Principi ed Aggiornamenti in Dermatologia
Roma, 6-7 Aprile 2018

Grand rounds

Lorenzo Cerroni, *Graz*

"Computer palms"

- Described in patient using computer keyboards for long periods; similar features described in swimmers ("pool palms")
- Similar changes in other types of repeated mechanical irritation
- Teleangectatic vessels in the upper dermis
- No inflammatory infiltrate
- In rare cases may show features of palmar eccrine hidradenitis

Computer palms

Alan T. Lewis, MD, Sylvia Hsu, MD, Rhea M. Phillips, MD, and Jo Ann Lee, BS *Houston, Texas*

We describe a new occupation-related skin finding in 2 computer programmers and discuss its characteristics and causes. (J Am Acad Dermatol 2000;42:1073-5.)

We describe 2 patients in whom symmetric, well-demarcated, erythematous patches with telangiectases occurred at sites of chronic pressure on the palms. Both patients had been computer programmers for many years. This phenomenon has not been previously reported.

Case 1

A 47-year-old healthy white man presented with an asymptomatic eruption on his palms of 10 years' duration. He was a computer programmer who had spent 22 years using a keyboard, on average of approximately 12 to 15 hours a day, including weekends. The patient reported that he often leaned forward and rested his weight on his palms to alleviate back stress from prolonged sitting.

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0190-9622/2000/$12.00 + 0 **16/54/105166**
doi:10.1067/mjd.2000.105166

On clinical examination, there were 2 symme well-demarcated, blanchable, erythematous pat with telangiectases on the ulnar side of the palms 1). Routine laboratory work from an employr physical revealed no abnormal liver chemistries. patient does not drink alcohol.

Case 2

A 42-year-old white woman presented with year history of an asymptomatic eruption on palms. She was a computer programmer who spent 20 years typing at a keyboard, on averag 10 hours a day on weekdays and up to 18 hou day on weekends. She also admitted to leaning ward and placing pressure on her palmar surf to see the screen and to relieve lower back Examination of her palms revealed findings id cal to those of case 1.

DISCUSSION

In 1948, Ronchese[1] described some of the acteristics of skin changes in a wide variety of l ers. These included scars, calluses, eczema patches, nail changes, and erythema ab igne

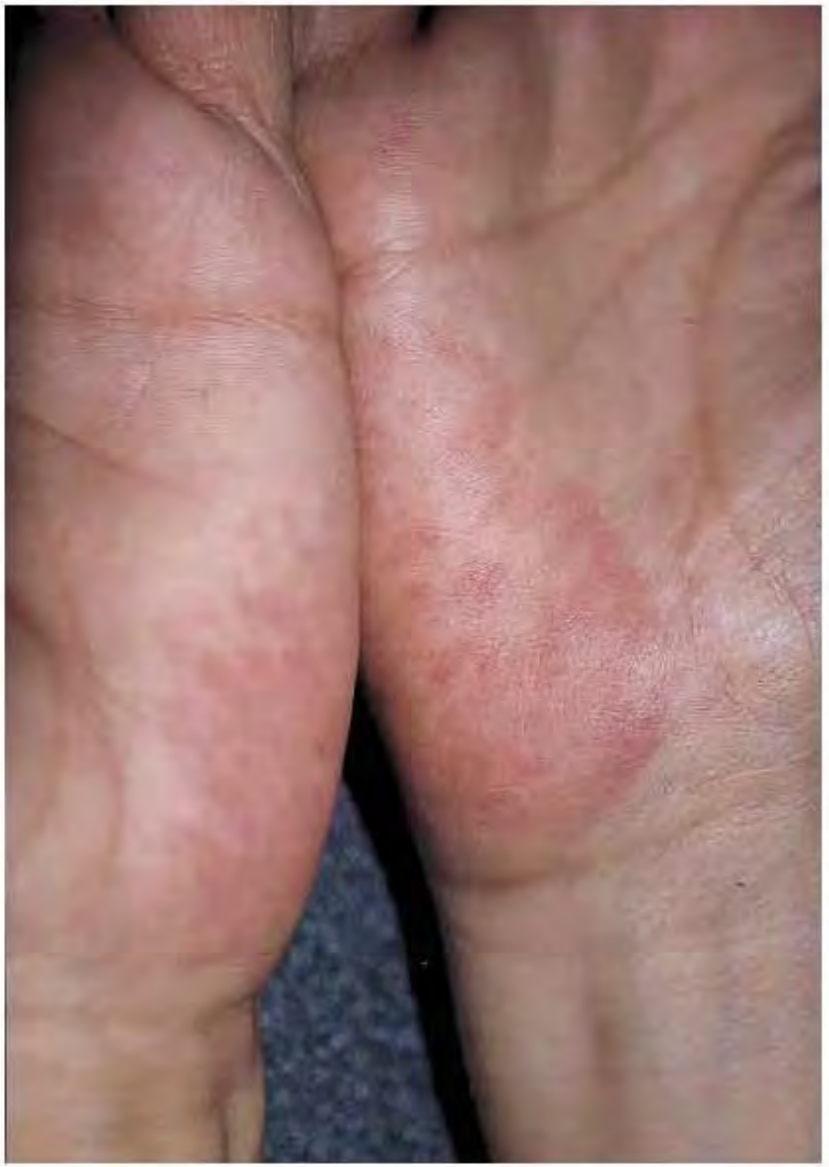

Fig 1. Well-demarcated blanchable erythema with telangiectases.

Pediatric Dermatology Vol. 34 No. 5 e283–e285, 2017

Palmar Eccrine Hidradenitis Secondary to Trauma from Computer Gaming in an Adolescent After Bone Marrow Transplantation

Abstract: **A 14-year-old boy who had undergone a matched sibling bone marrow transplant for acute lymphoblastic leukemia presented with painful nodules on his palms after prolonged gaming on his computer and mobile phone. Histology showed a neutrophilic inflammatory infiltrate surrounding the acrosyringium and eccrine sweat coils in the deep dermis. The lesions resolved spontaneously with conservative management.**

A 14-year-old Chinese boy presented with multiple painful nodules on both palms (Fig. 1) for 2 days. He had undergone matched-sibling bone marrow transplantation (BMT) for acute lymphoblastic leukemia (ALL) 40 days before the skin lesions developed. Before BMT he was given intrathecal methotrexate, oral allopurinol, intravenous cytarabine, cyclophosphamide, and cyclosporine.

He played computer games on his laptop and mobile phone 8 hours/day for 2 weeks before the

Figure 1. Erythematous nodules over the palms, especially over finger pulps (top). The position of the patient's hands on his mobile phone and laptop when gaming, causing repeated trauma mainly to his palms and finger pulps (bottom).

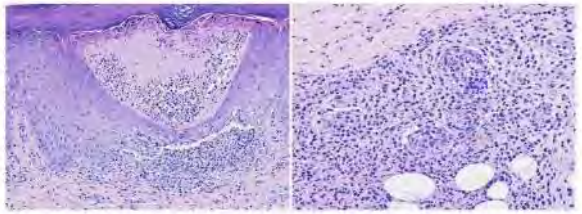

Figure 2. A dense nodular neutrophilic infiltrate around eccrine sweat units (left) and neutrophilic infiltrate within the walls of the secretory tubules and proximal ducts of the eccrine units (right).

DOI: 10.1111/pde.13224

Collagenous vasculopathy

- Idiopathic microangiopathy of the superficial dermal vessels
- Clinically asymptomatic teleangectasia
- Histopathology shows teleangectatic vessels in the superficial dermis
- Perivascular, PAS+ deposits of type IV collagen

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Cutaneous collagenous vasculopathy with generalized telangiectasia: an immunohistochemical and ultrastructural study

We report a 54-year-old male, with a 5-year history of spreading asymptomatic generalized cutaneous telangiectases. The patient had no mucosal or nail involvement, no positive family history and no clinical evidence of systemic disease or bleeding diathesis. Histologically, the superficial small dermal blood vessels were dilated and showed thickened walls with hyaline perivascular material, staining as collagen. The vessel walls were PAS and colloidal iron stain positive, and immuno-histochemically lacked actin staining. Collagen IV, fibronectin and laminin antibodies showed the material deposited around the basement membrane zone. Ultrastructurally, the vessels were post-capillary venules (PCV) and showed marked collagen deposition around the basal lamina. There were many abnormally banded widely spaced fibres with 100–150 nm periodicity (Luse bodies), in addition to regular banded collagen. Pericytes were sparse and lacked intracytoplasmic filaments, and few veil or fibroblastic cells were seen embedded within the collagen. We believe this is a form of cutaneous microangiopathy not previously described, with distinct morphology and unique ultrastructural features. It may be due to a genetic defect with erroneous production of disorganized collagen in the cutaneous microvasculature. Dermatologists and Dermatopathologists should be aware of this unusual cutaneous vasculopathy.

Salama S, Rosenthal D. Cutaneous collagenous vasculopathy with generalized telangiectasia: an immunohistochemical and ultrastructural study.
J Cutan Pathol 2000; 27: 40–48. © Munksgaard 2000.

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The human dermal microvasculature is composed of two plexuses, an upper horizontal network in the papillary dermis (subpapillary plexus), from which arcades of capillary loops arise, and a lower horizontal plexus at the dermal-subcutaneous interface. The detailed ultrastructural studies by Braverman[1] provide a sound framework for studying and understanding the organization of the cutaneous microcirculation in normal and pathologic states. The arteriolar and venular sides of the microvasculature can be identified by the ultrastructure of the basement membrane (B.M.) material.[1]

Telangiectasia denotes permanent dilatation of venules, and occasionally capillaries and arterioles of the subpapillary plexus. It may be secondary to vari-

* This case was presented in part at the Joint Meeting of the International Society of Dermatopathology, American Society of Dermatopathology, European Society of Dermatopathology and Latin American Society of Dermatopathology, Orlando Florida USA, February 25–26, 1998; and the American Society of Dermatopathology, Denver Colorado, USA, October 25–November 1, 1998.

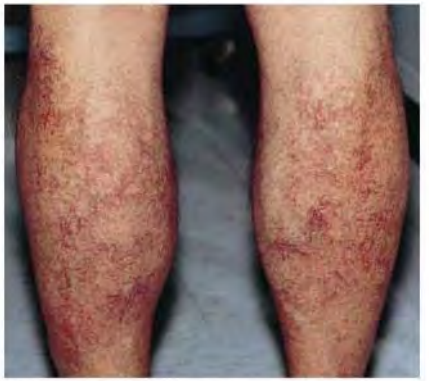

Fig. 1. View of patient's legs showing symmetrical superficial telangiectasia.

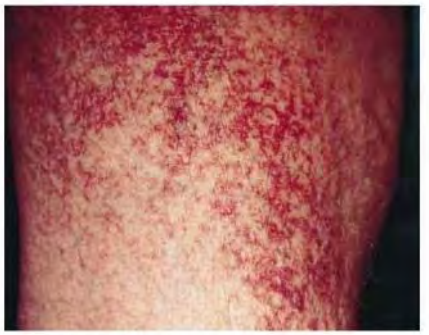

Fig. 2. Close up showing arborizing or branched linear telangiectases with dusky red colour.

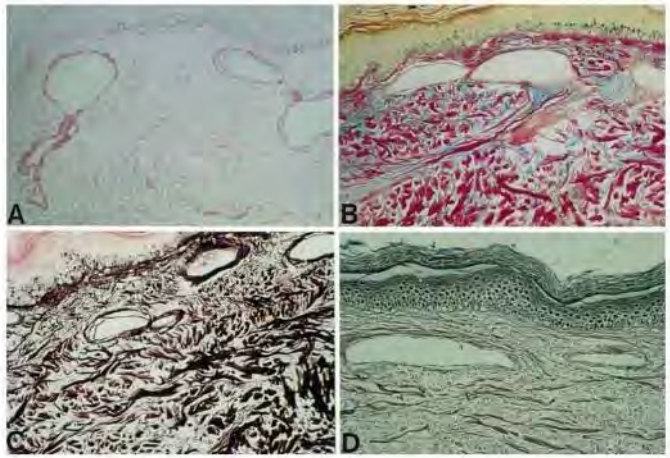

Fig. 4. Histochemical staining. a) The vessel wall staining red with PAS (-D) stain. B) Colloidal Iron (Hale) stain showing basophilic deposits of acid mucopolysaccharides around the dilated vessels. C) The abnormal blood vessels show thickening of the walls, with one vessel showing "splitting" or reduplication (Methanamine silver stain). D) Increased reticulum fibres, shown with the reticulin stain.

Cutaneous Collagenous Vasculopathy: Report of Two Cases Presenting as Disseminated Telangiectasias and Review of the Literature

Laure Bondier, Mathilde Tardieu, MD,*† Perrine Leveque, MD,*† Isabelle Challende,* Nicole Pinel, MD,‡ and Marie T. Leccia, MD, PhD*†*

Abstract: Cutaneous collagenous vasculopathy is a recently described idiopathic microangiopathy characterized by acquired diffuse cutaneous telangiectasias and specific histological features: dilated capillaries in the superficial dermis, with walls thickened by hyaline material containing collagen IV by immunohistochemistry. The authors describe 2 cases and review all cases reported in the literature to date, 34 cases including our own. Cases were mainly observed in women (sex ratio 0.41), median age 63.5 (16–85). Hypertension and diabetes seem more frequent in these patients than in the general population. Typical clinical presentation is fine hair telangiectasias appearing on the lower limbs and progressing toward the trunk and upper limbs, sparing the face. Facial and neck involvement are however reported. When faced with isolated acquired diffuse cutaneous telangiectasias, clinicians should perform a skin biopsy to rule out cutaneous collagenous vasculopathy.

Key Words: cutaneous collagenous vasculopathy, telangiectasias, luse bodies, type IV collagen

(*Am J Dermatopathol* 2017;39:682–688)

INTRODUCTION

Cutaneous collagenous vasculopathy (CCV) was first described in 2000 by Salama and Rosenthal.[1] It presents clinically as diffuse cutaneous telangiectasias, localized mainly on the limbs, sparing the face. Histology is essential for diagnosis and shows dilated vessels with walls thickened with hyaline material positive for collagen IV staining. Electronic microscopy shows scattered collagen fibrils among thinly grainy material. CCV is rare (unknown incidence, 32 reported cases to date), but probably underdiagnosed, because histology is not routinely performed in cases of acquired telangiectasias. We herein describe 2 cases of histologically proven CCV and review all reported cases to date.

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The authors declare no conflicts of interest.

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PATIENTS AND METHODS

Case Description

The first patient is a 77-year-old woman presenting with telangiectasias that had first appeared 14 years earlier on the lower limbs and extended progressively. Medical history was significant for atrial fibrillation, coronary thrombosis, hypertension, dyslipidemia, chronic renal insufficiency (creatinin clearance 22 mL/min), type 2 diabetes, sleep apnea syndrome. Medical treatment included flunidone, lysine acetylsalicylate, rosuvastatin, insulin, bisoprolol, amlodipine, furosemide, pregabalin, vitamin D3. Family history was unremarkable. She reported no abnormal bleeding or history of anemia.

Physical examination showed widespread, symmetrically distributed, macular fine branching telangiectasias. They predominated on the trunk (chest, upper back and buttocks), the posterior face of the arms, and the feet (Fig. 1). Lesions were also noted on the face, chin, retroauricular and glabellar areas (Fig. 1). Neither Darier sign, mucosal involvement, nor cutaneous atrophy was noted. General physical examination was unremarkable.

Histology showed dilated capillaries in the superficial dermis with thickened walls containing hyaline material, identified by PAS (Periodic acid Schiff) staining (Fig. 2A). This material showed stratification and was labeled by anti-collagen IV antibodies (Fig. 2B). On electron microscopic examination, thickened vascular walls contained collagen fibrils scattered in a fine granular material. Luse bodies (long spacing collagen) were noted (Figs. 2C, D). Based on these findings, CCV was diagnosed. No treatment was sought by the patient whose quality of life was not impaired.

The second patient is a 60-year-old woman who sought laser therapy for telangiectasias that had been appearing for the past 20 years. Medical history included epilepsy since age 9, hypertension and in situ breast cancer. Medications included phenobarbital, sodium valproate, spironolactone, and altizid. Family history was unremarkable. She reported no abnormal bleeding or history of anemia.

Telangiectasias had initially appeared on the lower limbs, followed by the forearms, with a symmetrical distribution (Fig. 3). The trunk, face, and mucosa were spared. Telangiectasias were macular with fine branching on the legs, were livedoid on the thighs, and diffusely erythematous on the forearms (Fig. 3). Physical examination was otherwise unremarkable.

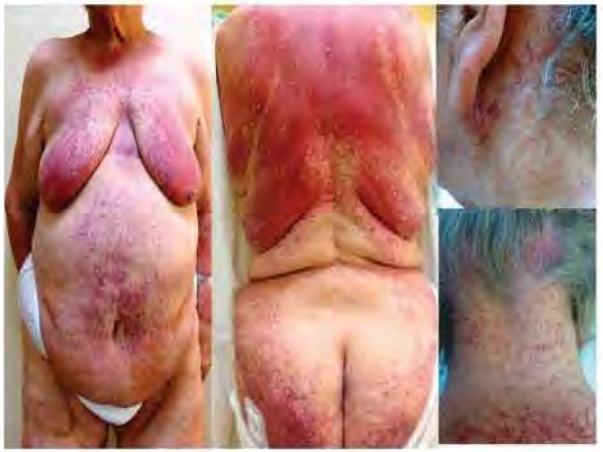

FIGURE 1. Diffuse telangiectasias on the trunk, on the glabellar, chin, and retroauricular.

Histology was typical of CCV, showing dilated capillaries in the superficial dermis, with marked wall thickening by an eosinophilic hyaline amorphous PAS-positive material with staining characteristic of collagen. Immunohistochemistry showed type IV collagen (Fig. 4A). Electron microscopy showed granular material with short and scattered collagen fibrils, with stratification of the basal membrane (Fig. 4B). No Luse bodies were found. Complete blood count, hemostasis, protein electrophoresis, antinuclear anti-DNA, antiphospholipid antibodies, and rheumatoid factor were normal or negative. A treatment by KTP laser was attempted on a sample area on the right lower limb. It was discontinued because of poor tolerance and inefficiency.

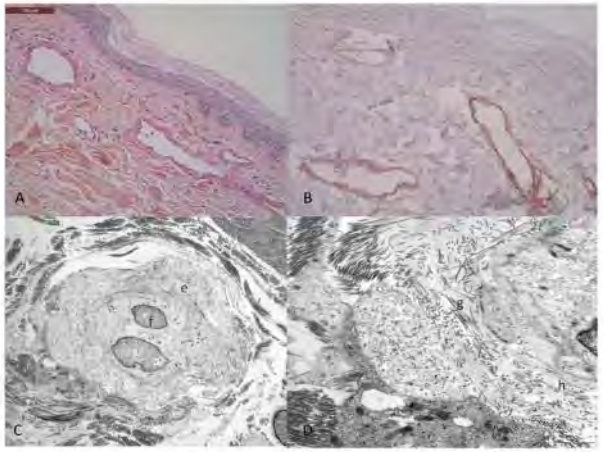

FIGURE 2. A, Dilated capillaries in the superficial dermis with thickened walls containing hyaline material, outlined by PAS staining. (PASx20). B, Positivity for collagen IV with stratification by histochemistry. C, Capillaries on electron microscopic examination, e/collagen fibrils scattered in a fine granular material, f/endothelial cell. D, Capillary wall on electron microscopic examination, g/collagen fibrils scattered in a thinly grainy material, h/Luse bodies.

