Pityriasis lichenoides and its subtypes

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Pityriasis lichenoides represents a unique group of inflammatory skin disorders that include pityriasis lichenoides et varioliformis acuta (PLEVA), febrile ulceronecrotic Mucha-Habermann disease (a subtype of PLEVA), and pityriasis lichenoides chronica. The history, epidemiology, clinical features, pathophysiology, and treatment of this group of conditions are reviewed in this manuscript. (J Am Acad Dermatol 2006;55:557-72.)

Learning objective: At the completion of this learning activity, participants should be familiar with the clinical manifestations, histopathological findings, proposed mechanisms for pathogenesis, methods of treatment, and potential outcomes of pityriasis lichenoides and its subtypes.

Historically, pityriasis lichenoides has been confused with a host of other dermatoses, some relatively benign and others potentially malignant. This review focuses on the history, epidemiology, clinical manifestations, histopathology, immunopathology, proposed mechanisms for cause and pathogenesis, differential diagnosis, treatment, and course and prognosis of pityriasis lichenoides. The term *pityriasis lichenoides* refers to the group of disorders known as pityriasis lichenoides et varioliformis acuta (PLEVA), febrile ulceronecrotic Mucha-Habermann disease (a subtype of PLEVA), and pityriasis lichenoides chronica (PLC).

Abbreviations used:

CMV:	cytomegalovirus
EBV:	Epstein-Barr virus
MF:	mycosis fungoides
PCR:	polymerase chain reaction
PLC:	pityriasis lichenoides chronica
PLEVA:	pityriasis lichenoides et varioliformis acuta
PUVA:	psoralen plus ultraviolet A
TCR:	T-cell receptor

HISTORY

Experts date the first descriptions of what is currently termed pityriasis lichenoides to separate case reports in 1894 by Neisser[1] and Jadassohn,[2] who described what would now be considered the acute and chronic forms, respectively (Table I). In 1899 Juliusberg described pityriasis lichenoides in a chronic form and thus coined the term *pityriasis lichenoides chronica* (PLC).[3] In 1902 Brocq described pityriasis lichenoides as a form of parapsoriasis under the category of parapsoriasis en gouttes because of its clinical resemblance to guttate psoriasis.[4] This classification lasted for several years, and it was not until 1926 that pityriasis lichenoides was first distinguished on clinical grounds as an entity separate from parapsoriasis.[5] This sentiment was echoed by others, who believed that the term *parapsoriasis* was not only arbitrary but also illogical and served only as a source of confusion.[6] Thus today most experts agree that pityriasis lichenoides is an entity separate from the parapsoriasis group.

Mucha first separated the acute form of pityriasis lichenoides from PLC in 1916.[7] It was not until 1925, however, that this acute form was given the name *pityriasis lichenoides et varioliformis acuta* (PLEVA) by Habermann.[8] Because of this joint contribution, PLEVA is also commonly known as Mucha-Habermann disease. Degos et al, in 1966, reported an ulceronecrotic subtype of PLEVA associated with a high fever.[9] This subtype is usually referred to as febrile ulceronecrotic Mucha-Habermann disease.

EPIDEMIOLOGY

Pityriasis lichenoides in the general population

The prevalence, incidence, and risk factors of pityriasis lichenoides in the general population are

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Table I. Historical evolution of pityriasis lichenoides and its subtypes

Year	Author	Event
1894	Neisser[1]	Described acute form
1894	Jadassohn[2]	Described chronic form
1899	Juliusberg[3]	Coined term *PLC*
1902	Brocq[4]	Categorized pityriasis lichenoides as parapsoriasis en gouttes
1916	Mucha[7]	Differentiated acute form from PLC
1925	Habermann[8]	Coined term *PLEVA*
1926	Wile[5]	Removed pityriasis lichenoides from parapsoriasis classification
1966	Degos et al[9]	Described ulceronecrotic PLEVA

PLC, Pityriasis lichenoides chronica; *PLEVA,* pityriasis lichenoides et varioliformis acuta.

unknown. Neither an ethnic nor a geographic predisposition has been reported.[6,10] The average ages and other data regarding patients with pityriasis lichenoides from several studies are summarized in Table II.[11-14] A study with one of the largest populations showed an average age of 29 years.[12] In studies performed by Willemze and Scheffer[12] and Marks et al,[14] prevalence was shown to peak in the third decade of life and, in 79% and 78% of patients, respectively, pityriasis lichenoides was diagnosed before the fifth decade. Although pityriasis lichenoides was initially thought to predominate in males, a review of the literature shows no strong predisposition in either sex in the general population (age, >18 y). There are also isolated reports of the development of PLEVA during pregnancy.[15-17]

Pityriasis lichenoides in the pediatric population

Epidemiologic data collected from the review of various studies of pediatric cases of pityriasis lichenoides are presented in Table II.[18-20] These studies showed peaks at 5 and 10 years of age, with predominance in males.

