluten loading, the rash, serum antibodies, granular IgA deposition at the DEJ, and villous atrophy all returned.

Gluten is the protein fraction of most grains that gives dough its elasticity.[22] Prolamines are the implicated agents within the gluten protein fraction, and gliadin is the prolamine found in wheat. Because gluten is ubiquitous in foods throughout the United States, it is life altering for patients to remove gluten entirely from their diets. Rottmann[26] thoroughly reviewed details of the GFD. Involving a dietician at the initiation of a patient's GFD and then again several months later at the patient's reevaluation is often critical to the diet's success,[22] particularly in teenage, diabetic,

and athletic patients. The risks associated with a GFD include deficiencies in total calories, protein, iron, fiber, and occasionally calcium and vitamins B and C.

Benefits of a GFD include reduction or abolition of symptoms and reversal of mucosal atrophy. Because of improved intestinal absorption, patients on a GFD are at decreased risk of pernicious anemia and deficiencies of vitamin B_{12} and folate. Most importantly, a decreased risk of all cancers in conjunction with CD and of lymphoma in conjunction with both CD and DH has been observed in patients following strict GFDs compared with those following gluten-reduced or normal diets.[17,18]

Contact information for support groups such as the American Celiac Society, Celiac Disease Foundation, Gluten Intolerance Group of North America, Celiac Sprue Association, and National Center for Nutrition and Dietetics, may be found on the National Institutes of Health's National Digestive Diseases Information Clearinghouse Web site (http://www.niddk.nih.gov/health/digest/pubs/celiac/index.htm)[27]; assistance from these groups may be critical to the success of patients on a GFD.

Even a strict GFD takes an average of 25 to 29 months to bring a patient's rash and villous atrophy under control; thus, adjuvant immunosuppressive medications are usually necessary.[28] Diaminodiphenyl sulfone (dapsone) is the most effective treatment for the pruritus of DH; a dose of 100 mg/d is reasonable for the average adult. Many clinicians give an initial 25-mg test dose, and some prefer to give a gradually increasing dose. It is important, however, to reevaluate the patient at 2 weeks for response. Generally, the maximum dose recommended is 300 mg/d. A gradual decrease in dosing will reveal a threshold for each patient (when symptoms return) above which the lowest effective dose can be determined. The advantage of lowering the dose of dapsone is to avoid sequelae, including hemolysis (a 1-g decrease of hemoglobin in the first month is common), methemoglobinemia, and headaches. Idiosyncratic reactions that are not necessarily dose-related may occur, including agranulocytosis, peripheral neuropathy, psychosis, hypersensitivity, and hepatotoxicity. Severe hemolysis may occur in the presence of glucose-6-phosphate deficiency. Prior to initiation of therapy, patients should be screened for glucose-6-phosphate dehydrogenase deficiency, liver dysfunction, and severe anemia. CBCs may be monitored at 2 weeks, one month later, and every 3 months for the first year, then every 6 months thereafter.

If the maximum dose of dapsone is reached without response, or its use is contraindicated, sulfapyridine (2 g/d, maximum 4 g/d) or sulfamethoxypyridazine (0.5 g/d, maximum 1.5 g/d) may be used instead; however, neither drug is available in the United States.[28] A combination of these 3 medications at lower doses may offer a cumulative effect without increased side effects.

Although drug therapy improves the patient's rash, it does not reverse villous atrophy, decrease serum antibodies, or decrease IgA deposits in the skin; therefore, drug therapy often is used in conjunction with a GFD. One study showed that patients who started to follow a strict GFD were able to tolerate reduced doses of dapsone in an average of 8 months.[23]

After patients are weaned off dapsone and maintain a GFD, their general and dietary histories should be taken as part of an annual follow-up visit that also should include a physical examination (screening for malignancy and endocrinologic symptoms and signs) and tests for CBCs, vitamin B_{12}, and thyroid function.[20]

Pathogenesis

As in CD, IgA antibodies (AEA, ARA, and AGA) have been found in DH and are useful for diagnosis and for monitoring patients' compliance with the GFD. This is because the titers of all 3 antibodies decrease when patients follow a strict GFD.[13] Among these antibodies, AEA is the most sensitive and specific for small bowel pathology associated with untreated CD and DH.[29] Under ideal laboratory conditions, the specificity approaches 100%, with a sensitivity of nearly 100% for CD and of around 80% for DH.[13] This discrepancy may be due to the lower frequency of intestinal pathology in patients with DH in the absence of gluten loading. AEA, ARA, and AGA rarely may be positive when the DIF is negative.[30]

IgA antibodies are produced in the mucosa and are distributed equally between types IgA1 and IgA2.[15] Serum IgA is about 90% IgA1 and 10% IgA2. Almost 100% of the IgA deposits in the skin of patients with DH are IgA1.