TABLE 1. Clinical and Histopathological Characteristics of the 34 Patients With Cutaneous Collagenous Vasculopathy

Reference	Sex	Age on Diagnosis (yr)	Duration of CCV on Diagnosis (yr)	Comorbidities	Treatments	Location of Telangiectasias	Histopathology
Salama et al[1]	M	52	0.4	Depression, alcoholism	Amitriptylin	Trunk, upper and lower limbs	Typical* − Luse bodies
Davis et al,[2] 2008	M	59	7	Type 2 diabetes, dyslipidemia, hypertension	Metoprolol, glibenclamide, exenatide, cyclobenzaprine, insulin, fluoxetine, rosuvastatin	Chest, abdomen, forearms	U
Davis et al,[2] 2008	M	62	U	Type 2 diabetes, hypertension, psoriasis, polyarthritis	Lisinopril, metformin, alloprurinol, clobetasol	Thighs	U
Davis et al,[2] 2008	M	80	U	Atrial fibrillation, gastroesophageal reflux, venous insufficiency	Warfarin, metoprolol, omeprazol	Abdomen, thighs, hands, back	U
Monteagudo et al[3]	M	68	15	Hypertension, dyslipidemia, prostatic adenoma, hyperuricemia, alopecia	Atenolol, atorvastatin, allopurinol, tamsulosin	Abdomen, legs, feet, forearms, thighs	Typical*
Perez et al[4]	F	51	16	Hypothyroidism, psoriasis	U	Trunk, neck, limbs, retroauricular, nape of the neck	Typical* + the perivascular hyaline material was highlighted by laminin stains
Perez et al[4]	F	71	7	Pituitary tumor, osteoporosis	Calcium, radiotherapy	Feet, chest, upper and lower limbs, cheeks	Typical*
Kanitakis et al[5]	M	65	5–6	Hypertension, coronary thrombosis, prostatic adenoma,	Losartan, diltiazem, pravastatin, aspirin, ranitidine, molsidomine	Feet, legs, abdomen, back, flanks, buttocks, arms	Typical* + no Luse bodies
Lloyd et al[6]	F	16	3	Mood disorder	U	Trunk, legs, arms	Typical* − a normal to slightly high number of mast cells
Bernard et al[7]	F	47	0.6	Hypertension, type 1 diabetes, hypothyroidism, psoriasis	Ramipril, amlodipine, levothyroxine, insulin	Lower limbs, forearms, abdomen	Typical*
Burdick et al[8]	M	59	<1	Type 2 diabetes, hypertension, dyslipidemia, depression, osteoarthritis	U	Legs, thighs, abdomen	Typical*
Burdick et al[8]	F	68	>50	Hypertension, dyslipidemia, gastroesophageal reflux, sleep apnea syndrome	U	Extremities	Typical*
Burdick et al[8]	M	70	10	Hypertension, type 2 diabetes, dyslipidemia	U	Right leg	Typical*
Burdick et al[8]	F	41	>1	Basal cell carcinoma, hepatitis cured	U	Forearms	Typical*
Echeverria et al[9]	F	42	7	U	No	Foot, legs, abdomen, arms, neck	Typical*
Gonzalez Fernandez et al[10]	F	83	>20	Atrial fibrillation, mitral valve plasty, hepatitis C, benign prostatic hypertrophy	Eplerenone, lorazepam, furosemide, acenocoumarol	Upper and lower limbs, abdomen	Typical* − colloidal iron staining showed deposits of mucin in the hyaline material
Gonzalez Fernandez et al[10]	F	74	11	Discoidal lupus, venous insufficiency, depression	Sertraline, pentoxifylline, alprazolam, omeprazol	Lower limbs	Typical* − discrete deposits of colloidal iron-positive mucin in the hyaline material
Bertolotti et al[11]	F	46	10	Dyslipidemia, diabetes, dilated cardiomyopathy	U	U	Typical*
Bardazzi et al,[12] 2014	F	57	9	Uveitis, hypertension, allergy	Losartan, hydrochlorothiazide	Legs, trunk, arms, fingers, buttocks	Typical*

(continued on next page)

TABLE 1. (*Continued*) Clinical and Histopathological Characteristics of the 34 Patients With Cutaneous Collagenous Vasculopathy

Reference	Sex	Age on Diagnosis (yr)	Duration of CCV on Diagnosis (yr)	Comorbidities	Treatments	Location of Telangiectasias	Histopathology
Salama et al[13]	M	84	3	Type 2 diabetes mellitus, myelodysplastic syndrome, celiac disease, supraventricular tachycardia	Metformin, raloxifene, rosuvastatin, eprex	Lower extremities, trunk	Typical* + intravascular organizing fibrin thrombi associated with proliferation of endothelial cells
Borroni et al,[14] 2015	F	58	5	Hypertension, arthritis, asthma, coronary artery bypass grafting	Nebivolol, acetylsalicylic acid, budesonide, atorvastatin, olmesartan, amlodipine	Breasts, trunk, feet	Typical*
Ma et al[15]	F	38	2			Trunk, arms, legs	Typical*
Meah et al[16]	F	76	2	Hypertension, chronic kidney disease	Doxazosin, simvastatin, losartan, omeprazole, benzodiumethiazide	Limbs, trunk	Typical* + solar elastosis
Basso et al[17]	F	77	57	Ischemic heart disease with arrhythmias, chronic renal insufficiency	Pharmocommor, acetylsalicylic acid, oxazepam, levocetirizine	Legs, thighs, arms, chest	Typical*
Toca-Brito et al[18]	F	67	5	Hypertension, coronary heart disease, obesity, dyslipidemia, chronic venous insufficiency	Perindoxril, bisoprolol, clopidogrel, atorvastatin.	Upper extremities, lower extremities	Typical*
Salama[19]	F	68	U	Mild chronic renal failure, cryofibrinogenemia	U	Lower extremities	Typical* − few lymphoid or mononuclear cells around the abnormal blood vessels + Luse bodies
Salama[19]	F	85	10	Type 2 diabetes mellitus	U	Lower extremities	Typical* − Luse bodies
Salama[19]	F	50	2	U	U	Lower extremities, upper extremities	Typical* − few lymphoid or mononuclear cells around the abnormal blood vessels − Luse bodies
Salama[19]	F	69	U	Type 2 diabetes mellitus	U	Lower extremities, upper extremities, abdomen	Typical* − Luse bodies
Salama[19]	F	56	25	U	U	Lower extremities, upper extremities, trunk	Typical* − Luse bodies
Salama[19]	F	42	20	Raynaud	U	Lower extremities	Typical* − few lymphoid or mononuclear cells around the abnormal blood vessels − Luse bodies
Salama[19]	M	73	2.5	U	U	Lower extremities, upper extremities	Typical* − Luse bodies
Current case	F	77	14	Atrial fibrillation, coronary thrombosis, hypertension, dyslipidemia, chronic renal insufficiency, type 2 diabetes, sleep apnea syndrome, obesity	Flunitrazepam, rosuvastatin, lysine acetylsalicylate, insulin, bisoprolol, amlodipin, furosemide, prégabaline, vitamin D3	Trunk, upper limbs, buttocks, thighs, face, chin, retroauricular, glabellar	Typical* − Luse bodies
Current case	F	60	20	Epilepsy, hypertension, carcinome in situ breast cancer	Phenobarbital, sodium valproate, spironolactone, altizide	Lower limbs, forearms	Typical*

Summary of Variables	Sex Ratio	Median (Range)	Median (Range)	Percentage	Percentage	Percentage	Percentage
	0.7/1	63.5 (16–85)	7 (0.4–57)	Hypertension 41.2, diabetes 29.4, dyslipidemia 20.6	Statins 23.5, beta blockers 18	Lower extremities 91, upper extremities 70	Typical in all cases described

*Typical: dilated blood vessels of the superficial dermal plexus with marked wall thickening due to deposition an eosinophilic hyaline amorphous material that showed staining characteristic of collagen and was PAS positive. Immunohistochemically, this material showed immune reactivity to collagen type IV.
F, female; M, male; U, unknown.

Degos disease-like scleroderma

- A wedge-shaped sclerosis with mucin deposition and surrounded by inflammatory infiltrate may mimic the wedge-shaped degenerative changes of Degos disease
- Guttate scleroderma may present clinically with "porcelain-like" small lesions, akin to Degos disease
- Accurate clinicopathologic correlation important in order to avoid mistakes

Lesions Resembling Malignant Atrophic Papulosis in a Patient With Progressive Systemic Sclerosis

Clive M. Liu, MD; Ronald M. Harris, MD, MBA; C. David Hansen, MD

Malignant atrophic papulosis (MAP), or Degos syndrome, is a rare disorder of unknown etiology. It is characterized by a deep subcutaneous vasculopathy resulting in atrophic, porcelain-white papules. We report the case of a 42-year-old woman with a history of progressive systemic sclerosis who presented with painful subcutaneous nodules on her abdomen along with chronic atrophic papules on her upper and lower limbs. Biopsy results of both types of lesions revealed vascular thrombi without surrounding inflammation. We briefly review the literature on MAP and its association with various connective tissue diseases. To our knowledge, there have been no previous reports of a patient with the clinical and histologic presentations described here. Although the histologic appearance of the subcutaneous nodules was very similar to that of the atrophic papules, the clinical characteristics of the 2 types of lesions were strikingly different. It is fair to theorize that Degos lesions do not start as atrophic porcelain-white papules but rather evolve from a primary lesion. We hypothesize that these lesions start as painful red nodules and may represent part of the disease spectrum in the evolution of MAP.

Cutis. 2005;75:101-104.

Malignant atrophic papulosis (MAP), or Degos syndrome, is characterized as a vasculopathy of unknown etiology. Described by Degos and colleagues[1] in 1942, the disease presents as multiple porcelain-white erosions. Associated symptoms often include abdominal pain, gastrointestinal bleeding, and neurologic deficits. The prognosis is usually poor. Histologic characteristics include a vasculopathy below the necrobiotic zone with endothelial swelling, proliferation, and thrombosis. To our knowledge, only a few cases of MAP associated with connective tissue disease have been reported: 4 cases with systemic lupus erythematosus, 1 with dermatomyositis, and 1 with progressive systemic sclerosis.[2-5] We present the case report of a woman with progressive systemic sclerosis and MAP-like lesions.

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The authors report no conflict of interest.

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Case Report

Round erosions with dry central crusts developed on a 42-year-old woman with a long history of progressive systemic sclerosis, significant pulmonary hypertension, and right heart failure. Although the lesions were scattered on all limbs, the most prominent lesions extended from the right labium majus down the anterior aspects of both limbs. Associated symptoms included mild pruritus.

One month after the appearance of these lesions, painful subcutaneous nodules developed on the patient's abdomen in a background of mild diffuse erythema. The nodules were exquisitely tender on palpation. Abdominal pain was confined to the area of the cutaneous lesions. The patient denied any fever, chills, diarrhea, nausea, or vomiting. In addition to progressive systemic sclerosis, the patient's medical history included iron deficiency anemia, restless legs syndrome, gastroesophageal reflux disease, and depression. Her medications included treprostinil (UT-15, an experimental prostaglandin used to treat her pulmonary hypertension), levothyroxine, lansoprazole, sertraline, furosemide, spironolactone, and hydromorphone hydrochloride. There were no known drug allergies.

Significant findings from the physical examination included a mask with multiple matted telangiectasias and cyanosis. The phalanges were firm and sclerotic with marked cyanosis. On the lower

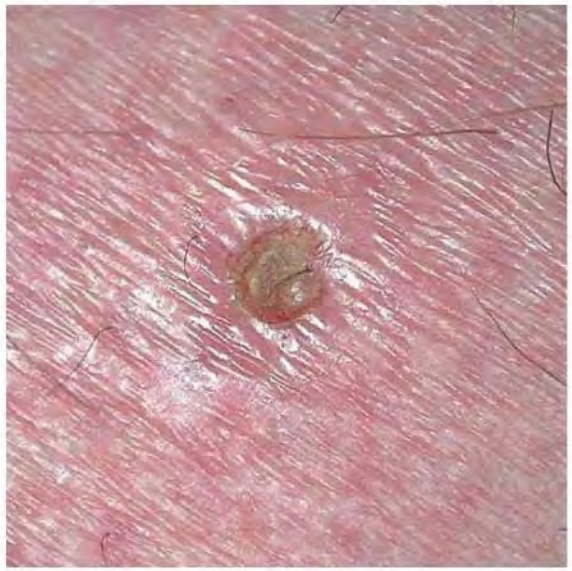

Figure 1. Necrotic atrophic papule on the lower limb of a 42-year-old woman.

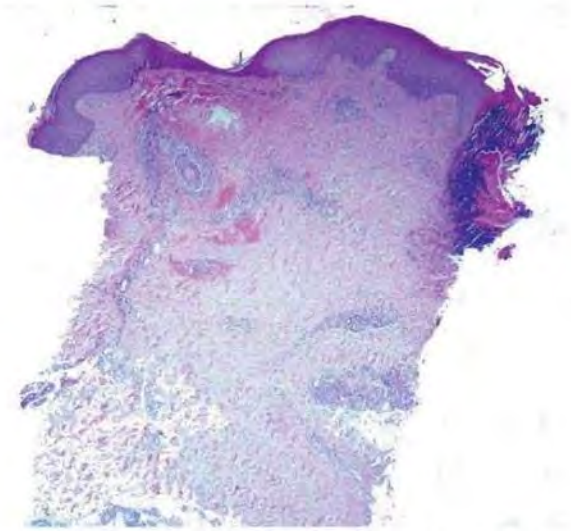

Figure 2. Crusted necrotic papule with wedge-shaped architecture on the proximal thigh. Full-thickness epidermal ulceration, mild neutrophilic inflammatory diapedesis, and deep dermal hemorrhage (H&E, original magnification ×20).

S-100 positivity in leprosy

- Old reports mentioned positivity of histiocytes for S-100 in some cases of leprosy
- Modulation of S-100 within macrophages has been suggested as a possible cause; Unlikely due to cross-reactivity with mycobacteria
- S-100 positivity may be misinterpreted as a histiocytic tumor
- Old literature, sometimes, still helps…

Rev. Inst. Med. trop. São Paulo
32(1): 70-71, janeiro-fevereiro, 1990

LETTER TO THE EDITOR

COMMERCIALLY AVAILABLE ANTI-S-100 PROTEIN SERUM STAINS M. LEPRAE IN LEPROSY TISSUES BY IMMUNOHISTOCHEMICAL PROCEDURES.

Demonstration of bacilli and consequently of their antigenic products is easily feasible in multibacillary (LL, BL, BB) forms of leprosy. However, the presence of a non specific chronic inflammatory infiltrate, as seen in indeterminate leprosy, or the persistence of a granuloma in the paucibaccilary (BT, TT) forms of leprosy in the absence of demostrable bacilli, may indicate that free antigenic products are initiating the apparently non-specific inflammation and/or perpetuating the granuloma (9).

Immunohistochemistry proved to be useful to demonstrate infectious organisms and/or their antigens in tissues. Antigenic analysis indicates that there are common antigenic sites among mycobacterial species. On this basis rabbit anti-BCG serum has been widely used as the primary antibody to demonstrate both the bacilli and their antigens in leprosy tissues (5,6). Recently monoclonal antibodies against **M. leprae** have been produced which recognise specific antigens on cell surfaces of leprosy lesions (8).

A phenolic glycolipid with a structure related to mycoside A of **Mycobacterium kansasii** was found in **M. leprae** preparation and had its structure elucidated by HUNTER & BRENNAN (3) and HUNTER, FUJIWARA & BRENNAN (4). A highly specific trisaccharide for serodiagnosis of leprosy was synthesized and proved to be highly sensitive in ELISA (1). This synthetic trisaccharide (ST) is antigenic and anti-serum against it was raised in rabbits by a standard procedure, using incomplete Freund's adjuvant, and was used as primary antibody in an avidin-biotin peroxidase immunohistochemical reaction by us. In multibacillary leprosy, bacilli and/or their antigens were heavily stained in essentially similar manner by anti-BCG and anti-ST sera. In paucibacillary leprosy isolated macrophages in the granuloma were stained by both anti-sera, probably indicating antigenic products which might be relevant in the perpetuation of the granulomatous inflammation.

S-100 is an acidic calcium binding protein so-named because of its solubility in 100% ammonium sulphate solution at neutral pH; it is distributed in the brain of a wide variety of species and is regarded as species non-specific (7). The finding of S-100 antigen in non-nervous tissues and, particularly in antigen-presenting cells of the skin in normal conditions, suggests that S-100 should no longer be considered strictly as a nervous system specific protein. In paucibacillary leprosy S-100 antigen detection was used as a marker to cutaneous nerve branches, since dermal nerves impairment by inflammatory reaction permits the differential diagnosis between paucibacillary leprosy and other skin granulomatosis (2).

A positive staining of **Mycobacterium leprae** and/or its antigens with commercially available (DAKO, Denmark) polyclonal anti S-100 rabbit serum was detected by us in multibacillary leprosy. Essentially similar antigenic sites were demostrated by S-100, anti BCG and anti ST sera. Lepromin absorbed anti S-100 serum failed to stain bacilli but maintened its staining properties as far as antigen presenting cells and dermal nervous branches were concerned. Therefore, the use of non-specifically absorbed commercial anti S-100 protein polyclonal serum in paucibacillary leprosy stains structures known to be usually stained by this anti-serum together with bacillary antigens. The staining properties of **M. leprae** by commereially available (DAKO) polyclonal anti S-100 protein serum is really an artefact. This anti-serum is raised in rabbits using complete Freund's adjuvant, which contain mycobacteria. Consequently different antibodies are present in the anti-serum, some recognizing **M. leprae** and others recognizing S-100 protein.

Therefore, care should be taken when using in immunohistochemical procedures commercially available anti-serum in infectious diseases, chiefly in countries where tuberculosis and leprosy are endemic.

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Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13a

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In the defense against *Mycobacterium leprae*, macrophages play an essential part in the mechanism of bacterial lysis but require the presence of cytokines such as interleukin 2 and gamma interferon from lymphocytes in order to effectively kill the organisms in any number. While there have been many studies of the lymphocytes in lesions of leprosy, less attention has been given to the immunohistochemical characterization of the macrophage populations. In this study, the cutaneous lesions of 69 patients with leprosy (42 lepromatous, 5 mid-borderline, and 22 tuberculoid) were evaluated by immunohistochemistry for the expression of S100 protein, CD1a, CD68, muramidase, HLA-DR, and Factor 13a. The macrophages from lesions of polar, subpolar, and borderline lepromatous leprosy patients expressed S100 protein intensely and constantly. In contrast, the lesions of polar and subpolar tuberculoid leprosy had very few cells that were immunoreactive for S100 protein ('S100+') in the granulomas in the dermis. The macrophages in all lesions were reactive for CD68 and muramidase. In paraffin sections, macrophages of lepromatous lesions failed to stain for HLA-DR, whereas in tuberculoid lesions, they were strongly positive for HLA-DR. Three patients with histoid leprosy (relapse lesions) had lesions that were strongly positive for Factor 13a and were negative for S100 protein ('S100-'). Given the possible chemotactic and migration inhibition effects of the calcium-binding proteins of the S100 family, these data suggest a possibly important role for S100 protein in the accumulation of macrophages in lepromatous leprosy, and also reveal infection of Factor 13a + dermal dendritic cells in histoid leprosy.

Cuevas-Santos J, Contreras F, McNutt NS. Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13a.
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The intracellular residence of *Mycobacterium leprae* makes cytolytic activity of the macrophages essential for the destruction of the organisms. The presence of lymphokines, such as interleukin-2 and gamma interferon, from T-lymphocytes is essential for the activation of cytolytic activity by the macrophages after phagocytosis (2–9). Genetic factors also play a role in the type of lymphocytic response to *M. leprae* organisms (10–13).

The cutaneous reactions to *M. leprae* have been divided into histological patterns based on the number and state of aggregation of macrophages, the foamy appearance of the cytoplasm of the

This work is a portion of the doctoral thesis of Dr. Jesús Cuevas-Santos, approved in 1996 by the Facultad de Medicina, University of Alcalá de Henares, Spain, under the direction of Dr. Félix Contreras-Rubio and Dr. José Luis Bardasano-Rubio (1).

Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13a

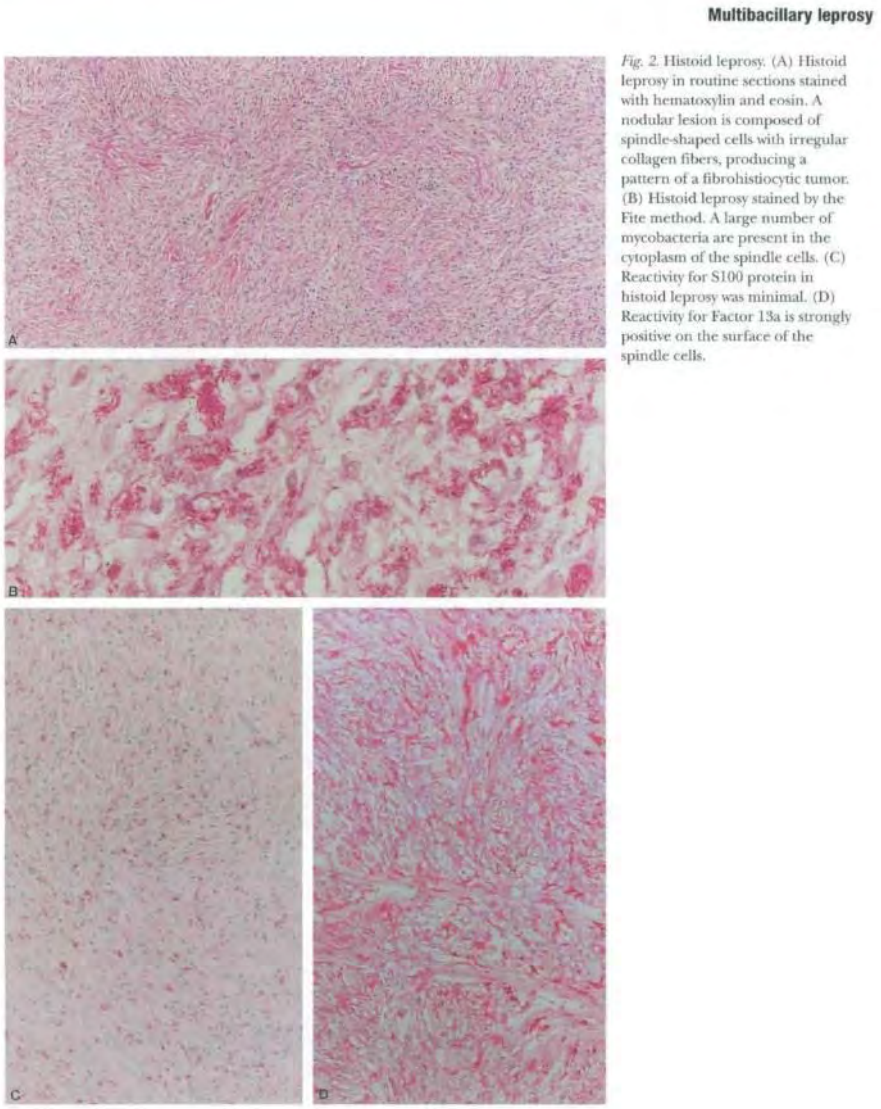


Fig. 2. Histoid leprosy. (A) Histoid leprosy in routine sections stained with hematoxylin and eosin. A nodular lesion is composed of spindle-shaped cells with irregular collagen fibers, producing a pattern of a fibrohistiocytic tumor. (B) Histoid leprosy stained by the Fite method. A large number of mycobacteria are present in the cytoplasm of the spindle cells. (C) Reactivity for S100 protein in histoid leprosy was minimal. (D) Reactivity for Factor 13a is strongly positive on the surface of the spindle cells.