Febrile ulceronecrotic Mucha-Habermann disease subtype of PLEVA

A total of 29 cases of febrile ulceronecrotic Mucha-Habermann disease have been reported.[9,21-45] A meta-analysis of these cases shows that the mean age of patients with this disease is 30.6 years, with a peak in the second decade of life. The proportion of males in the pediatric and adult cases was 72.7% (8 males of 11 patients) and 72.2% (13 males of 18 patients), respectively, for an overall male predominance of 72.4%. No ethnic or geographic predisposition has been reported for febrile ulceronecrotic Mucha-Habermann disease.[10]

CLINICAL FEATURES

It is generally accepted that PLEVA and PLC represent 2 ends of a continuous spectrum, and therefore it is not uncommon to observe both acute and chronic lesions in the same person, as well as lesions at intermediate stages between PLEVA and PLC. The descriptive terms *acute* and *chronic* refer to the characteristics of the individual lesions and not the course of the disease.

PLEVA

PLEVA is characterized by 2- to 3-mm-diameter erythematous macules that quickly evolve into papules with a fine micaceous scale. As the scale thickens, it often becomes free at the periphery but remains attached centrally. The papule often has a central punctum that becomes vesiculopustular, undergoes hemorrhagic necrosis, and becomes ulcerated, with overlying red-brown crusts (Fig 1). Varioliform scars and postinflammatory hyper- and hypopigmentation may result. Symptoms include burning and pruritus. PLEVA most often occurs on the trunk, extremities, and flexural areas, but diffuse and generalized patterns may also occur. The eruption is polymorphous, as lesions exist in all stages of development, and successive crops of lesions can last indefinitely, from a few weeks to months or years.[46-48]

Febrile ulceronecrotic Mucha-Habermann disease subtype of PLEVA

Febrile ulceronecrotic Mucha-Habermann disease is differentiated from PLEVA by a rapid progression of necrotic papules to large coalescent ulcers with necrotic crusts, hemorrhagic bullae, and pustules.[9] There may be extensive, painful necrosis of the skin, as well as secondary infection of the ulcers. Oral and genital mucosa may be affected as well. The ulcers often heal with hypopigmentation and atrophic scars. Systemic manifestations include high fever, sore throat,[43] diarrhea,[43] central nervous system symptoms,[9] abdominal pain,[9,23] interstitial pneumonitis,[22] splenomegaly,[25] arthritis,[27] sepsis,[27] megaloblastic anemia,[30] conjunctival ulcers,[34] and death. To date, there have been 6 reported fatalities, which have been limited to adults.[25,31,36,41,45] Laboratory abnormalities may include elevated levels of leukocytes,[28,37,39] erythrocyte sedimentation,[28,31,37] C-reactive protein,[31,37,45] lactate dehydrogenase,[31] and liver enzymes,[28,37] as well as anemia[45] and hypoproteinemia.[44]

Table II. Epidemiology of pityriasis lichenoides in the general population

Study, by population type	No. of patients	Disorders	Age range (y)	Mean age (y)	Male predominance (%)
General population					
Magro et al[11]	35	28 PLC; 7 PLEVA	8-90	40	40
Willemze and Scheffer[12]	82	Pityriasis lichenoides	2-80	29	64.6
Benmaman and Sanchez[13]	29	PLC	10-60	32	44.8
Marks et al[14]	128	Pityriasis lichenoides	1-63	Not reported	58.6
Weighted average				32.3	56.6
Pediatric population					
Romani et al[18]	22	Pityriasis lichenoides	3-15	9.3	54.5
Gelmetti et al[19]	89	Pityriasis lichenoides	0.7-14	7.5	60.7
Truhan et al[20]	22	Pityriasis lichenoides	2-15	Not reported	72.7
Weighted average				7.9	61.7

PLC, Pityriasis lichenoides chronica; *PLEVA,* pityriasis lichenoides et varioliformis acuta.

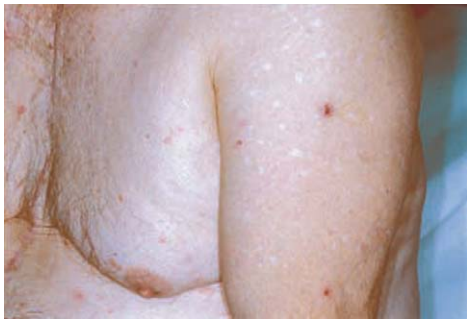

Fig 1. PLEVA lesions on the arm and trunk of a male patient.

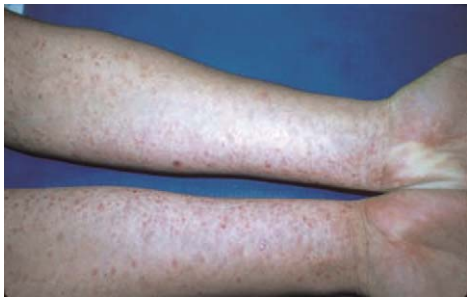

Fig 2. PLC lesions on the ventral surfaces of both arms.