The autoantigen to which AEA reacts in CD and DH has been identified as tissue transglutaminase (TG).[29,31,32] Indirect immunofluorescence to TG antibodies shows sensitivity and specificity similar to AEA antibodies in DH,[24,25,29,30] and there is a strong correlation between each of their titers.[29,32,33] The titer of anti-TG antibodies also decreases with a strict GFD,[24,25,29,30] reflecting the amount of involvement of the mucosa. Sardy et al[34] have devised an enzyme-linked immunosorbent assay test for human TG that also has excellent sensitivity (98.1%) and specificity (98.2%) for CD

and DH and may obviate the need for monkey esophagus AEA studies.

Tissue TG is a calcium-dependent enzyme that preferentially accepts dietary gliadin as a substrate. It is found in muscle cells, fibroblasts, and leukocytes.[33] TG catalyzes γ-glutamyl-lysine bonds[33] and deamidates glutamine residues in gliadin,[29] thus catalyzing gliadin-gliadin cross-links and incorporating gliadin into complexes with TG and other proteins. TG cross-links extracellular matrix proteins including type VII collagen, which connects the basement membrane to the dermis.[29] TG also is involved in fibrogenesis, wound healing, and apoptosis.[33] Dieterich et al[29] theorize that the deamidating of glutamine residues in gliadin may potentiate the antigenic properties of gliadin peptides by creating negatively charged anchor residue for the HLA-DQw2 molecules (in HLA-predisposed patients). Also, anti-TG antibodies may cross-react with TG or other unknown transglutamidases in the skin and interfere with TG's activity as a cross-linker. Rose et al[32] also suggest that TG may create autoantigen epitopes in HLA-susceptible people by modifying gliadin.

Concordance studies in monozygotic twins reveal a very high (0.91) concordance of CD and DH.[35] This suggests that the multifactorial genetic influence may be relatively simple and that environmental factors play a smaller role than previously predicted in the phenotypes of CD and DH. Furthermore, a search for non-HLA genes has revealed loci on 11q, 5q, and 2q in GSE.[36] The strongest non-HLA linkage in DH was 11q23, and a 2q33 locus linked more strongly with CD than with DH. Interestingly, the 2q33 locus (CTLA4/CD28) is near several genes that control T-cell regulating proteins such as CD3 genes and the IL-10 receptor gene.

Local expression of chemokines and proteinases suggests a T-cell mediated response. Matrix metalloproteinases (MMPs) are enzymes that degrade extracellular matrix structures; they consist of collagenases (including MMP-1), stromelysins (MMP-3 and MMP-12), gelatinases, and membrane-type MMPs.[37] MMP-1 and MMP-3 are expressed in the basal keratinocytes near neutrophilic abscesses in DH. They may degrade type VII collagen, type IV collagen, and laminin-1. Both also are expressed in subepithelial macrophages and fibroblasts of intestinal mucosa in GSE. MMP-3 has been shown to cause villi to atrophy in a fetal intestine model.

MMP-12 (human macrophage microelastase) is a stromelysin that is mostly elastolytic, degrading type IV collagen, laminin-1, fibronectin, vitronectin, and prostaglandins. Increased MMP-12 production has been noted in gastrointestinal mucosa macrophages of patients with DH, with nearby degradation of the basement membrane zone (as determined by defects in type IV collagen staining). Increased MMP-12 production also has been noted in skin macrophages of patients with DH, with nearby degradation of the basement membrane zone,[37,38] suggesting that it may be a mediator of the damage that leads to microvesicle formation.

$CD4^+$ T cells in the lymphohistiocytic infiltrate in DH have been shown to have a restricted receptor expression, indicating an antigen-specific response.[39] Generalized cytokines of the T_H2 response (IL-4, IL-5, and IL-8) have been demonstrated in the lymphohistiocytic infiltrate in DH, as has the specific T_H2 cytokine IL-13. Eotaxin, an eosinophilic chemotactic cytokine, also has been found in the microabscesses and lymphohistiocytic infiltrate.

TG and plasmin are required for proteolytic activation of transforming growth factor-β1, which prevents upregulation of MMP-12 by tumor necrosis factor α, IL-$1\beta_1$, and other cytokines related to T-cell activation.[37] Antibodies against TG may decrease its activity, resulting in reduced levels of transforming growth factor-β1 and increased MMP-12, tumor necrosis factor α, IL-$1\beta_1$, and other T-cell cytokines.

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