Of several possible explanations for the S100 positivity, the modulation of the amount of S100 protein in the macrophages seems more reasonable than other possibilities (…).

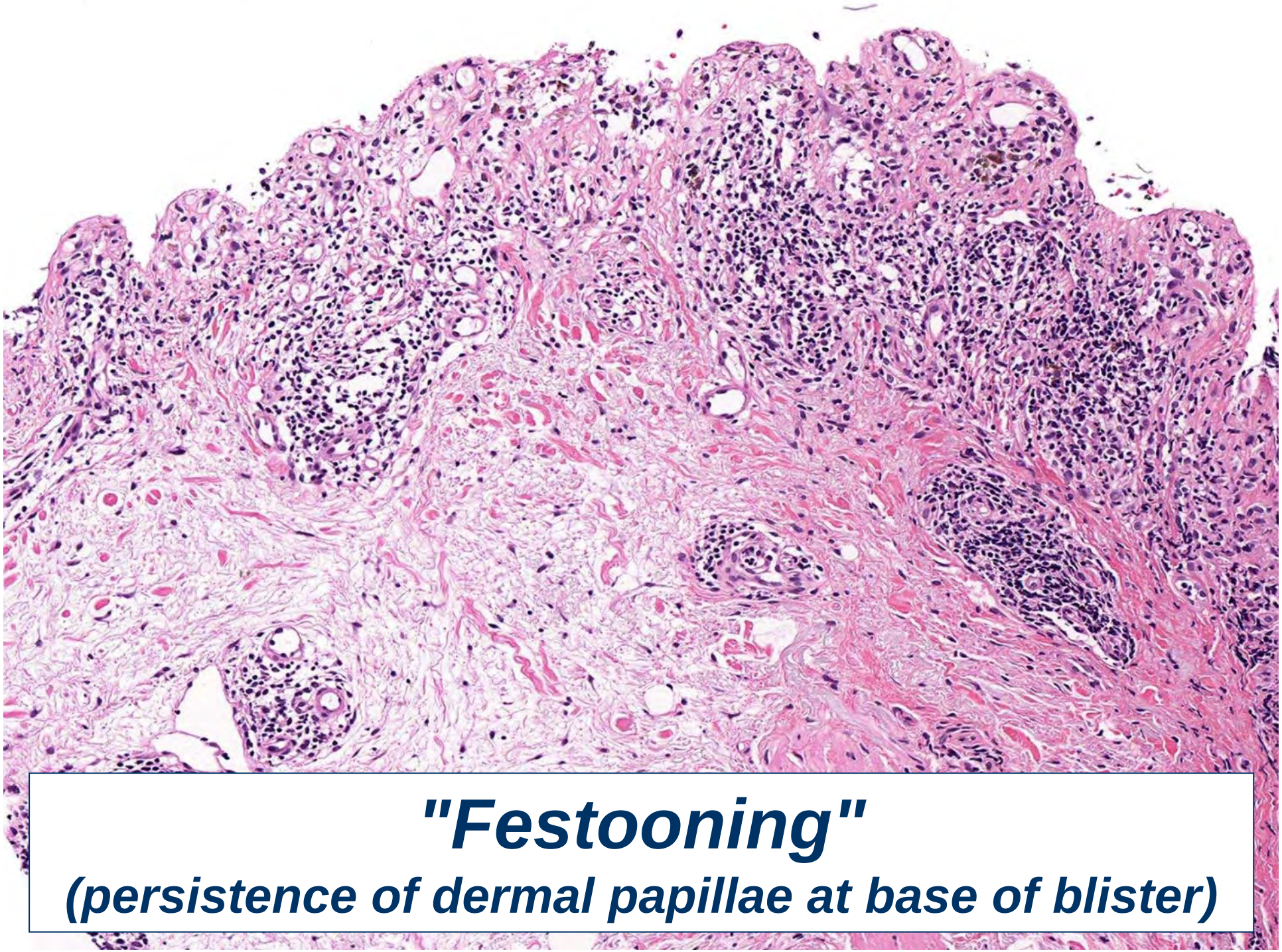
The trivial possibility that the antibody to S100 protein cross-reacts with some component of the mycobacteria themselves is ruled out by the observations that lepromatous patients who have been treated so that few bacilli can be stained still retain S100 positivity in the macrophages.
Also the observation that the lesion from three patients with histioid leprosy contained abundant mycobacteria but were S100 negative is evidence against any hypothesis that the bacteria themselves react with the anti-S100 antibody.

Lichen sclerosus

- Circumscribed changes observed in guttate LSA
- Sometimes associated with morphea ("sclerolichen"); may be guttate as well
- Other unusual histopathological presentations: pseudolymphomatous with band-like, epidermotropic lymphocytes and without sclerosis of the dermis (observed almost only on genital skin); haemorrhagic lymphangioma-like (both genital and non-genital skin)

Bullous lichen planus

- Should be distinguished from lichen planus pemphigoides
- In many (most?) cases subepidermal cleft visible on histology, but bullous lesions not present clinically (post-excision fixation artifact?)
- Develops as a result of extensive junctional damage *(i.e. exaggerated Max-Joseph spaces)*
- Does not show any differences from conventional lichen planus in terms of treatment and prognosis



"Festooning"

(persistence of dermal papillae at base of blister)

Festooning

- Porphyria cutanea tarda; other forms of porphyria including drug-induced pseudoporphyria
- Epidermolysis bullosa
- Cell-poor bullous pemphigoid
- Suction blisters
- This case: lichen planus

Cutaneous IgG4-related disorders

- IgG4 related to different disorders at extracutaneous sites
- In the skin IgG4+ plasma cells found in unrelated conditions (e.g., granuloma faciale, AHWE, cutaneous plasmacytosis); IgG4+ plasma cells may be observed also in lesions unrelated to IgG4-related disorders
- In some cases skin rash in extracutaneous IgG4-related disorders; clinicopathological features not well described

Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders

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ABSTRACT

Background IgG4-related systemic fibrosclerosis is a recently defined disorder characterised by a diffuse or tumefactive inflammatory reaction rich in IgG4-positive plasma cells associated with sclerosis and obliterative phlebitis. Although characteristic histopathological features are essential for the diagnosis of these disorders, to date there exists no consensus regarding the cut-off values used to define a 'significant IgG4-positive plasma cell count,' and data regarding the distribution of IgG4-positive plasma cells under common (non-specific) inflammatory conditions are lacking.

Methods The authors analysed 121 randomly selected histopathological specimens containing prominent lymphoplasmacytic infiltrates (71 obstructive sialadenitis, 27 inflammatory lesions of the oral cavity, 24 inflammatory gastrointestinal lesions, 15 rheumatoid synovitis, 15 non-specific synovitis, eight non-specific dermatitis and 27 primary carcinomas with a peritumoral inflammatory response). For comparison, seven cases of sclerosing sialadenitis (Küttner tumour) were examined.

Results High counts of IgG4 plasma cells were found in sclerosing sialadenitis (mean 40/high-power field (hpf)), contrasting sharply with sialadenitis caused by sialolithiasis (mean 3/hpf). Greatly varied but generally high counts of IgG4-positive plasma cells were also seen in several of the other lesions, particularly in rheumatoid synovitis (mean 55/hpf), oral cavity lesions (mean 79/hpf) and carcinoma-associated inflammatory response (mean 74/hpf). The mean IgG4/IgG ratios for all lesions varied between 0 and 0.4.

Conclusions The results demonstrate the ubiquitous occurrence of variably high numbers of IgG4-positive plasma cells under diverse non-specific inflammatory conditions, indicating that high IgG4-positive plasma cell counts and high IgG4/IgG ratios per se do not reliably distinguish IgG4 associated systemic disease from non-specific conditions, and that the IgG4 counts must be cautiously interpreted in the context of appropriate clinical and histopathological features.

INTRODUCTION

IgG4-associated sclerosing disease (ISD) has emerged recently as a unifying concept for several previously described inflammatory organ-specific conditions characterised by an elevated serum level of IgG4 and the occurrence of sclerosing lymphoplasmacytic inflammatory reaction rich in IgG4-positive plasma cells in one or more organs.[1–4] Autoimmune pancreatitis (AIP) represents the prototype of these disorders and has been the subject of extensive studies.[5 6] Recent publications have documented similar lesions in almost all body organ systems, including in particular sclerosing cholangitis,[7] sclerosing sialadenitis/Küttner tumour,[8–10] chronic sclerosing dacryocystitis,[11] idiopathic retroperitoneal fibrosis,[12] sclerosing angiomatoid nodular transformation of the spleen[13] as well as IgG4-related renal,[14] lymphadenopathic,[15] hypophyseal,[16] mediastinal,[17] pleuropulmonary[18] and soft-tissue[19] diseases. The diagnosis of any of these conditions is based on a set of both clinical and histopathological features. Dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells accompanied by a prominent (typically storiform) sclerosis and obliterative phlebitis are considered the histopathological hallmarks of ISD.

As these fibroinflammatory conditions frequently present as tumefactive lesions, concern about malignancy may prompt biopsy of the lesion. Thus, pathologists are increasingly being confronted with this differential diagnostic challenge. Several working groups have attempted to define a set of diagnostic criteria based on clinical and histopathological characteristics which allows a precise and reliable diagnosis of AIP and other ISD. However, the reliability of histopathological evaluation in the diagnosis of ISD has been challenged by the fact that variable recommendations exist by different working groups, in particular regarding the most appropriate threshold to define a 'significant IgG4-positive plasma cell count.' Thus, variable cut-off values of >10,[5 21 22] >20[23 24] and >50[25] IgG4-positive plasma cells/high-power field (hpf) have been used to define AIP in different publications. Other groups have suggested a four-tiered scoring system to assess the severity of IgG4-positive plasma cell infiltrates as severe (>50/hpf), moderate (10–50/hpf), slight (5–10/hpf) and few (<5/hpf).[26 27] However, this scoring system does not take into account the density of plasma cell aggregates and thus does not help to distinguish between real ISD and lesions that fall into the 'physiological' range of IgG4-positive plasma cell infiltration in ordinary non-specific inflammatory conditions. The use of IgG4/IgG ratios proved to be more valuable in identifying ISD than the absolute counts of IgG4 plasma cells. In their cross-sectional study of 118 cases of ISD in the most recent study, Zen *et al* used an IgG4/IgG ratio of 0.8 as a threshold for the diagnosis of ISD.[28] To our knowledge, the distribution and ranges of IgG4-positive plasma cells as

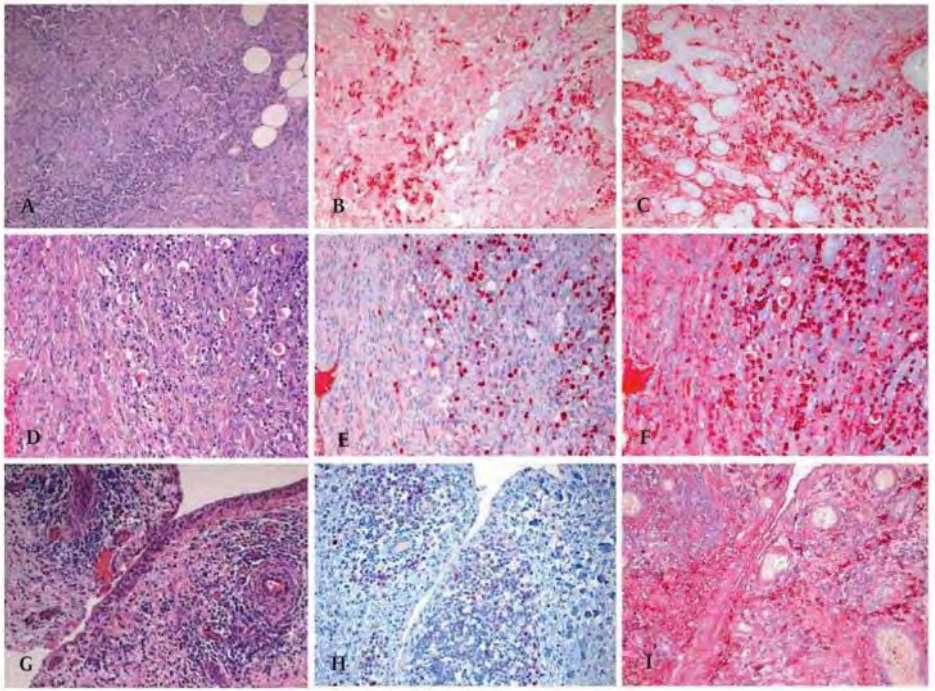

Figure 1 Representative images of H&E (left column), IgG4 (mid-column) and IgG (right column) from chronic inflammatory conditions (original magnification: 200×). (A–C) Sclerosing sialadenitis, Küttner tumour. (D–F) Rheumatoid synovitis. (G–I) Non-specific synovitis.

Table 1 Distribution of the IgG4 counts and the IgG4/IgG ratios in the study cohort (n=128 including the seven Küttner tumour cases)

Localisation	Diagnosis	n	Mean IgG4/hpf	Range IgG4/hpf	Mean IgG/hpf	IgG4/IgG mean ratio	Range IgG4/IgG ratio
Salivary glands	Sclerosing sialadenitis/Küttner tumour	7	40	4–104	74	0.59	0.23–1
	Sialadenitis caused by sialolithiasis	11	3	0–26.8	54.0	0.02	0–0.15
Oral cavity	All lesions	27	79	0–235	235	0.32	0–0.84
	Epulis plasmocellularis	12	69	27–102	232	0.32	0.18–0.77
	Radicular cysts	11	93	23.3–234	278	0.32	0.1–0.84
	Oral lichen ruber	4	67	0–217	126	0.35	0–0.84
Lower gastrointestinal tract	All lesions	24	11	0–40	187	0.06	0–0.2
	Crohn's disease	9	8	1–22	160	0.046	0.008–0.08
	Ulcerative colitis	9	8	0–18	210	0.04	0–0.06
	Diverticulitis	6	19	0–40	194	0.11	0–0.2
Synovitis	All lesions	30	35	0–181	122	0.27	0–1
	Rheumatoid arthritis	15	55	0–181	153	0.4	0–1
	Non-specific synovitis	15	15	0–79	92	0.15	0–0.44
Carcinomas	All lesions	21	24	0–88	117	0.22	0–0.51
	Adenocarcinomas	10	6	0–88	73	0.21	0–0.48
	Squamous cell carcinomas	11	34	1–81	156	0.23	0–0.51
Skin	All lesions	8	26	1–120	85	0.21	0.04–0.67

hpf, high-power field.

CME/SAM

Increased Immunoglobulin (Ig) G4–Positive Plasma Cell Density and IgG4/IgG Ratio Are Not Specific for IgG4-Related Disease in the Skin

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Key Words: Dermatopathology; Skin neoplasms; Anatomic pathology

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ABSTRACT

Objectives: *Immunoglobulin (Ig) G4–related disease (IgG4-RD), a fibroinflammatory condition that can affect multiple organs, is suggested by lymphoplasmacytic inflammation, fibrosis, phlebitis, and increased IgG4+ plasma cell (PC) tissue density. In patients with suspected IgG4-RD and skin changes, skin biopsy may serve as a diagnostic screen or to supplement nondiagnostic visceral biopsy specimens. We aimed to determine whether increased cutaneous IgG4+ PCs or IgG4/IgG ratio is specific for IgG4-RD.*

Methods: *We examined 50 mucocutaneous specimens representing seven PC-rich dermatoses and reactive PC-rich infiltrates with IgG and IgG4 immunohistochemical stains.*

Results: *IgG4+ density exceeded 10 cells per high-power field in 22 (44%) of 50 specimens, representing six of seven diagnoses and reactive infiltrates. In five specimens (10%), the IgG4/IgG ratio exceeded 0.40.*

Conclusions: *Moderately elevated IgG4+ PC density or IgG4/IgG ratio is a nonspecific finding in the skin. In cutaneous biopsy specimens showing increased IgG4+ PCs, careful consideration should be given to clinical, serologic, and other histopathologic features before attributing clinical changes to IgG4-RD.*

Upon completion of this activity you will be able to:
- list skin conditions other than immunoglobulin (Ig) G4–related disease that can be associated with increased tissue density of IgG4-positive plasma cells.
- outline the current histologic criteria for the diagnosis of IgG4-related disease.
- recognize that the presence of IgG4-positive plasma cells in the skin is not specific to IgG4-related blood disease.

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The editorial staff and the planning committee members and reviewers have no relevant financial relationships with commercial interests to disclose. Questions appear on page 244. Exam is located at www.ascp.org/ajcpcme.

Immunoglobulin (Ig) G4–related disease (IgG4-RD) is a fibroinflammatory process first described in the context of autoimmune (sclerosing) pancreatitis.[1] It has since been found to affect virtually every organ, including the gallbladder (chronic cholecystitis), lung (interstitial pneumonia), and salivary gland (chronic sclerosing sialadenitis).[2-4] Patients may present with mass lesions of the involved organ(s), often have elevated serum IgG, IgG4, and IgE, and generally improve with systemic corticosteroid treatment.[2-5]

A recent consensus statement addressed the pathology of IgG4-RD.[6] After acknowledging that certain organs do not usually become fibrotic (such as the lacrimal gland, lymph node, salivary gland, lung, and kidney), the authors summarized the characteristic histopathology as lymphoplasmacytic inflammation, fibrosis that is often storiform in nature, and obliterative phlebitis. They proposed that increased tissue

Table 1
IgG4+ Plasma Cell Density in Each Tissue Section and Mean IgG4+ Plasma Cell Density by Case and Category[a]

Diagnosis	Case No.	Field 1: IgG4 Cells/hpf	Field 2: IgG4 Cells/hpf	Field 3: IgG4 Cells/hpf	Mean per Case, IgG4 Cells/hpf	Mean per Case, IgG4/IgG Ratio	Mean per Category, IgG4 Cells/hpf	Mean per Category, IgG4/IgG Ratio
Necrobiotic xanthogranuloma	1	7	**13**	**18**	**12.67**	0.17	8.2	0.07
	2	**41**	**55**	6	**34.00**	0.17		
	3	1	0	0	0.33	0.02		
	4	**39**	2	6	**16.33**	0.14		
	5	1	2	1	1.33	0.03		
	6	0	0	0	0.00	0.00		
	7	0	2	0	0.67	0.08		
	8	1	0	0	0.33	0.03		
Pemphigus vulgaris	1	**17**	10	4	**10.33**	0.37	**15.6**	**0.44**
	2	5	6	3	4.67	0.18		
	3	10	**21**	x	**15.50**	0.22		
	4	**44**	**35**	**19**	**32.67**	**0.92**		
	5	**32**	**14**	**10**	**18.67**	**0.67**		
	6	1	0	0	1.33	0.11		
	7	7	7	9	7.67	0.39		
	8	**17**	**39**	**47**	**34.33**	**0.67**		
Plasmacytoma	1	**28**	**94**	**54**	**58.67**	**0.71**	**19.5**	0.24
	2	0	0	0	0.00	0.00		
	3	0	0	0	0.00	0.00		
Plasma cell mucositis	1	**11**	**11**	**12**	**11.33**	0.27	**16.7**	0.18
	2	**97**	**87**	**95**	**93.00**	**0.67**		
	3	**35**	**18**	**14**	**22.33**	0.39		
	4	**12**	9	**12**	**11.00**	0.10		
	5	**14**	8	9	9.67	0.10		
	6	**11**	3	6	4.67	0.14		
	7	**16**	9	8	**11.00**	0.08		
	8	7	0	x	3.50	0.01		
	9	4	7	8	6.33	0.13		
	10	3	2	6	3.67	0.08		
	11	2	3	3	2.67	0.05		
Lupus panniculitis	1	9	**11**	32	**16.00**	0.33	8.4	0.12
	2	**14**	**21**	4	**13.00**	0.12		
	3	3	2	1	2.00	0.16		
	4	1	2	1	1.33	0.05		
	5	8	7	5	6.00	0.16		
	6	0	NA	NA	3.00	0.00		
	7	3	2	2	2.33	0.06		
Morphea	1	1	0	0	0.33	0.03	2.0	0.02
	2	1	0	0	0.33	0.03		
	3	0	0	0	0.00	0.00		
	4	0	0	0	0.00	0.00		
	5	1	0	0	0.33	0.02		
Rosai-Dorfman disease	1	5	7	4	5.33	0.04	8.4	0.15
	2	10	16	NA	**13.00**	0.26		
Reactive inflammatory infiltrates	1	5	7	4	5.33	0.08	**15.4**	0.21
	2	4	11	10	8.33	0.20		
	3	9	7	NA	8.00	0.16		
	4	**35**	17	13	**21.67**	0.43		
	5	1	1	0	0.67	0.06		
	6	**55**	**48**	**33**	**45.33**	0.33		

hpf, high-power field; IgG, immunoglobulin G; IgG4, immunoglobulin G4; NA, not enough tissue was available to evaluate an additional high-power field; x, a third hpf was not available for review due to limited tissue size.
[a] Mean IgG4/IgG ratio by case and category. Bolded IgG4+ plasma cell densities are those displaying more than 10 cells/high-power field. IgG4/IgG ratios are greater than 0.40.

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Clinicopathologic analysis of IgG4-related skin disease

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IgG4-related disease is a recently recognized systemic syndrome characterized by mass-forming lesions with lymphoplasmacytic infiltration, increase in the number of IgG4 + cells in affected tissues and elevation of serum IgG4 levels. In 2009, we were the first to report skin lesions in patients with IgG4-related disease, but no large case series has been reported and clinicopathological findings remain unclear. To clarify these features, we herein report 10 patients (9 men and 1 woman; median age, 64 years; age range, 46–81 years) with IgG4-related skin disease. All patients had erythematous and itchy plaques or subcutaneous nodules on the skin of the head and neck, particularly in the periauricular, cheek, and mandible regions, except for one patient, whose forearm and waist skin were affected. In addition, eight patients had extracutaneous lesions: these were found on the lymph nodes in six patients, the lacrimal glands in three patients, the parotid glands in three patients, and the kidney in one patient. Histologically examined extracutaneous lesions were consistent with IgG4-related disease; five of six lymph node lesions showed progressively transformed germinal centers-type IgG4-related lymphadenopathy. Cases of IgG4-related skin disease were classified into two histological patterns: those exhibiting a nodular dermatitis pattern and those with a subcutaneous nodule pattern. The infiltrate was rich in plasma cells, small lymphocytes, and eosinophils; the majority of the plasma cells were IgG4+. The IgG4+ cell count was 49–396 per high-power field (mean ± s.d., 172 ± 129), with an IgG4+/IgG+ cell ratio ranging from 62 to 92%. Serum IgG4 levels were elevated in all examined patients. In conclusion, patients with IgG4-related skin disease had uniform clinicopathology. Lesions were frequently present on the skin of the periauricular, cheek, and mandible regions, and were frequently accompanied by IgG4-related lymphadenopathy.
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Keywords: IgG4-related disease; lymphadenopathy; periauricular region; progressively transformed germinal centers; skin

IgG4-related disease is a recently recognized syndrome characterized by mass-forming lesions with lymphoplasmacytic infiltration, an increased number of IgG4+ cells in the affected tissues, and elevated serum IgG4 levels. It is usually found in middle-aged and older patients, with men predominantly affected, and normally has a favorable clinical response to steroid therapy.[1–4]

IgG4-related disease can affect multiple organs, including the pancreas, hepatobiliary tract, lacrimal glands, salivary glands, lungs, kidneys, retroperitoneum, prostate, aorta, and lymph nodes. In most patients with this disease, two or more sites in various combinations are involved.[2–4]

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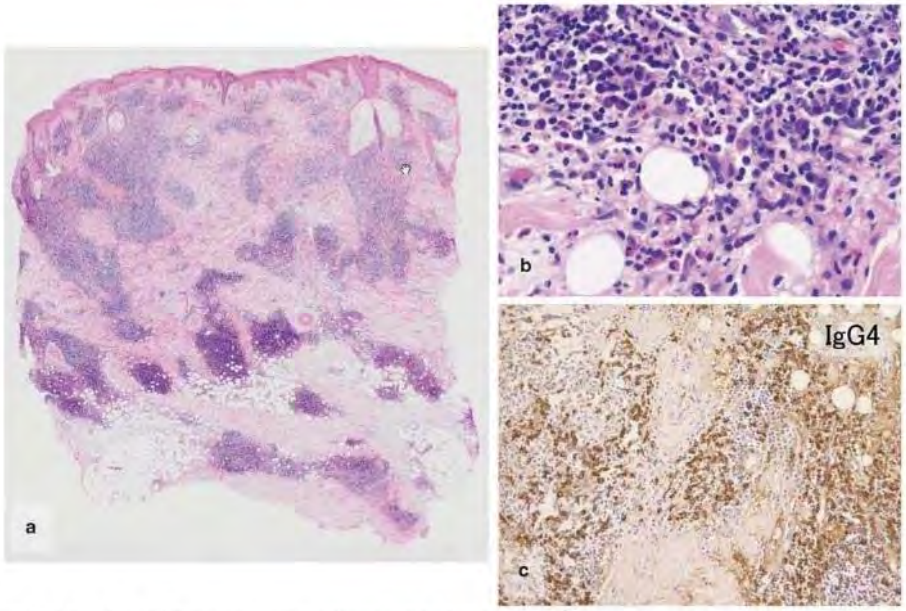

Figure 3 Patient 6: (a, b) Perivascular and periadnexal nodular lymphoplasmacytic infiltrates with eosinophils in the dermis and subcutis is observed. Fibrosis is seen in the subcutis (H&E). (c) Many plasma cells are IgG4+.

10 patients (M:F = 9:1)
9 patients: erythematous and itchy plaques or subcutaneous nodules on the head & neck; 1 patient: forearm and waist
8 patients had extracutaneous lesions at one or more locations: *(LN: 6, lacrimal glands: 3, parotid glands: 3, kidney: 1)*

REVIEW ARTICLE

BJD
British Journal of Dermatology

IgG4-related skin disease

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Conflicts of interest
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Summary

IgG4-related disease (IgG4-RD) is a recently established clinical entity characterized by high levels of circulating IgG4, and tissue infiltration of $IgG4^+$ plasma cells. IgG4-RD exhibits a distinctive fibroinflammatory change involving multiple organs, such as the pancreas and salivary and lacrimal glands. The skin lesions of IgG4-RD have been poorly characterized and may stem not only from direct infiltration of plasma cells but also from IgG4-mediated inflammation. Based on the documented cases together with ours, we categorized the skin lesions into seven subtypes: (1) cutaneous plasmacytosis (multiple papulonodules or indurations on the trunk and proximal part of the limbs), (2) pseudolymphoma and angiolymphoid hyperplasia with eosinophilia (plaques and papulonodules mainly on the periauricular, cheek and mandibular regions), (3) Mikulicz disease (palpebral swelling, sicca syndrome and exophthalmos), (4) psoriasis-like eruption (strikingly mimicking psoriasis vulgaris), (5) unspecified maculopapular or erythematous eruptions, (6) hypergammaglobulinaemic purpura (bilateral asymmetrical palpable purpuric lesions on the lower extremities) and urticarial vasculitis (prolonged urticarial lesions occasionally with purpura) and (7) ischaemic digit (Raynaud phenomenon and digital gangrene). It is considered that subtypes 1–3 are induced by direct infiltration of $IgG4^+$ plasma cells, while the other types (4–7) are caused by secondary mechanisms. IgG4-related skin disease is defined as $IgG4^+$ plasma-cell-infiltrating skin lesions that form plaques, nodules or tumours (types 1–3), but may manifest secondary lesions caused by $IgG4^+$ plasma cells and/or IgG4 (types 4–7).

What is already known about this topic?

- IgG4-related disease (IgG4-RD) is a recently established clinical entity characterized by fibroinflammatory lesions, high levels of circulating IgG4 and tissue infiltration of $IgG4^+$ plasma cells.

What does this study add?

- We comprehensively categorized the skin lesions of IgG4-RD into primary lesions with direct infiltration of $IgG4^+$ plasma cells (three subtypes) and secondary non-specific inflammatory lesions where the role of IgG4 remains to be elucidated (four subtypes).
- Our study clarifies IgG4-related skin disease and its differential diagnoses.

IgG4-related disease (IgG4-RD) is a recently proposed clinical entity characterized by high levels of circulating IgG4 and tissue infiltration of $IgG4^+$ plasma cells.[1–4] IgG4-RD exhibits a distinctive fibroinflammatory change involving multiple organs, including the pancreas,[5] salivary glands,[6] lacrimal glands,[6] biliary tract,[7,8] peritoneum,[9] kidney,[10] pituitary gland,[11] thyroid gland,[12] lung,[13] prostate/testis[14] and aorta[15,16] (Table 1). Even lymph node lesions[17] and orbital pseudotumours[18] have been

Table 2 Types of skin lesions in IgG4-related disease

Type	Symptoms	Differential diagnoses	References
1 Cutaneous plasmacytosis	Multiple circular or ellipsoid patches with pigmentation	Multicentric Castleman disease	24–28, 30
2 Pseudolymphoma and angiolymphoid hyperplasia with eosinophilia	Plaques and papulonodules mainly on the periauricular and facial areas	B-cell pseudolymphoma, mucosa-associated lymphoid tissue syndrome	2, 31, 32, 37
3 Mikulicz disease or IgG4-related dacryoadenitis and sialadenitis	Palpebral swelling, sicca syndrome, exophthalmos	Sjögren syndrome	6, 19, 24, 38–40
4 Psoriasis-like eruption	Scaly erythematous plaques	Psoriasis vulgaris	41, 42
5 Unspecified maculopapular or erythematous eruptions	Multiple maculopapular or exudative erythematous lesions	Drug eruption, toxic erythema	45, 46
6 Hypergammaglobulinaemia, purpura and urticarial vasculitis	Bilateral palpable purpuric lesions, prolonged urticarial lesions	Anaphylactoid purpura, Sjögren syndrome, lupus erythematosus	47–49
7 Ischaemic digit	Raynaud phenomenon, digital gangrene	Systemic sclerosus, thrombosis, antiphospholipid syndrome	52

Cutaneous manifestations of IgG4-related disease (RD): A systematic review

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Background: IgG4-related disease (RD) is a recently described fibroinflammatory condition with both cutaneous and systemic manifestations. To our knowledge, the cutaneous manifestations have not been well characterized or systematically investigated to date in the literature.

Objective: We sought to describe the cutaneous manifestations of IgG4-RD to guide clinical practice, aid in the diagnosis of IgG4-RD, and contribute to the creation of robust cutaneous diagnostic criteria.

Methods: A systematic search of peer-reviewed publications pertaining to cutaneous manifestations of IgG4-RD yielded 56 cases from 32 case reports and series. The clinical findings among the diagnostic categories were compared.

Results: Forty cases of IgG4-RD with cutaneous disease were identified. Cutaneous head and neck involvement was significantly associated with a diagnosis of IgG4-RD ($P = .02$). Macules and bullae were not described in any of the included cases. Among cases of systemic IgG4-RD, cutaneous head and neck involvement was most common and statistically significantly associated with the diagnosis of IgG4-RD ($P = .001$).

Limitations: These findings are limited by reporting and publication bias of particular cases and by small sample size.

Conclusions: Papules, plaques, and nodules of the head and neck appear to characterize patients with cutaneous IgG4-RD, which nevertheless usually presents with systemic manifestations. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.01.046.)

Key words: cutaneous manifestations; diagnosis; fibroinflammatory; hyper-IgG4 disease; IgG4-related disease; IgG4-related sclerosing disease; IgG4-related systemic disease; lymphoplasmacytic infiltrate.

IgG4-related disease (RD) is a recently described inflammatory condition with cutaneous and systemic manifestations[1] including IgG4$^+$ plasma cell organ infiltration[2] and often, but not always, elevated levels of circulating IgG4. Although the initial description identified a systemic condition in patients with autoimmune pancreatitis with extrapancreatic manifestations,[3] recent reports suggest IgG4-RD can affect virtually any organ system including but not limited to the salivary glands, lacrimal glands, periorbital tissues, thyroid gland, biliary tract, kidneys, lungs, aorta, meninges, pituitary gland, and skin. Fibrosing conditions such as Mikulicz syndrome, Riedel thyroiditis, and Küttner tumor, originally described within an organ-specific context, are now included as in the IgG4-RD clinical spectrum given pathologic similarities to IgG4-RD.[2,4] Likewise, recent reports suggest other skin

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Drs Charrow and Imadojemu contributed equally and are co-first authors.
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Table II. Cutaneous and systemic findings

Findings	All cases N = 56	IgG4 diagnosis: Definite N = 15	Probable N = 7	Possible N = 18	No N = 16	*P* value
Cutaneous involvement location						
Head/neck, N (%)*	30 (53.6)	11 (73.3)	5 (71.4)	10 (55.6)	4 (25.0)	.02
Trunk, N (%)*	14 (25.0)	3 (20.0)	2 (28.6)	4 (22.2)	5 (31.3)	.95
Upper extremity, N (%)*	16 (28.6)	2 (13.3)	1 (14.3)	4 (22.2)	9 (56.3)	.06
Lower extremity, N (%)*	13 (23.2)	3 (20.0)	1 (14.3)	5 (27.8)	4 (25.0)	.94
Genitalia/buttocks, N (%)*	3 (5.4)	0 (0)	0 (0)	1 (5.6)	2 (12.5)	.76
Cutaneous morphology						
Macules, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	>.05
Papules, N (%)	15 (26.8)	4 (26.7)	1 (14.3)	3 (16.7)	7 (43.8)	.34
Patches, N (%)	2 (3.6)	0 (0)	1 (14.3)	1 (5.6)	0 (0)	.38
Plaques, N (%)	14 (25.0)	4 (26.7)	2 (28.6)	7 (38.9)	1 (6.3)	.15
Nodules, N (%)	19 (33.9)	5 (33.3)	4 (57.1)	4 (22.2)	6 (37.5)	.42
Purpura, N (%)	5 (8.9)	1 (6.7)	0 (0)	4 (22.2)	0 (0)	.12
Bullae, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	>.05
Rash, N (%)	3 (5.4)	1 (6.7)	1 (14.3)	1 (5.6)	0 (0)	.52
Other, N (%)	8 (14.3)	1 (6.7)	0 (0)	3 (16.7)	4 (25.0)	.39
Systemic involvement‡						
Systemic involvement, N (%)	37 (66.1)	15 (100)	2 (28.6)	16 (88.9)	4 (25.0)	<.001
Head/neck, N (%)	24 (64.9)	14 (93.3)	2 (100)	8 (50.0)	0 (0)	.001
Pulmonary/airways/sinuses, N (%)	8 (21.6)	4 (26.7)	1 (50.0)	2 (12.5)	1 (20.0)	.38
Gastrointestinal, N (%)	10 (27.0)	3 (20.0)	1 (50.0)	5 (31.3)	2 (40.0)	.81
Hematologic/lymphadenopathy, IgG4$^+$, N (%)	13 (35.1)	3 (20.0)	1 (50.0)	7 (43.8)	3 (60.0)	.42
Renal, N (%)	6 (16.2)	3 (20.0)	0 (0)	2 (12.5)	2 (40.0)	.79
Joints, N (%)	2 (5.4)	0 (0)	0 (0)	1 (6.3)	1 (20.0)	.30
Vascular, N (%)	3 (8.1)	0 (0)	0 (0)	2 (12.5)	1 (20.0)	.36
Neurologic, N (%)	1 (2.7)	1 (6.7)	0 (0)	0 (0)	0 (0)	.57
Other, N (%)	3 (8.1)	0 (0)	0 (0)	1 (6.3)	2 (40.0)	.03
Lymphadenopathy, other, N (%)†	21 (37.5)	6 (40.0)	1 (14.3)	12 (66.7)	2 (12.5)	.001

*Data were not reported for 2 (3.6%) cases.
†Lymphadenopathy is nonspecific, ie, lymph node not biopsied or biopsy specimen not consistent with IgG4-related disease lymph node involvement.
‡Percentages of specific categories of systemic involvement are calculated only among those with systemic involvement.

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Bullous pemphigoid and eruptive milia

- Milia are commonly observed in epidermolysis bullosa acquisita but are comparatively rare in bullous pemphigoid
- Eruptive milia described in some patients with bullous pemphigoid; may be associated to particular subtypes of the disease

Bullous Pemphigoid with Prominent Milium Formation

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SUMMARY Milia are very common superficial keratinous cysts, clinically seen as pearly white dome-shaped lesions with a diameter of 1-2 mm. Bullous pemphigoid (BP) is an autoimmune bullous disease characterized clinically by tense bullae on the extremities and trunk. The major target autoantigens of BP are BP180 and BP230. We report a 55-year-old Polish BP patient presenting prominent milium formation. Physical examination revealed multiple tense bullae on the erythemas scattered on the extremities and trunk. Histopathology revealed subepidermal blisters with infiltration of eosinophils in and around the blister. Direct immunofluorescence showed IgG and C3 depositions at basement membrane zone. Although indirect immunofluorescence of normal human skin sections was negative, indirect immunofluorescence of salt-split skin sections showed IgG reactivity with epidermal side. Immunoblotting showed that IgG antibodies in the serum reacted with recombinant protein of the BP180 NC16a domain. ELISA of BP180, but not BP230 and type VII collagen, showed positive results. Several months after oral prednisolone therapy, multiple large milia appeared on the healed BP lesions. Histopathology showed cysts with flaky keratinous inclusions in the mid-dermis. We diagnosed the patient as BP with milia. Since milia are occasionally found in BP, they are not a definite differential criterion from epidermolysis bullosa acquisita.

KEY WORDS: BP180, BP230, bullous pemphigoid, epidermolysis bullosa acquisita, milia

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disease affecting the elderly. BP is characterized clinically by tense bullae on the extremities and trunk, histopathologically by subepidermal blisters with eosinophilic infiltration, and immunologically by autoantibodies to BP180 and BP230 (1). Direct immunofluorescence of perilesional skin showed depositions of IgG and C3 at basement membrane zone (BMZ). Indirect immunofluorescence of normal human skin sections as a substrate detects circulating IgG anti-BMZ antibodies, which react with epidermal side of 1M NaCl-split skin sections (1).

Immunoblotting of normal human epidermal extracts as a substrate detects IgG antibodies reactive with BP180 and/or BP230 (1). Immunoblotting shows IgG reactivity with recombinant protein of the NC16a domain of BP180. In some BP patients, immunoblotting

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CONCISE COMMUNICATION

Refractory bullous pemphigoid leaving numerous milia during recovery

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ABSTRACT

Recovery with milia may occur in bullous pemphigoid (BP), mucous membrane pemphigoid (MMP) and epidermolysis bullosa acquisita (EBA). Scarring commonly occurs in MMP and EBA. Here, we report a 62-year-old man patient with BP, who was left with numerous milia during recovery. The patient had immunoglobulin (Ig)G autoantibodies to the recombinant protein of the BP180-NC16a domain and the soluble 120-kDa ectodomain of BP180 (linear IgA bullous dermatosis [LAD]-1). There are cases of BP with IgG autoantibodies to LAD-1 and/or the recombinant protein of BP180 C-terminal domain. Extensive milia formation during recovery may be associated with immunological predisposition and/or improper interaction between hemidesmosomes and the extracellular matrix components.

Key words: BP180-NC16a domain, bullous pemphigoid, epidermolysis bullosa acquisita, linear immunoglobulin A bullous dermatosis-1, milium, mucous membrane pemphigoid.

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disorder caused by immunoglobulin (Ig)G autoantibodies to two hemidesmosomal components, BP180 and BP230.[1,2] Here, we report a 62-year-old man patient with refractory BP showing numerous milia during recovery. The patient had IgG autoantibodies which were reactive to the recombinant protein (RP) of the immunodominant NC16a domain of BP180 (BP180-NC16a) and the soluble 120-kDa ectodomain of BP180 (linear IgA bullous dermatosis [LAD]-1), as well as weak IgA reactivity with the BP180-NC16a RP.

CASE REPORT

A 62-year-old Japanese man complaining of increasing skin lesions was referred to us in September 2013. At the first visit, physical examination revealed multiple erythemas with papules and vesicles on the entire body. Then, the erythemas spread and coalesced, forming many large erythemas with tense vesicles and bullae, pustules and erosions (Fig. 1a). Mucosal membranes were not involved.

Laboratory examinations at the first visit showed slight increases of leukocytes (10 200/μL; normal, 3900–9300/μL) and eosinophils (4.2%; normal, 0.2–4.1%) and increased C-reactive protein (CRP; 1.111 mg/dL; normal <0.3). One week later, leukocytes increased to 16 300/μL, eosinophils increased to 15.3% and CRP increased to 4.434 mg/dL. Indexes in enzyme-linked immunosorbent assays (ELISA) were negative for desmoglein (Dsg)3, Dsg1 and BP230, but positive for the BP180-NC16a RP (137; normal, <9).

A biopsy taken from a bullous skin lesion revealed a subepidermal blister and infiltration of many eosinophils and few neutrophils and mononuclear cells both in the blister and in the upper dermis (Fig. 1b). Direct immunofluorescence (IF) showed strong linear depositions of IgG and C3 and faint linear deposition of IgA in the basement membrane zone (BMZ).

Indirect IF using normal human skin revealed circulating IgG, but not IgA, anti-BMZ autoantibodies at 1:160 dilution, which reacted with the epidermal side of 1-M NaCl normal human split skin (Fig. 1c).

Immunoblotting of normal human epidermal extract showed that IgG antibodies in the patient serum reacted with BP180. The patient serum showed strong IgG and weak IgA reactivity with the BP180-NC16a RP (Fig. 2a), but no reactivity with the RP of BP180-C-terminal domain was detected. Immunoblotting of concentrated culture supernatant of HaCaT cells demonstrated that IgG antibodies in the patient serum reacted with LAD-1 (Fig. 2b). Immunoblotting of either normal human dermal extract or purified human laminin-332 demonstrated no positive reactivity.

Intravenous prednisolone 60 mg/day with oral dapsone 75 mg/day did not suppress the progress of blister formation. Then, the patient was treated with two cycles of i.v.

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"Neutrophilic dermatosis of dorsal hands"

- Neutrophilic dermatosis of the dorsal hands is a term used in the literature for haemorrhagic-bullous lesions with dense neutrophilic infiltrates (initially named "pustular vasculitis of the hands")
- Most likely represents a variant of Sweet syndrome
- Association with hematological disorders may be found (as in conventional Sweet syndrome)

Neutrophilic dermatosis of the dorsal hands: Pustular vasculitis revisited

Noreen A. Galaria, BSc, Jacqueline M. Junkins-Hopkins, MD, Douglas Kligman, MD, and William D. James, MD *Philadelphia, Pennsylvania*

An entity termed "pustular vasculitis of the hands" was recently described. Patients with this condition presented with low-grade fevers and erythematous plaques, pustules, and bullae limited to the dorsal hands and fingers, which were characterized histologically by a dense neutrophilic infiltrate and leukocytoclastic vasculitis. We describe patients with a similar clinical presentation, but who lacked vasculitis on biopsy findings. We describe 3 otherwise asymptomatic patients with hemorrhagic bullae, plaques, and pustules solely on the dorsal hands. Biopsy specimens showed a neutrophilic infiltrate and leukocytoclasis, but no necrotizing vasculitis, and were reminiscent of Sweet's neutrophilic dermatoses. In our patients, corticosteroids or dapsone led to clearing of the lesions, and small maintenance doses of dapsone prevented their recurrence. Our 3 patients had clinical lesions similar to those termed pustular vasculitis of the hands, but which lacked leukocytoclasric vasculitis on biopsy findings. Because of histologic findings and a therapeutic response more characteristic of Sweet's syndrome, we propose the term *neutrophilic dermatosis of the dorsal hands*. In addition, low-dose dapsone is proposed as a possible first-line therapy in this condition, especially in those with recurrent disease. (J Am Acad Dermatol 2000;43:870-4.)

The term *pustular vasculitis of the hands* was recently introduced to describe a distinct entity characterized by erythematous plaques, pustules, and hemorrhagic bullae presenting solely on the dorsal hands.[1] These lesions clinically and histologically resembled Sweet's neutrophilic dermatosis but differed based on the presence of leukocytoclastic vasculitis and the limited distribution of the lesions. The condition was recalcitrant to antibiotics, but responded well to corticosteroids.[1] We present 3 cases that we believe represent the same entity; however, our patients lacked systemic symptoms, and a true vasculitic component was not present. We propose the term *neutrophilic dermatosis of the dorsal hands* to describe this entity and categorize it as a subset of Sweet's syndrome (SS). In addition, we describe the use of dapsone in the treatment of the active lesions and its usefulness in preventing the frequent recurrences that were present in all of our patients.

Abbreviations used:

PG: pyoderma gangrenosum
SS: Sweet's syndrome
WBC: white blood cell

CASE REPORTS

Case 1

A 59-year-old man was seen in 1978 with a several-year history of recurrent bouts of acute pustular eruptions of the dorsal hands (Fig 1). The distribution of the lesions was remarkably limited to the radial aspect of both hands. Although the lesions were painful, no systemic manifestations such as fever, arthralgias, or generalized malaise accompanied them. There was no associated systemic disease. The results of several cultures were negative for bacteria and fungi. Repeated biopsy specimens revealed only an intense neutrophilic infiltrate in the dermis without associated vasculitis. Special stains for organisms were negative. There was no response to oral antibiotics; however, rapid clearing was obtained with prednisone. No residual scarring remained, even after repeated recurrences. A diagnosis of atypical SS was most consistent with his presentation.

Case 2

A 49-year-old white woman presented with a 2-year history of painful, recurrent lesions limited to the dorsal hands. On one occasion a lesion had occurred at the site of an intravenous line on the hand. When evaluated for her active lesion she was

From the Department of Dermatology, University of Pennsylvania.

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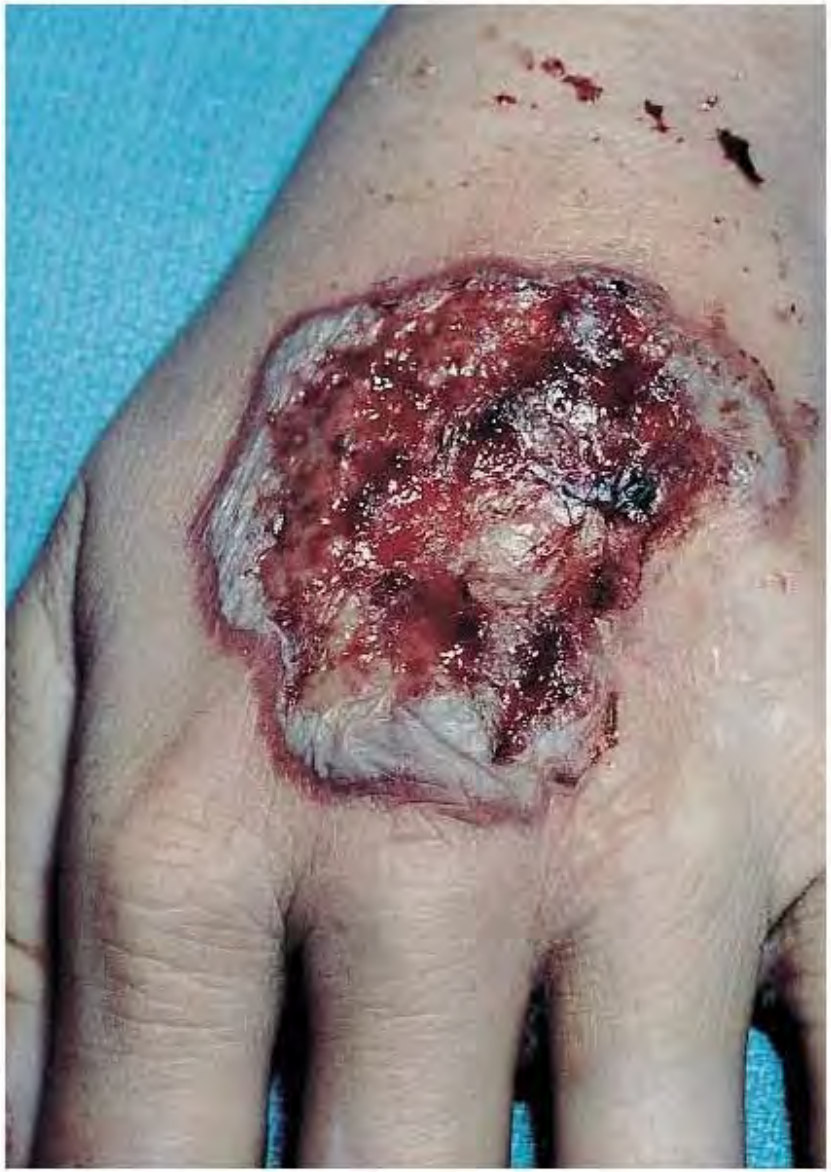

Fig 2. Patient 2. Large active lesion.

SCIENTIFIC ARTICLE

Neutrophilic Dermatosis of the Hands: A Review of 17 Cases

Anthony M. Y. Cheng, BHB, MBChB,* Harriet S. Cheng, BHB, MBChB,† Belinda J. Smith, BAppSc,‡ David A. Stewart, MBChB*

Purpose Neutrophilic dermatosis of the hands is an inflammatory skin condition related to Sweet syndrome that responds to corticosteroids. It commonly affects the dorsum of the hand and often mimics infection, with violaceous inflammatory papules and plaques that may ulcerate. The aim of this study was to review the clinical presentation of neutrophilic dermatosis of the hands.

Methods A retrospective review was undertaken of all cases of neutrophilic dermatosis of the hands seen at a tertiary hospital in New South Wales, Australia, over a 5-year period.

Results Seventeen cases were identified. The mean time to diagnosis was 9 days after lesion onset. Most cases were older adults (mean age, 71 years). The most common referral diagnoses were infection or a nonhealing wound and 65% of cases reported a history of trauma. The dorsal index finger was the site of involvement in 41% of cases. One case involved the palm. Histopathology reports were available for skin punch biopsy for 14 of 17 cases, which showed dermal neutrophilic infiltrate (93%) and epidermal involvement with necrosis, ulceration, or pustulation (64%). Six cases were treated surgically prior to the correct diagnosis and management being introduced.

Conclusions Neutrophilic dermatosis of the hands was often misdiagnosed as infection. A history of trauma is common and may be misleading. Dermatological consultation and skin punch biopsy are useful in confirming the diagnosis, ideally prior to surgical management. *(J Hand Surg Am. 2017;■(■):1.e1-e5. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Diagnostic IV.

Key words Hand, neutrophilic dermatosis, Sweet syndrome.

Online Exclusive

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NEUTROPHILIC DERMATOSES ARE SKIN disorders characterized by dense dermal or subcutaneous neutrophilic infiltrate. The spectrum includes acute febrile neutrophilic dermatosis (ie, Sweet syndrome), neutrophilic eccrine hidradenitis, erythema elevatum diutinum, Behçet disease, and pyoderma gangrenosum (PG). These conditions may occur in association with recognized predisposing factors including rheumatoid arthritis, inflammatory bowel disease, and hematological malignancy.[1]

Neutrophilic dermatosis of the hands (NDH) represents a dilemma in diagnosis and in classification. It presents with violaceous papules, nodules, and plaques

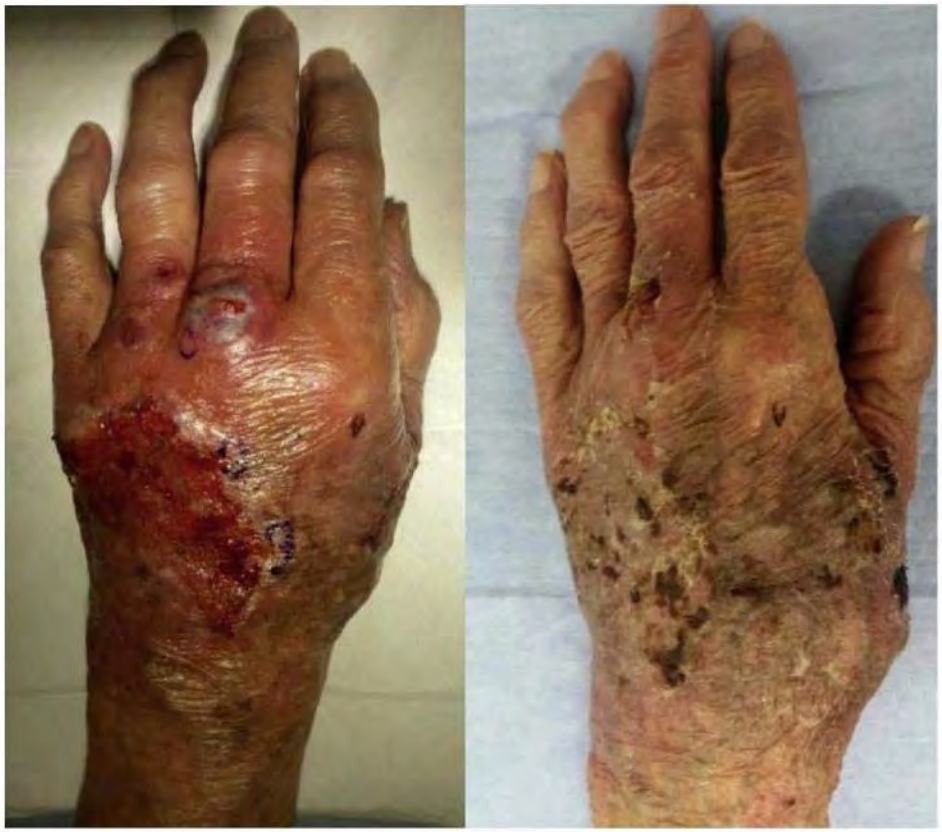


FIGURE 4: Patient at presentation (left) and following 10 days of oral corticosteroids (right).

Clinical Letter

A case of neutrophilic dermatosis of the dorsal hand in acute leukemia – a distributional variant of Sweet's syndrome

DOI: 10.1111/ddg.12644

Dear Editors,

A 50-year-old Japanese woman presented with a two-week history of fatigue and shortness of breath. Workup revealed an elevated total white blood cell count with blast cells, and myeloperoxidase-positive blast cells in the bone marrow. The patient was diagnosed with acute myeloid leukemia (AML). Two days later, a painful rash appeared on the nail fold of the left middle finger. Over the following ten days, the lesion increased in size, subsequently showing bullous hemorrhagic changes with erythematous borders and spreading onto the back of the left hand, accompanied by fever (Figure 1a).

The day after the cutaneous lesion had initially appeared, she had already undergone chemotherapy for AML. Because of progressive chemotherapy-induced pancytopenia and a high-grade fever, the lesion was suspected to be caused by an infection. However, after administration of various antibiotics, the lesion did not regress. Blood cultures were negative.

Histologic examination of a biopsy taken ten days after the lesion had initially appeared showed a necrotic epidermis with marked exocytosis of polymorphonuclear neutrophils and erythrocytes (Figure 2a). There was prominent papillary edema and a dense dermal neutrophilic infiltrate without any signs of leukocytoclastic vasculitis (Figure 2b). Immunohistochemical staining with myeloperoxidase and CD117 did not reveal a neoplastic myeloid infiltrate.

Based on the characteristic distribution and pathologic findings, we diagnosed the condition as neutrophilic dermatosis of the dorsal hands (NDDH) without leukemic infiltration. Upon normalization of the white blood cell count, the lesion resolved without contracture of the finger after five weeks (Figure 1b).

NDDH, a term proposed by Galaria et al. in 2000 [1], is an entity clinically and histologically similar to Sweet's syndrome (SS). In 1995, Strutton et al. [2] had described this condition as "pustular vasculitis of the dorsal hands", which

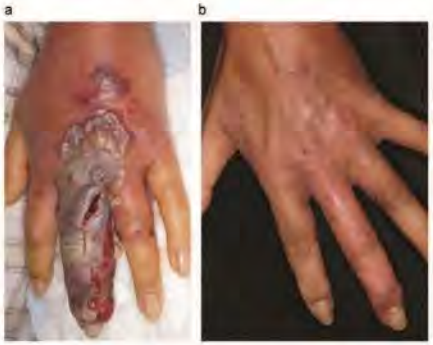


Figure 1 Nine days after initial examination. Erythematous and hemorrhagic bullous lesions on the back of the left hand. Thirty-nine days after initial examination (a). There was no contracture of the finger after resolution (b).

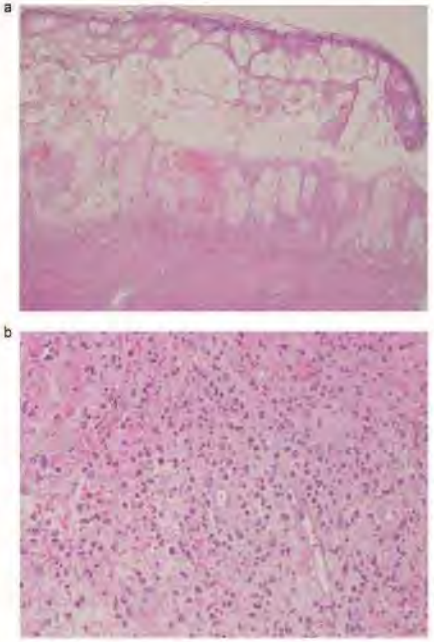
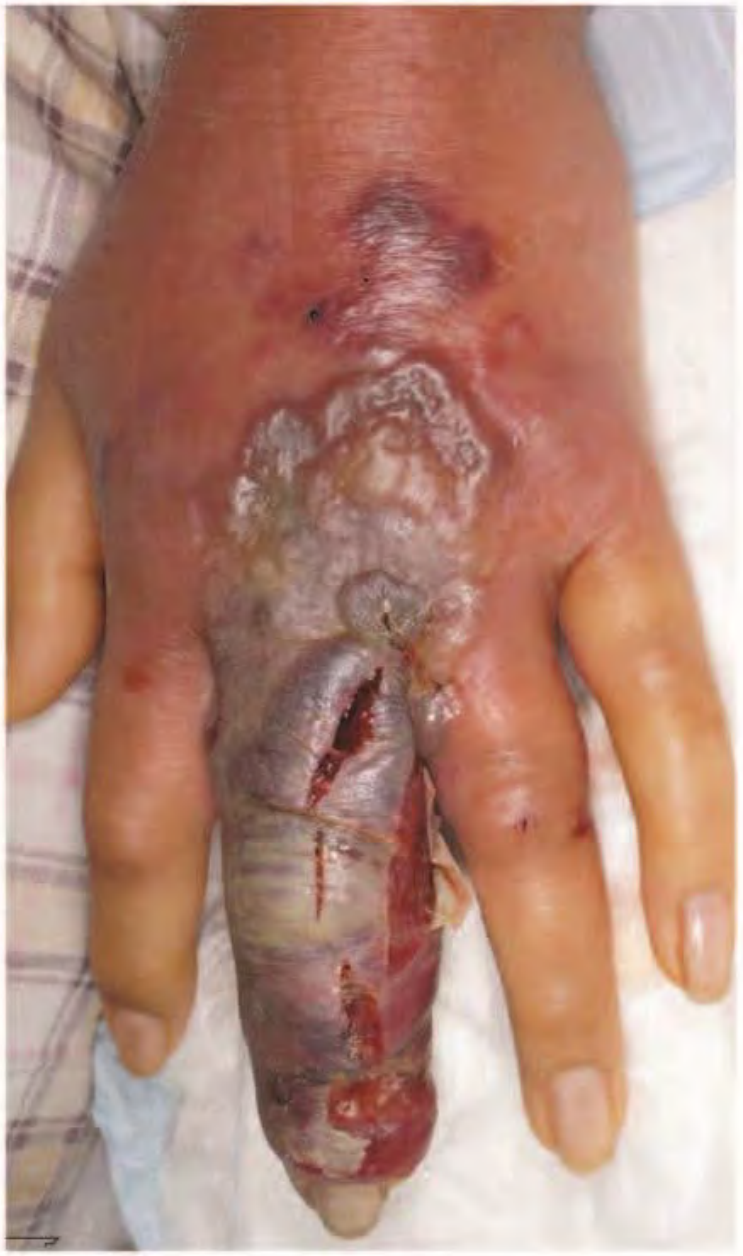


Figure 2 Histopathologic examination of hematoxylin-eosin stained sections. Necrotic epidermis with marked exocytosis of neutrophils and prominent papillary edema (original magnification x 40) (a). Dense dermal neutrophilic infiltrate (original magnification x 200) (b).



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Sweet's syndrome: diagnostic criteria revisited

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Summary

The diagnosis of Sweet's syndrome (SS) is based on a set of criteria that requires the presence of two major and at least two minor criteria. In some cases, however, the diagnosis is not as straightforward due to the absence of certain criteria. The objective of the present study was to review the clinical, histopathological, and laboratory features of the current diagnostic criteria for SS, and to evaluate their validity in the cases reported in the literature as well as in 40 patients treated at our institution. Our comprehensive review of the current criteria for SS reveals that the two major criteria have been consistently present in all cases – including ours – since the first description of SS in 1964. With regard to the minor criteria, on the other hand, there has been marked variability between different studies, and many cases failed to fulfill the requirement of showing two minor criteria. In order to simplify the diagnosis, avoid misdiagnosis, and allow for prompt treatment, we propose two sets of revised diagnostic criteria for SS. The first set comprises constant clinical and histopathological features that must be present and are by themselves sufficient for the diagnosis of SS to be established. The second set includes variable features whose absence does not warrant ruling out SS.

Introduction

First described by Dr. Sweet in 1964 [1], Sweet's syndrome (SS) is characterized by a constellation of findings that include painful erythematous plaques and a dense dermal neutrophilic infiltrate, which may be associated with fever, neutrophilia, leukocytosis, and a dramatic response to systemic corticosteroids [2]. In 1986, Su and Liu [3] proposed a set of major and minor criteria for the diagnosis of SS. Following the review of data from 38 patients, von den Driesch [4] published a modification of these diagnostic criteria in 1994 (Table 1), according to which both major criteria and two minor criteria were required for SS to be diagnosed. In 1996, Walker and Cohen [5] proposed individual diagnostic criteria for drug-induced SS (Table 2).

As evidenced by the available literature, the diagnosis of SS generally seems to be based on the aforementioned current criteria [4]; in some cases, however, the diagnosis is not as straightforward, potentially resulting in delayed diagnosis. Moreover, published reports show the absence of certain criteria as well as non-inclusion of some emerging variants, thus highlighting the need for more precise diagnostic criteria [2, 6–11].

Herein, we review the various clinical, laboratory, and histopathological aspects of the current diagnostic criteria for SS, evaluate their validity in the reported literature and in 40 (new) patients treated at our institution, and subsequently propose a modification of said criteria.

Patients and methods

The study included 40 patients with SS who attended the Dermatology Outpatient Clinic at Zagazig University Hospital from January 2012 to January 2016. Initially, a detailed history was taken. All individuals were then subjected to a thorough dermatological and clinical examination, histopathological studies, and detailed workup for any associated disorders. In addition, patients were assessed for laboratory abnormalities, type and response to treatment, as well as potential recurrences. Finally, the validity of the current criteria

Table 4 Revised diagnostic criteria for Sweet's syndrome.

Constant features*
Clinical: Abrupt onset of painful or tender erythematous papules, plaques, or nodules
Histopathological: Dense dermal neutrophilic infiltrate
Variable features**
Clinical
1. Fever > 38°C
2. Atypical skin lesions (including hemorrhagic blisters, pustular lesions, cellulitis-like-lesions)
Histopathological
1. Presence or absence of leukocytoclastic vasculitis
2. Subcutaneous variant
3. Histiocytoid variant
4. Xanthomatoid variant
5. Cryptococcoid variant
Laboratory
1. Elevated ESR
2. Elevated C-reactive protein levels
3. Leukocytosis
4. Neutrophilia
5. Anemia

*Constant clinical and histopathological features must be present to establish a definitive diagnosis.
**Variable features help avoid misdiagnosis of certain cases and may include any new finding yet to emerge

Circumscribed palmar (plantar) hypokeratosis

- Localized disorder of aberrant differentiation or keratinization
- Usually adults; one congenital case
- Different keratins have been involved in different patients
- K10 and K16 were expressed in a mutually exclusive manner at the boundary between the affected and unaffected skin in a recent case (K16+ in affected, K10+ in unaffected skin)

Actas Dermosifiliogr. 2014;105(6):574–582

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Full English text available at www.actasdermo.org

CONTROVERSIES IN DERMATOLOGY

Circumscribed Palmar or Plantar Hypokeratosis 10 Years After the First Description: What Is Known and the Issues Under Discussion☆

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KEYWORDS
Stratum corneum;
Hypokeratosis;
Palms and soles;
Palmoplantar surfaces;
Keratinization;
Keratinocytes

Abstract This review of the literature on palmoplantar hypokeratosis, a process that was first indentified only 10 years ago, discusses the current state of our understanding, the therapeutic options available, and the debate about etiology. Forty-four publications reporting 69 cases were found. Palmar or plantar hypokeratosis occurs mainly in women (76.8%) and age at the time of a first visit to a physician ranges from 42 to 84 years. Most cases present between the ages of 51 and 70 years. The majority of patients have had solitary lesions usually located on the right palm, particularly in the regions of the thenar (in 44/79 lesions [55.7%]) or hypothenar eminences (in 11/79 lesions [13.9%]). In only 8 cases was there a history of prior trauma at the site. Studies using polymerase chain reaction techniques to identify human papillomavirus involvement were negative in most cases. These hypokeratotic lesions are localized epidermal depressions formed by an abrupt thinning of the stratum corneum, providing a singular histopathologic feature. This condition can currently be considered a localized keratinization disorder affecting zones where there is a thick stratum corneum. The precipitating cause is unknown and a definitive treatment remains to be found. The mechanism would be the localized failure of a clone of keratinocytes during differentiation toward normal palmoplantar hyperkeratinization.

PALABRAS CLAVE
Capa córnea;
Hipoqueratosis;
Palmas y plantas;

Hipoqueratosis circunscrita palmar o plantar. Conocimientos y controversias tras 10 años de su descripción

Resumen Se revisa el estado actual de un nuevo proceso y los avances que han ido apareciendo en la literatura respecto a su estudio, posibilidades terapéuticas y controvertida etiología, tras

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Table 1 Clinical Characteristics of 69 Cases of Circumscribed Palmar or Plantar Hypokeratosis, Listed According to the Year of Publication.

Year	Ref. No.	Sex	Age	Time Since Onset	Lesion Site
2002	2	F	64	Since childhood	Right thenar eminence
		F	69	30 y	Left hypothenar eminence
		F	53	20 y	Right thenar eminence
		F	79	Many years	Right thenar eminence
		F	66	Many years	Right thenar eminence
		F	42	Many years	Right hypothenar eminence
		F	59	Many years	Right thenar eminence
		F	70	Many years	Right thenar eminence
		F	68	3 y	Left mid-plantar region
		M	45	-	Palmar aspect of left thumb
2003	3	F	71	7 y and 3 y	Left thenar and hypothenar eminences
	4	F	61	Several years	Right thenar eminence
2004	5	F	71	15 y	Right thenar eminence
	6	M	68	-	Left hypothenar eminence
		F	81	2 y	Right hypothenar eminence
	7	F	73	Many years	Left hypothenar eminence
		F	64	Many years	Sole of left foot
	8	M	61	20 y	Right thenar eminence
		M	66	-	Right thenar eminence
2005	9	F	55	Years	Right thenar eminence
	10	F	63	6 y	Right thenar eminence
2006	11	F	80	30 y	Right thenar eminence
				3-4 y	Base of left thumb
		F	42	10 y	Right hypothenar eminence
		M	69	1 y	Left thenar eminence
		F	60	Several months	Right index finger and left ring finger
	12	M	60	6 mo	Right thenar eminence
	13	F	52	3-4 y	2 lesions on left thenar eminence
	14	F	50	More than 10 y	Left hypothenar eminence
	15	F	53	6 y	Left thenar eminence
	16	F	75	20 y	Pulp of right thumb
2007	17	M	71	2 y	Right thenar eminence
	18	F	66	40 y	Left thenar eminence
	19	M	73	5 y or more	Right thenar eminence
	20	F	58	3 y	Left thenar eminence
		F	73	10 y	2 lesions on left thenar eminence
	21	F	75	10 y	Left thenar eminence and sole of left foot
		F	49	10 y	Sole of left foot
		M	84	40 y	Left thenar eminence
2008	22	M	59	30 y	Sole of right foot
		F	60	30 y	Right thenar eminence
2009	23	F	47	3 y	Left thenar eminence
	24	M	65	15 y	Border of left foot
		F	75	Months	Dorsum of right index finger
	25	F	47	10 y	Left thenar eminence
	26	M	62	2 y	Sole of right foot
		F	73	8 y	Left palm
	27	F	67	2 y	Right palm
				After the above lesion	Right thumb
	28	F	59	Many years	Left thenar eminence
	29	F	76	3 y	Left thenar and hypothenar eminences
	30	F	80	20 y	Right thenar eminence
2010	31	F	68	5 y	Left hypothenar eminence, right thumb, and little finger
	32	F	84	11 y	Right thenar eminence
2011	33	F	79	10-20 y	Left thenar eminence
		F	73	10-20 y	Right thenar eminence
	34	F	61	Several years	Left thenar eminence
		F	84	11 y	Right thenar eminence[a]
		F	56	-	Right foot
		F	61	-	Proximal phalanx left middle finger
		F	62	-	Medial surface of distal phalanx of left ring finger
	35	F	68	-	Right thenar eminence
	36	F	78	-	Right thenar eminence
	37	F	65	5 y	Right thenar eminence
	38	F	67	10 y	Right index finger
	39	M	74	10 y	Right thenar eminence
	40	F	76	10 y	Right thenar eminence
2012	41	M	48	15 y	Left ring finger
	42	M	54	More than 10 y	Right thenar eminence
		F	55	6 y	Left thenar eminence
	43	F	61	10 y	Right hypothenar eminence
	44	M	10	Congenital	Medial border of left foot

[a] Described previously.[32]

Research letter

Mutually exclusive expression pattern of keratin markers for differentiation and proliferation in circumscribed palmar hypokeratosis

DOI: 10.1111/bjd.15407

Dear Editor, Circumscribed palmar or plantar hypokeratosis (CPH) has been regarded as a benign clonal epidermal differentiation or keratinization disorder.[1–3] CPH is characterized by a well-demarcated annular depressed erythematous lesion on the thenar or hypothenar eminences of the palms and sole. Its distinctive histopathological features are an abrupt decrease in the thickness of the corneal layer and hypogranulosis in the affected lesion.[2,4] Herein we present a case of CPH and also demonstrate a mutually exclusive expression pattern of keratin markers for differentiation and proliferation between the affected and unaffected epidermis.

A 64 year old woman presented with a 5 year history of erythema with a sense of irritation on the left thenar muscle, which gradually extended into the periphery. Physical examination revealed a well-defined, 3.6 × 3.0-cm depressed erythema on the left thenar muscle (Fig. 1a). Microscopic examination of a biopsy specimen showed a 'sharp step'-like thinning of the corneal and granular layers in the affected skin lesion (Fig. 1c), leading to a diagnosis of CPH. To the best our knowledge, our case was the second largest CPH in the literature.[4] Unfortunately, previous topical administration of corticosteroids, heparinoid cream and tacrolimus ointment for years resulted in no improvement. Therefore, with consent by the patient to undergo surgical treatment, after the possible risk was explained, the lesion was excised and covered with a full-thickness skin graft from the lower abdomen (Fig. 1b). No recurrence was observed 2 years after the surgery, to the patient's satisfaction.

Subsequently, we analysed the balance between proliferation and differentiation in the affected lesions by immunostaining with antibodies to various keratins. Deparaffinized sections of 10% formalin-fixed, paraffin-embedded biopsy specimens were autoclaved in 10 mmol L^{-1} citrate buffer solution (pH 6.0) at 105 °C for 10 min, followed by immunohistochemical staining using the EnVision+ Kit according to the manufacturer's protocol (Dako, Glostrup, Denmark). There were no marked differences between the involved and uninvolved skin in the immunoreactivity to antikeratin (anti-K)1/10 and anti-K5/14 antibodies (34βE12; Roche Diagnostics Limited, Burgess Hill, U.K.) and anti-pan-keratin antibody (AE1/3, Dako) (not shown). However, the immunoreactivity to anti-K10 antibody (MS-611; Thermo Fisher Scientific Inc., Waltham, MA, U.S.A.), which is a specific marker for epidermal differentiation, abruptly decreased in the affected area (Fig. 1d). Conversely, the immunoreactivity to anti-K16 antibody (31075; Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.), which is a specific marker for keratinocyte hyperproliferation, was highly upregulated in the affected area (Fig. 1e).

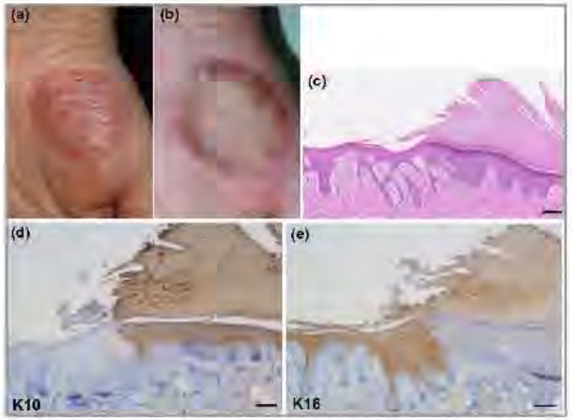

Fig 1. Clinical findings at the first visit (a) and 6 months after surgery (b). (c) Histopathological findings of the boundary between the affected and unaffected skin. Note a 'sharp step'-like thinning of the corneal and granular layers in the affected skin lesion (the left half of figure c). Scale bar = 100 μm. (d, e) Immunoreactivity to either antikeratin (anti-K)10 or K16 antibodies at the above lesion. Scale bars = 100 μm.

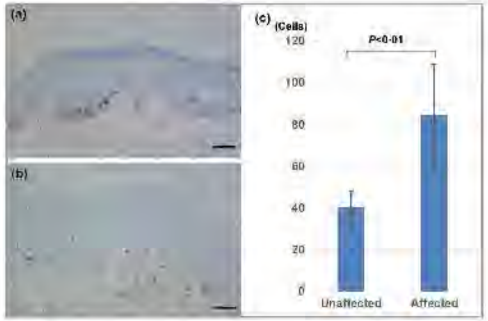

Fig 2. Cell proliferation was increased in the affected area. Immunohistochemistry with anti-Ki67 antibody in the normal skin (a) and the affected lesion (b). Scale bar = 100 μm. (c) Ki-67-positive cells were counted from 10 randomly selected microscopic fields. Data are presented as the mean ± SD.

This mirror-image pattern of K10 and K16 expression was reproduced by immunofluorescence analyses for K10 and K6, another hyperproliferation-associated keratin and a binding partner for K16 (not shown). Thus, K10 and K6 were expressed in a mutually exclusive manner at the boundary between the affected and unaffected skin: no cells expressing both K10 and K6, which were supposed to be detected as yellow cells, were present. Consistently with the upregulation of K6 and K16, Ki-67 positive cells were significantly increased in the affected epidermis (Fig. 2a, b). Statistically, the affected lesion showed about a twofold increase in Ki-67-positive cells compared with the unaffected area (Fig. 2c).

As several previous studies reported distinct patterns of keratin expression, the biological significance of keratin expression has remained controversial.[1–5] In our case, the expression of differentiation-specific K10 and hyperproliferation-specific K6/K16 showed a mutually exclusive pattern at the boundary between the affected and unaffected skin, suggesting that the transcriptional dysregulation of these keratins underlies the pathogenesis of CPH. In the cultured keratinocytes, K16 replaces K10 in response to proliferative stimuli and antagonizes the growth-inhibitory effects of K10.[6] Our results suggest that a similar antagonistic mechanism between K10 and K16 induces the sharp contrast of differentiation and proliferation at the boundary. Given that most cases of CPH gradually increase in size, a single epidermal clone may expand incrementally to form the lesion, where K16 (proliferation-related mechanism) replaces K10 (cell-autonomous mechanism).

Dysregulation of the signalling pathways that govern inflammatory responses may also be involved in abnormal keratinization in CPH. Upregulation of K6/K16 expression is observed in psoriatic skin lesions,[7] where the signal transducer and activator of transcription (STAT)3 pathway is activated, as indicated by nuclear staining for phospho-STAT3.[8] In contrast, we found that nuclear phospho-STAT3 staining was absent from the affected lesions of CPH, suggesting that the mechanisms underlying acanthosis in psoriasis and CPH are different, and that the lack of correlation between K6/K16 upregulation and STAT3 pathway activation produces the unique clinical presentation of CPH.

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Pemphigus in young individuals

- Mean age of onset of pemphigus 50-60 (with the exception of fogo savagem, which is mostly observed in young adults and children)
- Cases of PV in children or young adults described
- No clinicopathological differences compared to cases in adults / elderly

"Collisions" in pemphigus

- Rarely features of an associated disorder on specimens of pemphigus vulgaris
- I have observed it with SCC (acantholytic AK and acantholytic SCC), fibropapilloma, scabies, and perforating collagenosis; described also in other conditions
- Probably, at least in part, a Köbner phenomenon

Papular acantholytic dyskeratosis of genitocrural region

- Histopathologic changes similar to those of Hailey–Hailey disease and Darier's disease
- Genitocrural localization
- Variant of acantholytic dyskeratosis? Darier? Hailey–Hailey? Grover?
- A mutation in *ATP2C1* observed in 3 cases of PAD of the genitocrural area lends support to the hypothesis that it represents a dyskeratotic variant of Hailey–Hailey disease

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Genitoperineal papular acantholytic dyskeratosis is allelic to Hailey–Hailey disease

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MADAM, Papular acantholytic dyskeratosis (PAD) of the genitoperineal area is a rare clinical and histopathological entity that belongs to the spectrum of focal acantholytic dyskeratoses.[1,2] We report two cases of familial PAD of the genital area. Genetic testing in both cases revealed a novel mutation in *ATP2C1* encoding the Golgi hSPCA1 pump, which is defective in Hailey–Hailey disease (HHD).

A 43 year old woman presented with a 4 month history of itching and burning of the genitoperineal area. Physical examination showed multiple coalescent skin coloured keratotic papules on the labia majora and the vulval fourchette (Fig. 1a), and the anal and perianal area (Fig. 1b). Histopathological examination of a vulval and a perianal papule revealed hyperkeratosis, suprabasal clefting, extensive acantholysis throughout the epidermis giving the appearance of a dilapidated brick wall, and dyskeratosis with the formation of grains and corps ronds (Fig. 1c). A 2 month treatment with topical tacrolimus 0·1% twice daily resulted in significant improvement of the vulval lesions. Her mother, a 70 year old woman, presented with a several year history of similar skin coloured hyperkeratotic papules of the vulva, the anal and perianal area, and the crural folds. Histopathological examination of a vulval and a perianal papule revealed acantholysis throughout the epidermis giving the appearance of a dilapidated brick wall, and hyperkeratosis with minimal dyskeratosis. Treatment with topical tacrolimus 0·1% applied twice daily resulted in significant improvement of the lesions after 2 months.

Genomic sequencing of the *ATP2C1* gene in both patients identified a heterozygous c.360+2T>A mutation at the invariant donor splice site of intron 5 (Fig. 2a). This mutation was not found in 50 controls. *In silico* analysis using automated splice site analysis and Human Splicing Finder[3,4] predicted that this mutation disrupts the donor splice site of intron 5 and abolishes an SRp55 protein binding motif (ESE finder)[5] (Fig. 2b). To confirm this prediction, total RNA was extracted from patient keratinocytes cultured from a skin biopsy. Reverse transcription–polymerase chain reaction (PCR) analysis with primers localized in exons 3 and 7 showed a smaller band of reduced intensity in addition to the wild type band. Cloning of the PCR products and sequencing of individual clones identified in-frame skipping of exon 5 in 27% (11/40) of the clones sequenced (Fig. 2c). Skipping of exon 5 (36 nucleotides) results in the in-frame deletion of 12 amino acids from the transmembrane 2 domain (M2) of the molecule, a functional region which is highly conserved among SPCA pumps between species. For these reasons, mutation c.360+2T>A is most likely to be the causative mutation in this family.

Genitoperineal PAD is a rare skin disorder with 15 cases previously described.[6,7] No family history of PAD has been reported to date. The disease is characterized by multiple skin-coloured to whitish smooth papules confined to the genitocrural area, mostly located on the labia majora. Erosions, crusts, or axillary, inframammary and cervical fold involve-

Fig 1. Clinical and histological features. (a) Multiple skin-coloured papules grouped on the labia majora of the vulva. (b) Multiple whitish papules on the perianal area. (c) Acantholytic dyskeratosis: hyperkeratosis and parakeratosis with suprabasal clefting throughout the epidermis and acantholytic dyskeratotic cells giving rise to corps ronds (granular layer) and grains (stratum corneum) (haematoxylin and eosin, original magnification ×20).

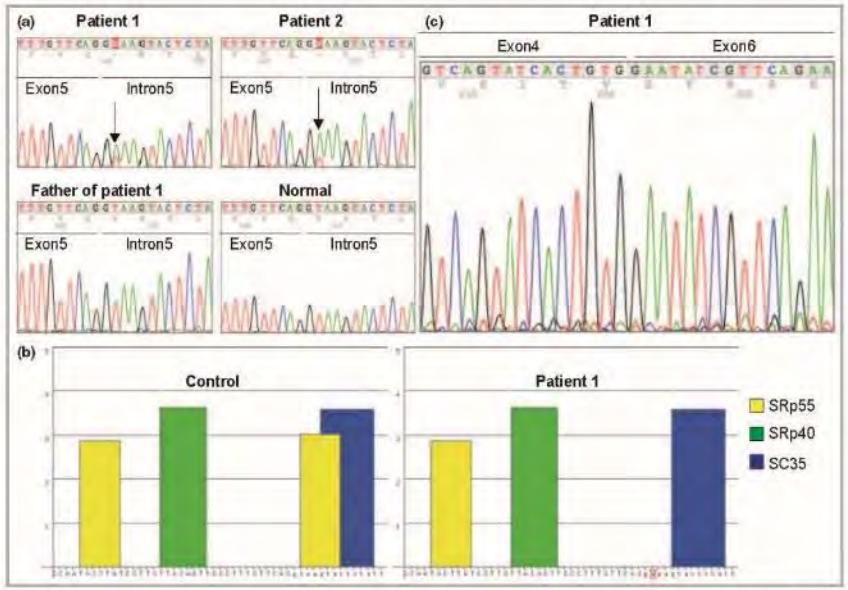

Fig 2. Molecular analysis. (a) Genomic sequence of *ATP2C1* showing a heterozygous c.360+2T>A mutation at the donor splice site of intron 5 present in patients 1 and 2. Father of patient 1 and a control show a normal gDNA sequence. (b) Prediction of putative exonic splicing enhancers specific for SRp55, SRp40 and SC35 proteins using ESEfinder3·0 for control and patient gDNA. The mutation abolishes a SRp55 binding sequence. (c) Sequencing of a cDNA clone from reverse transcription–polymerase chain reaction products from patient 1 showing in-frame skipping of exon 5 of *ATP2C1*.

Ulcero-necrotic PLEVA

- Considered as a severe form of PLEVA characterized by malaise, fever, arthritis, lymphadenopathy and large, confluent necrotic skin lesions as well as possible mucosal, gastrointestinal and pulmonary involvement
- Transition from PLEVA to the ulcero-necrotic form has been associated with increased serum levels of TNF-α
- May be fatal (in adults, not in children); yet evaluation of prognosis difficult in old reports (true fulminant lymphomas included in the same group?)

"Atypical" PLEVA

- A few case reports and small series described an "atypical" form of PLEVA with phenotypic aberrations but benign behaviour
- Overlapping features with PLEVA-like MF in children and with lymphomatoid papulosis (types B/D)
- Precise classification may be difficult or impossible in given cases
- Clear-cut phenotypic aberrations (e.g., loss of pan T-cell markers, etc.) should be regarded with great suspicion in an "inflammatory" condition
- Long-term follow-up advisable (akin to LyP)

British Journal of Dermatology 2000; 142: 347–352.

Pityriasis lichenoides-like mycosis fungoides in children

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Accepted for publication 16 September 1999

Summary We report three children with clinical features of pityriasis lichenoides (scaly red to brown papules and macules) in whom there were histopathological findings of mycosis fungoides (disproportionate epidermotropism, Pautrier's microabscesses, and wiry and coarse collagen bundles). Immunohistochemical staining revealed a prevalence of T lymphocytes in the infiltrate. T-cell receptor gene rearrangement analysis in lesional skin demonstrated rearrangement of the gamma chain in all cases. Human T-cell lymphotropic virus type 1 serology was negative in the two patients in whom this test was performed. Thus, lesions resembling pityriasis lichenoides can be an unusual and potentially misleading presentation of mycosis fungoides.

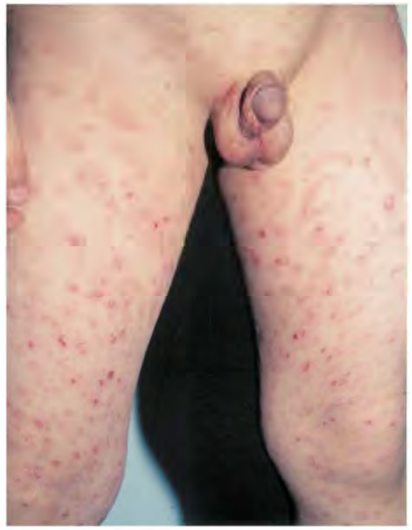

Figure 3. Polymorphous lesions, ranging from scaly or crusted red–tan papules to tan–brown macules and patches, were noted (patient 2).

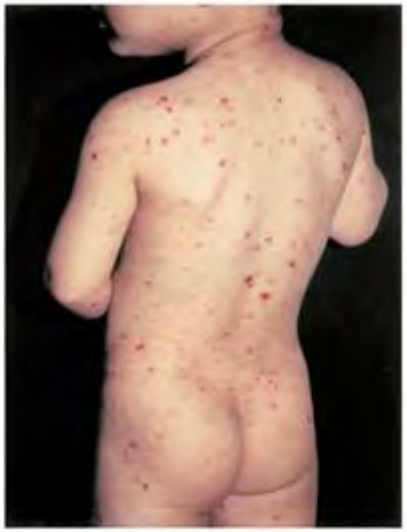

Figure 5. Brown–red scaling papules and macules, and some erythematous lesions with a haemorrhagic crust may be seen (patient 3).

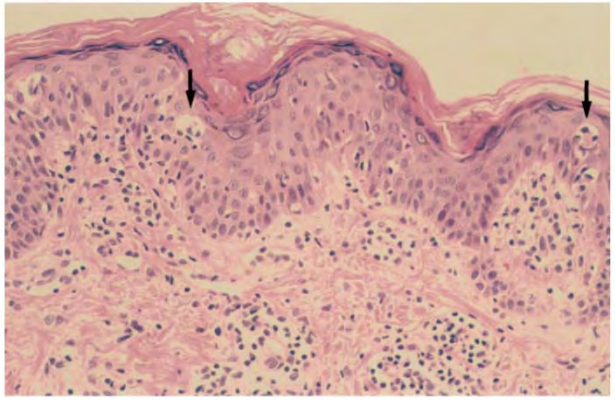

Figure 4. Photomicrograph showing slight focal epidermotropism, Pautrier's microabscesses (arrows) and coarse collagen bundles (patient 2) (haematoxylin and eosin; original magnification × 200).

British Journal of Dermatology 1997; 137: 983–987.

The transformation of pityriasis lichenoides chronica into parakeratosis variegata in an 11-year-old girl

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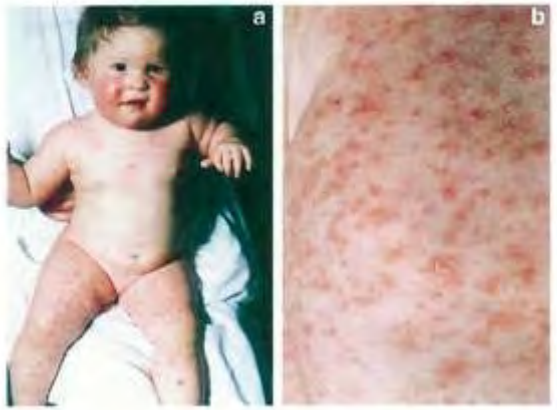
Accepted for publication 15 July 1997

Summary Parakeratosis variegata is a rare disorder with unknown aetiology. In a few cases it arises from benign skin diseases such as pityriasis lichenoides et varioliformis acuta (Mucha Habermann disease) or pityriasis lichenoides chronica. However, transformation into malignant diseases such as cutaneous T-cell lymphoma has been observed. We report an 11-year-old girl with a 10-year history of pityriasis lichenoides chronica now presenting with parakeratosis variegata. Analysis of skin infiltrating T cells showed clonally rearranged T-cell receptor γ chains occurring with a frequency of more than 2%. This finding is compatible with the clinical observation of parakeratosis variegata transforming into a malignant T-cell disorder. We therefore suggest that patients suffering from parakeratosis variegata and other diseases such as pityriasis lichenoides et varioliformis acuta or pityriasis lichenoides chronica should be continuously monitored.



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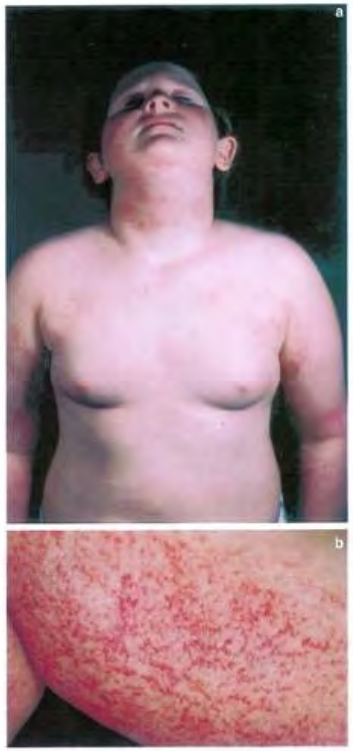

1995

CLINICAL AND LABORATORY INVESTIGATIONS

BJD
British Journal of Dermatology

γδ T-cell-rich variants of pityriasis lichenoides and lymphomatoid papulosis: benign cutaneous disorders to be distinguished from aggressive cutaneous γδ T-cell lymphomas

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Conflicts of interest
None declared.

DOI 10.1111/bjd.13364

Summary

Background T cells with a γδ phenotype have been associated with aggressive lymphomas. Yet, inflammatory skin disorders and low-grade lymphoproliferative disorders have rarely been described with a predominant γδ T-cell infiltrate.
Objectives To review our experience and determine the clinical relevance of the γδ T-cell phenotype in lymphomatoid papulosis (LyP) and pityriasis lichenoides (PL).
Methods A retrospective dermatopathology file review looking for LyP and PL characterized by a γδ T-cell phenotype was performed. Clinical manifestations and course, histological features and molecular data were analyzed.
Results Six of 16 cases of LyP and four of 23 cases diagnosed as PL during a 5-year period (2009–14) were identified. The median follow-up for the whole group was 16 months (range 3–64), showing an indolent clinical course in all cases.
Conclusions The detection of a predominantly γδ T-cell phenotype in papular lymphoid-rich infiltrates in the absence of other lesions is not associated with a clinically aggressive course. γδ T-cell-rich variants of LyP and PL may reflect a spectrum of related conditions. This is a single academic centre retrospective chart review of a relatively small sample.

What's already known about this topic?

- Most lymphoid-rich inflammatory skin conditions are composed of T cells expressing αβ T-cell receptors (TCRs) and, in general, TCR γδ T-cell infiltrates of the skin are associated with aggressive cutaneous lymphomas.

What does this study add?

- Regardless of the presence or absence of lymphoid atypia, a subset of γδ T-cell-rich cutaneous lymphoid infiltrates are self-limited and indolent. Pityriasis lichenoides and lymphomatoid papulosis may present as a predominant γδ T-cell infiltrate.

A small subset (< 5%) of human peripheral blood and skin lymphocytes are characterized by γδ heterodimer expression. γδ T cells are mostly distributed in lymphoid or intraepithelial tissues.[1–3] While their precise function remains elusive, they seem to play an important role in the innate immune system, as well as a modulatory role in adaptive immunity. The γδ T cells originate from $CD4^-$ $CD8^-$ 'double negative' precursors in the bone marrow, sharing functional and molecular similarities with other cytotoxic cells like natural killer (NK) T cells. Mature γδ T cells, when activated, are larger and granular,

γδ T-cell-rich variants of LyP and PL may reflect a spectrum of related conditions.

J Cutan Pathol 2015: 42: 1012–1017
doi: 10.1111/cup. 12601
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

Atypical cutaneous γδ T cell proliferation with morphologic features of lymphoma but with clinical features and course of PLEVA or lymphomatoid papulosis

Reactive lymphoid infiltrates of the skin composed predominantly of gamma-delta (γδ) T cells are not well described in the literature. Herein we report a case of an otherwise healthy 4-year-old male who presented with a waxing and waning papular rash characterized by small, discrete crusted papules spread across his trunk, face and extremities. Clinical evaluation revealed no evidence of systemic disease. Microscopic examination revealed a dermal, perivascular infiltrate of highly atypical lymphocytes with a γδ T cell phenotype, worrisome for primary cutaneous γδ T cell lymphoma. The clinical course, however, was that of a reactive condition and prompted consideration of a diagnosis of pityriasis lichenoides et varioliformis acuta (PLEVA) and lymphomatoid papulosis (LyP). In many ways, this case defies current classification schemes and seems to expand the spectrum of reactive γδ T cell infiltrates of the skin.

Keywords: T lymphocytes, atypical features, CUTANEOUS LYMPHOMAS, hematopathology,

King RL, Yan AC, Sekiguchi DR, Choi JK. Atypical cutaneous γδ T cell proliferation with morphologic features of lymphoma but with clinical features and course of PLEVA or lymphomatoid papulosis.
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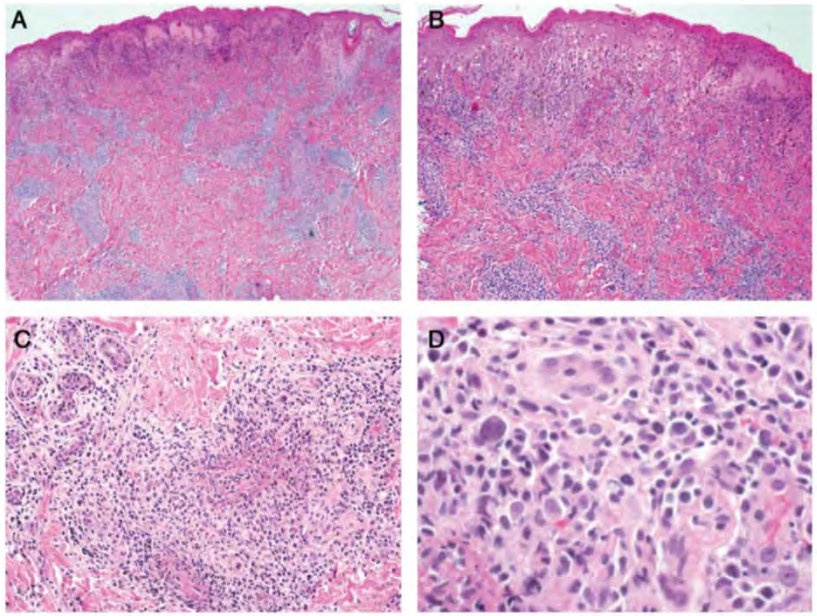
Gamma-delta (γδ) T cells represent a small subset of the normal human T cell repertoire accounting for approximately 1–5% of peripheral T cells.[1] However, reports have showed higher percentages of these T cells at epithelial sites, specifically, the skin and gastrointestinal tract.[1] γδ T cells function in both the innate and adaptive immune system and may play a critical role in bridging the two.[2–4] Primary cutaneous γδ T cell lymphoma and hepatosplenic γδ T cell lymphoma are the two subtypes of γδ T cell lymphoma currently recognized by the World Health Organization (WHO).[5] With the recent availability of commercial antibodies to detect the γδ T cell receptor in formalin-fixed paraffin-embedded tissue, the spectrum of γδ T cell neoplasia is expanding.[1] In addition, a few



Following completion of 6 months of clarithryomycin, therapy was discontinued; however, over the ensuing 15 months, he has subsequently suffered four episodes of recurrences and each episode promptly cleared with reinitiation of oral clarithromycin and graduated sun exposure (when seasonally appropriate).

Variants of lichen planus

- Actinic LP (LP actinicus, LP subtropicus, lichenoid melanodermatitis)
- Acute exanthematous LP (eruptive LP)
- Annular LP
- Atrophic LP
- Bullous LP
- Hypertrophic LP
- Inverse LP
- LP pigmentosus
- Lichen planopilaris
- Linear LP
- Ulcerative LP
- Nail LP
- Oral LP
- Vulvovaginal LP
- LP pemphigoides
- Discoid LE / LP overlap syndrome
- Drug-induced LP (lichenoid drug eruption)

Psoriasiform (PLEVA-like) drug reaction

- Pembrolizumab is an immune checkpoint inhibitors (anti-programmed cell death receptor 1)
- Cutaneous immune-related adverse events include both autoantibody-related (epidermolysis bullosa acquisita and bullous pemphigoid) and psoriasiform eruptions in addition to cytotoxic eruptions (morbilliform, lichenoid, vitiligo, Stevens-Johnson syndrome and erythema multiforme)

CASE REPORT

Pityriasis lichenoides chronica–like drug eruption developing during pembrolizumab treatment for metastatic melanoma

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Iowa City, Iowa

Key words: pembrolizumab; pityriasis lichenoides chronica; programmed death receptor 1.

INTRODUCTION

Immune checkpoint inhibitors such as ipilimumab (anticytotoxic T-lymphocyte–associated antigen), pembrolizumab, and nivolumab (anti–programmed death receptor 1) represent some of the newest and most promising medications for the treatment of metastatic melanoma.[1] As a class, immune checkpoint inhibitors interfere with tumoral suppression of T cells, resulting in a more robust immune response and subsequent benefit in the treatment of melanoma, non–small-cell lung cancer, and potentially other malignancies. Unfortunately, immune checkpoint inhibitors also interfere with suppression of autoimmunity, and several immune-related adverse events have been attributed to these medications.[2-4] Patients receiving programmed death receptor 1 (PD-1) inhibitors have had morbilliform eruptions, vitiligo, pruritus, neutrophilic dermatosis, lichen planus, psoriasis, bullous erythema multiforme, Stevens-Johnson syndrome, and bullous pemphigoid.[2,10] Here we present a novel case of a pityriasis lichenoides chronica–like drug eruption developing during pembrolizumab therapy.

Abbreviation used:
PD-1: Programmed death receptor 1

REPORT OF A CASE

A 67-year-old woman with metastatic melanoma, a medical history of hypertension and squamous cell carcinoma of the anus, and a family history of psoriasis was started on pembrolizumab, 2 mg/kg every 3 weeks. After her second infusion, she had dozens of pruritic 3- to 4-mm, red-brown, thin papules with centrally adherent micaceous scale on the forearms and lower legs (Fig 1, *A* and *B*). These lesions failed to respond to over-the-counter antihistamines and continued to worsen with each infusion. A punch biopsy was obtained from a representative area on the left lower leg (Fig 1, *A* and *B*).

Punch biopsy found a parakeratotic, spongiotic, and focally acanthotic epidermis with exocytosis of cytologically bland-appearing lymphocytes and rare neutrophils. Focal basal layer vacuolar degeneration with interface and perivascular lymphocytic inflammation and extravasated red blood cells were also observed (Fig 2, *A* and *B*). Immunohistochemistry found an equal ratio of $CD4^+$:$CD8^+$ cells in the epidermis and a slight CD4 predominance in the dermis.

The combined clinical and histopathologic findings were consistent with a diagnosis of pityriasis lichenoides chronica–like drug eruption. The skin lesions were treated with topical clobetasol with complete clearance within 2 months. About 1 month after clearance of her pityriasis lichenoides chronica–like drug eruption an inflammatory arthritis developed that resulted in discontinuation of pembrolizumab and required treatment with methotrexate. Eight months after discontinuation of pembrolizumab, she has not had a recurrence of her pityriasis lichenoides chronica–like drug eruption but is still on methotrexate for ongoing inflammatory arthritis.

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Funding sources: None.

Conflicts of interest: Dr Milhem serves on the advisory boards of BMS, EMDSERONO, Novartis, EISAI, and Genetech. Drs Mutgi, Swick, and Liu have no conflicts to declare.

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JAAD Case Reports 2016;2:343-5.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2016.06.012

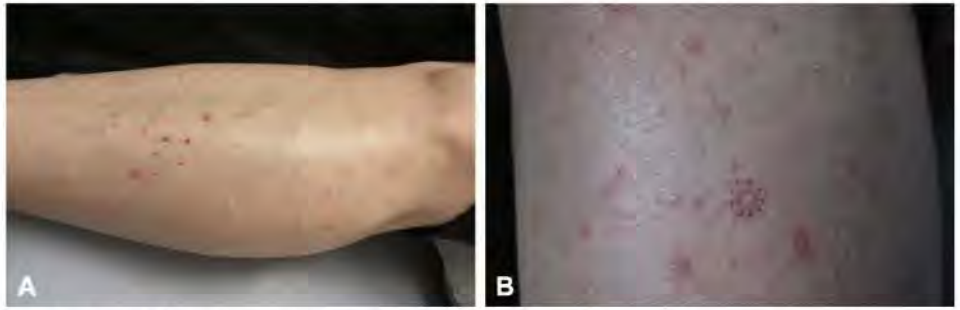

Fig 1. A and **B**, Pityriasis lichenoides chronica–like drug eruption. The lower legs show several, 3- to 4-mm, red-brown, thin papules with centrally adherent micaceous scale and intermixed erosions.

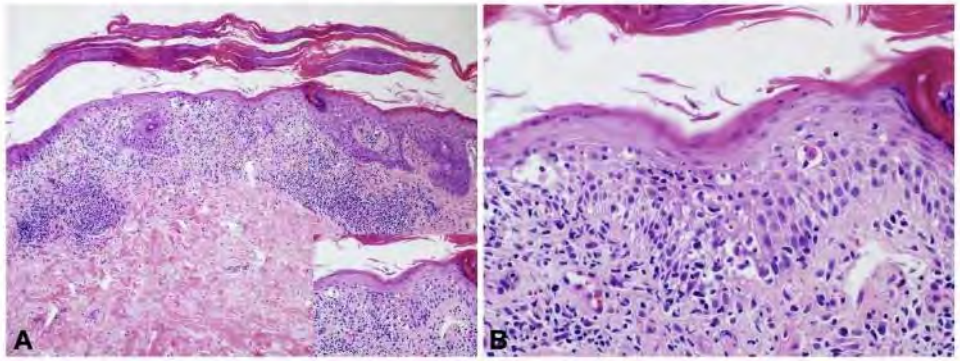

Fig 2. A and **B**, Microscopic examination of stained slides of a lower leg punch biopsy found a diffusely spongiotic epidermis with focal acanthosis dotted by exocytosis of bland-appearing lymphocytes, extravasated red blood cells, and rare neutrophils, surfaced by overlying parakeratosis. Focal basal layer vacuolar degeneration with interface and perivascular lymphocytic inflammation was also observed (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×100; **B**, ×400.)

Papulopustular eruption in targeted therapies

- Side-effect of systemic steroids, androgens and other "conventional" drugs
- Increasingly observed with several "targeted" drugs including anti EGFR, MEK 1 & 2 inhibitors, anti-BCR-ABL, anti HER2, anti VEGFR-1 and 2
- Pustular eruption particularly on the head and neck
- Comedones usually absent
- May be mistaken clinically for AGEP

Described mostly in inhibitors of the RAS-RAF-MEK-ERK pathway and in epidermal growth factor receptor inhibitors

Melanoma Res. 2017 Dec;27(6):641-644. doi: 10.1097/CMR.0000000000000397.

Intracorneal pustular drug eruption, a novel cutaneous adverse event in anti-programmed cell death-1 patients that highlights the effect of anti-programmed cell death-1 in neutrophils.

Zhao CY[1], Consuegra G, Chou S, Fernández-Peñas P.

Author information

Abstract

The introduction of anti-programmed cell death-1 (anti-PD1) monoclonal antibodies has revolutionized the treatment of various advanced malignancies. Despite its efficacy, anti-PD1 therapy is accompanied by a variety of cutaneous adverse events. A 79-year-old man developed erythematous scaly plaques and pustules of the forehead, legs and arms after four cycles of nivolumab infusions every 2 weeks. Histology showed intracorneal pustules with dermal neutrophils and eosinophils. He was treated successfully with topical corticosteroids without discontinuation of nivolumab. We report subcorneal pustular eruption as a novel cutaneous adverse event in patients on anti-PD1 therapy. Other neutrophilic eruptions (psoriasis, Sweet's syndrome, acute generalized pustulosis) have been reported in patients on anti-PD1 treatments, suggesting the neutrophil as another cell type modulated by anti-PD1 antibodies.

PMID: 28984691 DOI: 10.1097/CMR.0000000000000397

Panniculitis in checkpoint inhibitors

- Mainly lobular panniculitis
- Neutrophils in the infiltrate (r/o infectious panniculitis)
- May mimic clinically disease recurrence (subcutaneous indurated plaques / nodules)

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DOI: 10.1111/cup.13044

WILEY JCP

CASE REPORT

Erythema nodosum-like panniculitis mimicking disease recurrence: A novel toxicity from immune checkpoint blockade therapy—Report of 2 patients

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Immunotherapies targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death 1 (PD-1) receptor and its ligand (PD-L1) have showed substantial therapeutic benefit in patients with clinically advanced solid malignancies. However, autoimmune toxicities are common and often significant adverse events with these agents. While rash and pruritus remain the most common cutaneous complications in treated patients, novel dermatologic toxicities related to immune checkpoint blockade continue to emerge as the number of patients exposed to immunotherapy increases. Here, we describe 2 patients treated with combination immunotherapy with ipilimumab and nivolumab who developed painful subcutaneous nodules. Although the findings were clinically concerning for disease recurrence, histopathologic examination of biopsies from the lesions revealed a subcutaneous mixed septal and lobular erythema nodosum like panniculitis. Notably, neither patient received immunosuppressive therapy for these lesions, which subsequently remained stable, and both patients' cancer remained controlled. These cases show that the dermatologic toxicity profile of immune checkpoint blockade is diverse and continues to expand, and illustrates that recognition of such toxicities is critical to optimal patient management.

KEYWORDS
anti-CTLA-4, anti-PD-1, anti-PD-L1, dermatologic toxicity, immune checkpoint antibody

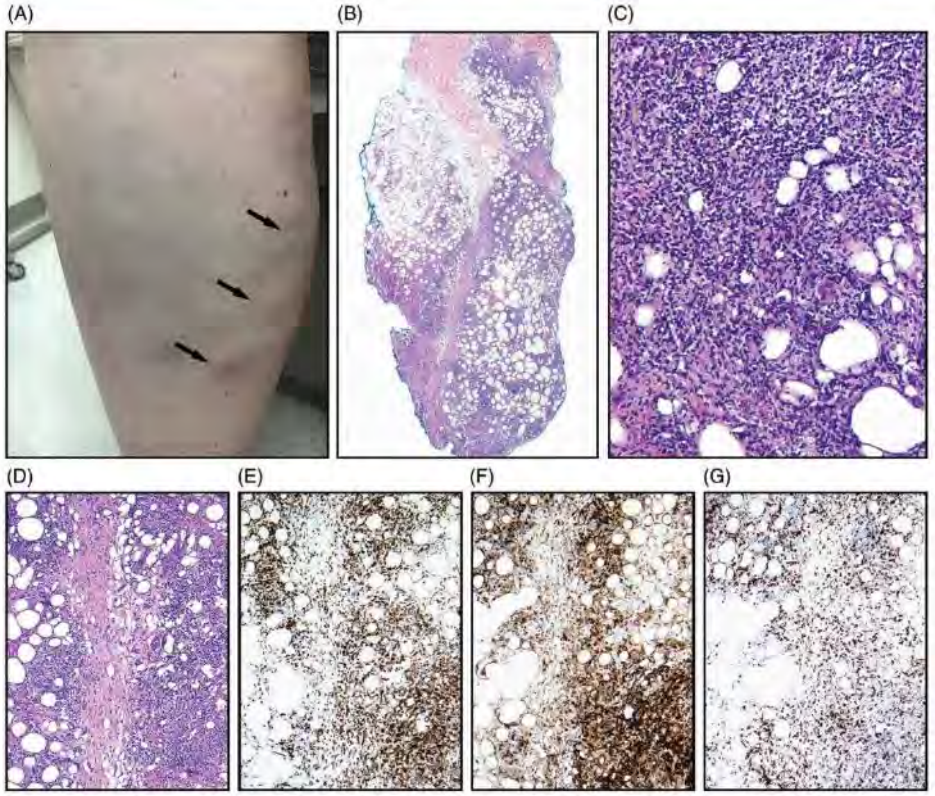

FIGURE 1 Erythema nodosum-like panniculitis arising in a 57-year-old woman treated with combination ipilimumab and nivolumab for clear cell carcinoma of the ovary. A, Multiple subcutaneous nodules (indicated by the arrows) on the right lower extremity. B, Scanning magnification of the subcutaneous tissue from the right hip reveals fibrotic thickened septa and a dense septal and lobular inflammatory infiltrate (H&E, ×20).C, The infiltrate is comprised of an admixture of lymphocytes, histiocytes and multinucleated giant cells (H&E, ×200). D, Fibrotic septa with mixed inflammatory infiltrate extending to the surrounding fat lobules (H&E, ×100). E, Immunohistochemical studies for CD3 show a predominance of T-cells comprising the infiltrate that are an admixture of (F) CD4+ and (G) CD8+ cells. Anti-CD4 additionally highlights histiocytes (F)

Michael T. Tetzlaff and Amir A. Jazaeri contributed equally to this study.

Cutaneous reactions to targeted therapy

- Different patterns related to the mechanism of the drugs; many eruptions similar to "conventional" drug reactions *(e.g., morbilliform, lichenoid, TEN, etc.)*
- Peculiar patterns: panniculitis, acneiform ("papulopustular") eruptions, eruptive KAs, psoriasiform – PLEVA-like eruptions, sarcoidosis-like lesions among many others

Cutaneous adverse effects of targeted therapies

Part I: Inhibitors of the cellular membrane

James B. Macdonald, MD,[a,b] Brooke Macdonald, BA,[c] Loren E. Golitz, MD,[d,e] Patricia LoRusso, DO,[f] and Aleksandar Sekulic, MD, PhD[g]
Provo, Utah; Aurora, Colorado; Detroit, Michigan; and Scottsdale, Arizona

Learning objectives
After completing this learning activity, participants should be able to identify the most common cutaneous adverse events associated with targeted therapies, describe the etiopathogenesis of cutaneous adverse effects associated targeted therapies, and recognize clinical features of common cutaneous adverse effects associated with targeted therapies.

Disclosures
None declared.

There has been a rapid emergence of numerous targeted agents in the oncology community in the last decade. This exciting paradigm shift in drug development lends promise for the future of individualized medicine. Given the pace of development and clinical deployment of targeted agents with novel mechanisms of action, dermatology providers may not be familiar with the full spectrum of associated skin-related toxicities. Cutaneous adverse effects are among the most frequently observed toxicities with many targeted agents, and their intensity can be dose-limiting or lead to therapy discontinuation. In light of the often life-saving nature of emerging oncotherapeutics, it is critical that dermatologists both understand the mechanisms and recognize clinical signs and symptoms of such toxicities in order to provide effective clinical management. Part I of this continuing medical education article will review in detail the potential skin-related adverse sequelae, the frequency of occurrence, and the implications associated with on- and off-target cutaneous toxicities of inhibitors acting at the cell membrane level, chiefly inhibitors of epidermal growth factor receptor, KIT, and BCR-ABL, angiogenesis, and multikinase inhibitors. (J Am Acad Dermatol 2015;72:203-18.)

Key words: adverse sequelae; alopecia; antiangiogenic agents; anticancer; BCR-ABL; bevacizumab; cancer treatment; canertinib; cetuximab; chemotherapy; cutaneous adverse effects; dasatinib; dermatologic toxicities; disturbed wound healing; drug eruption; drug rash; drug reaction; dry skin; dual kinase inhibitors; epidermal growth factor receptor inhibitors; erbB receptor; erlotinib; gefitinib; genital rash; HER2; hyperkeratotic hand–foot skin reaction; imatinib; KIT; lapatinib; macular eruption; monoclonal antibodies; morbilliform; mucocutaneous hemorrhage; mucositis; multikinase inhibitors; nilotinib; panitumumab; papulopustular eruption; paronychia; pazopanib; platelet-derived growth factor receptor; photosensitivity; pigment changes; ranibizumab; side effects; small molecule; sorafenib; stomatitis; sunitinib; supportive oncodermatology; targeted therapy; toxic erythema; tyrosine kinase inhibitors; vandetanib; vascular endothelial growth factor; xerosis.

INTRODUCTION

Key points

- **Targeted therapies offer more precise oncologic treatment options; however, they are not free of adverse effects**
- **Cutaneous adverse effects are among the most frequently encountered, and significantly impact both quality of life and health care economics**

From the Departments of Dermatology[a] and Pathology,[b] Central Utah Clinic, Provo; Macdonald Graphic Design, Inc,[c] Provo; Departments of Dermatology[d] and Pathology,[e] University of Colorado-Denver, Aurora; Department of Oncology, Wayne State University,[f] Detroit; and the Department of Dermatology,[g] Mayo Clinic, Scottsdale.
Funding sources: None.
Conflicts of interest: None declared.
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0190-9622/$36.00

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Date of release: February 2015
Expiration date: February 2018

Cutaneous adverse effects of targeted therapies

Part II: Inhibitors of intracellular molecular signaling pathways

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Provo, Utah; Aurora, Colorado; Detroit, Michigan; and Scottsdale, Arizona

Learning objectives
After completing this learning activity, participants should be able to describe the management strategies of cutaneous adverse effects associated with 11 families of targeted therapies currently in prevalent use.

Disclosures
None declared.

The last decade has spawned an exciting new era of oncotherapy in dermatology, including the development of targeted therapies for metastatic melanoma and basal cell carcinoma. Along with skin cancer, deregulation of the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK intracellular signaling pathways contributes to tumorigenesis of a multitude of other cancers, and inhibitors of these pathways are being actively studied. Similar to other classes of targeted therapies, cutaneous adverse effects are among the most frequent toxicities observed with mitogen-activated protein kinase pathway inhibitors, PI3K-AKT-mTOR inhibitors, hedgehog signaling pathway inhibitors, and immunotherapies. Given the rapid expansion of these families of targeted treatments, dermatologists will be essential in offering dermatologic supportive care measures to cancer patients being treated with these agents. Part II of this continuing medical education article reviews skin-related adverse sequelae, including the frequency of occurrence and the implications associated with on- and off-target cutaneous toxicities of inhibitors of the RAS-RAF-MEK-ERK pathway, PI3K-AKT-mTOR pathway, hedgehog signaling pathway, and immunotherapies. (J Am Acad Dermatol 2015;72:221-36.)

Key words: AKT inhibitor; autoimmune adverse effects; autoimmune dermopathies; B-RAF; dabrafenib; dermatitis; dual inhibitor; dysgeusia; everolimus; hair loss; hedgehog signaling pathway; immunotherapy; immune-related toxicities; ipilimumab; keratoacanthoma; keratosis pilaris; keratotic squamoproliferative lesion; lambrolizumab; loss of taste; MAP kinase pathway; MEK inhibitors; mTOR inhibitor; nivolumab; panniculitis; PD-1 inhibitor; PI3K-AKT-mTOR pathway; PI3 kinase inhibitor; pruritus; RAF inhibitors; rapamycin; RAS; seborrheic dermatitis; selumetinib; squamous cell carcinoma; taste alteration; temsirolimus; trametinib; vemurafenib; vitiligo; verrucal keratosis; vismodegib.

RAS-RAF-MEK-ERK PATHWAY

The RAS-RAF-MEK-ERK (mitogen-activated protein kinase [MAPK]) pathway is one of the most frequently deregulated signaling pathways leading to increased cellular proliferation in a broad spectrum of cancers. Patients who are taking inhibitors of the MAPK pathway frequently present with cutaneous adverse effects (AEs). The extensive interaction of the MAPK pathway with the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway by sharing common inputs and activation through oncogenic RAS (Fig 1) provides a possible mechanism for compensatory signaling and the development of tumor resistance to targeted

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T-VEC (talimogene laherparepvec)

- T-VEC (talimogene laherparepvec) is a genetically engineered oncolytic herpes virus used to treat metastatic melanoma
- Side effects: fatigue and chills, fever, nausea, flu-like symptoms, pain at the injection site, anemia, vasculitis, pneumonia, worsening psoriasis, glomerulonephritis
- Like herpes simplex virus, T-VEC may persist in neurons and cause latent infections

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

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See accompanying article on page 2812

ABSTRACT

Purpose
Talimogene laherparepvec (T-VEC) is a herpes simplex virus type 1–derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses. T-VEC was compared with GM-CSF in patients with unresected stage IIIB to IV melanoma in a randomized open-label phase III trial.

Patients and Methods
Patients with injectable melanoma that was not surgically resectable were randomly assigned at a two-to-one ratio to intralesional T-VEC or subcutaneous GM-CSF. The primary end point was durable response rate (DRR; objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points included overall survival (OS) and overall response rate.

Results
Among 436 patients randomly assigned, DRR was significantly higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%); odds ratio, 8.9; $P < .001$). Overall response rate was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 5.7%, 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; $P = .051$). T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease. The most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. The only grade 3 or 4 AE occurring in ≥ 2% of T-VEC–treated patients was cellulitis (2.1%). No fatal treatment-related AEs occurred.

Conclusion
T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR ($P < .001$) and longer median OS ($P = .051$), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.

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INTRODUCTION

Development of targeted therapy and immunotherapy has resulted in important advances in melanoma treatment. Improvement in overall survival (OS) has been reported with T-cell checkpoint inhibitors and BRAF inhibitors, with objective response rates ranging from 10% with single-agent ipilimumab to 78% with the combination of BRAF and MEK inhibitors, although drug resistance and recurrence are still challenges.[1-3] New strategies promoting tumor cell death and/or inducing protective host antitumor immunity are of high priority.

Oncolytic viruses are novel cancer treatments that include wild-type and modified live viruses. Talimogene laherparepvec (T-VEC) is a first-in-class oncolytic virus based on a modified herpes simplex virus (HSV) type 1 designed to selectively replicate in and lyse tumor cells while promoting regional and systemic antitumor immunity. T-VEC is modified through deletion of two nonessential viral genes.[5] Functional deletion of the herpes virus

Table 3. Patient Incidence of AEs

	T-VEC (n = 292)				GM-CSF (n = 127)			
	Any Grade		Grade 3 or 4		Any Grade		Grade 3 or 4	
AE*	No.	%	No.	%	No.	%	No.	%
Fatigue	147	50.3	5	1.7	46	36.2	1	0.8
Chills	142	48.6	0	0	11	8.7	0	0
Pyrexia	125	42.8	0	0	11	8.7	0	0
Nausea	104	35.6	1	0.3	25	19.7	0	0
Influenza-like illness	89	30.5	2	0.7	19	15.0	0	0
Injection-site pain	81	27.7	3	1.0	8	6.3	0	0
Vomiting	62	21.2	5	1.7	12	9.4	0	0
Diarrhea	55	18.8	1	0.3	14	11.0	0	0
Headache	55	18.8	2	0.7	12	9.4	0	0
Myalgia	51	17.5	1	0.3	7	5.5	0	0
Arthralgia	50	17.1	2	0.7	11	8.7	0	0
Pain in extremity	48	16.4	4	1.4	12	9.4	1	0.8
Pain	47	16.1	2	0.7	13	10.2	1	0.8
Peripheral edema	35	12.0	2	0.7	12	9.4	2	1.6
Constipation	34	11.6	0	0	8	6.3	1	0.8
Cough	31	10.6	0	0	10	7.9	0	0
Decreased appetite	30	10.3	0	0	14	11.0	0	0
Pruritus	28	9.6	0	0	19	15.0	0	0
Cellulitis	17	5.8	6	2.1	2	1.6	1	0.8
Injection-site erythema	15	5.1	0	0	33	26.0	0	0
Dyspnea	13	4.5	3	1.0	13	10.2	2	1.6
Injection-site pruritus	5	1.7	0	0	21	16.5	0	0

Abbreviations: AE, adverse event; GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.
*Treatment-emergent AEs of any grade with incidence ≥ 10% in either arm or grade 3 or 4 with incidence ≥ 2% in either arm.

One case of "plasmacytoma near the site of injection (without systemic disease)" reported to the company by an investigator, but never published.

BY NO MEANS AN EXHAUSTIVE LIST…

- RAS-RAF-MEK-ERK pathway *(Morbilliform eruption, Papulopustular eruption, Xerosis , Epidermal neoplasms, Keratosis pilaris-like reaction, Seborrheic dermatitis-like eruption, Hyperkeratotic hand-foot reaction, Photosensitivity, Panniculitis)*
- PI3K-AKT-mTOR pathway *(Stomatitis, Inflammatory eruptions)*
- Hedgehog signaling pathway inhibitors *(Alopecia, Dysgeusia)*
- Immunomodulatory agents (PD-1, PD-L1, CTLA-4 inhibitors) *(Autoimmune dermopathies, Immune-related colitis/diarrhea, Pruritus, Morbilliform eruption, Vitiligo-like hypopigmentation, Scleroderma, PLEVA-like eruption, Papulopustular eruption, Panniculitis)*
- Epidermal growth factor receptor inhibitors *(Papulopustular eruption, Xerosis, Hair changes, Mucositis, Nail changes, Photosensitivity)*
- *KIT* and *BCR-ABL* inhibitors *(Edema, Morbilliform eruption, Pigmentary changes, Alopecia, Other inflammatory eruptions)*
- Antiangiogenesis agents *(Mucocutaneous hemorrhage, Disturbed wound healing)*
- Multikinase inhibitors *(Hyperkeratotic hand-foot skin reaction, Inflammatory eruptions, Hair changes, Genital involvement)*