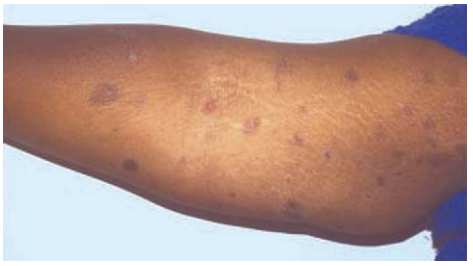

Fig 3. PLC lesions on a darker-skinned person.

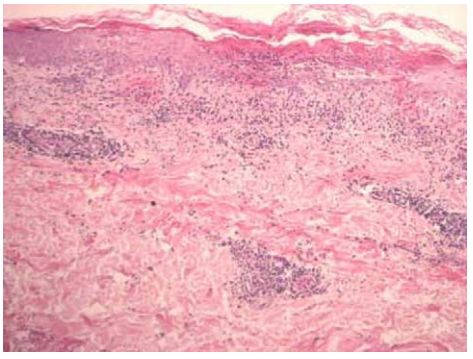

Fig 4. Biopsy specimen showing acute findings consistent with PLEVA. Histopathologic changes of pityriasis lichenoides are continuous along a spectrum. Images courtesy of Valda Kaye, MD. (Hematoxylin-eosin stain; original magnification: ×10.)

PLC

PLC has a much more indolent clinical course than PLEVA and febrile ulceronecrotic Mucha-Habermann disease. The lesion in PLC is also initially an erythematous papule that develops a reddish-brown hue and a centrally adherent micaceous scale that can easily be detached to reveal a shiny, pinkish-brown surface (Fig 2). Unlike PLEVA and febrile ulceronecrotic Mucha-Habermann disease, however, the papule spontaneously flattens and regresses over a period of weeks. It often leaves behind a hyper- or hypopigmented macule (Fig 3).[49] Each lesion can last for several weeks, and as in PLEVA, there are often exacerbations and remissions. The entire course of an eruption can take several years.[50] As with PLEVA, lesions may be present in all stages of development. Occasionally, in dark-skinned persons, the eruption can primarily present as generalized hypopigmented macules that lack scale.[51] PLC usually occurs on the trunk and proximal portions of the extremities, but acral and segmental distributions have also been described.[14,19,52-54] Unlike PLEVA, lesions are usually asymptomatic.

Table III. Histopathologic findings in PLEVA, febrile ulceronecrotic Mucha-Habermann disease, and PLC

Area of involvement	PLEVA	FUMHD	PLC
Epidermis	Focal and confluent parakeratosis, spongiosis, dyskeratosis, mild to moderate acanthosis, vacuolization of basal layer with necrotic keratinocytes, occasional intraepidermal vesicles, focal epidermal necrosis; advanced findings: extension of infiltrate into epidermis, invasion of erythrocytes, widespread epidermal necrosis, nuclear debris in necrotic areas	Similar to PLEVA but with extensive necrosis	Focal parakeratosis, mild to moderate acanthosis, focal areas of spongiosis, minimal amounts of necrotic keratinocytes, minimal vacuolar degeneration of the basal layer, focal invasion of small numbers of lymphocytes and erythrocytes
Dermis	Edema; moderately dense lymphohistiocytic perivascular inflammatory infiltrate, often wedge-shaped and extending deep into reticular dermis as well as diffusely obscuring the dermoepidermal junction; extravasation of lymphocytes and erythrocytes with epidermal invasion; subepidermal vesicles in later lesions; dermal sclerosis in older lesions	Dense perivascular infiltrate, usually without atypia[28,40,44]*; otherwise similar to PLEVA	Edema, mild superficial perivascular lymphohistiocytic infiltrate that only focally obscures the dermoepidermal junction, occasional extravasated erythrocytes
Vascular changes	Dilation and engorgement of blood vessels in papillary dermis with endothelial proliferation, vascular congestion, occlusion, dermal hemorrhage, and extravasation of erythrocytes	Similar to vascular changes in PLEVA	Dilation of superficial vessels, no invasion of vessel walls by inflammatory cells[47]
Vasculitis	Invasion of vessel walls by inflammatory cells,[12,47] rare fibrinoid deposits within vessel walls,[12,56] very rare leukocytoclasis[56]†	Fibrinoid necrosis of vessel walls, with leukocytoclastic vasculitis[9,24,25,27-32,34]	None

FUMHD, Febrile ulceronecrotic Mucha-Habermann disease; *PLC,* pityriasis lichenoides chronica; *PLEVA,* pityriasis lichenoides et varioliformis acuta.

*Except in Rivera.[42]

†Leukocytolysis found in 3% of 104 biopsies.

HISTOPATHOLOGY

A major supporting aspect of the view that PLC and PLEVA are intimately related disorders, separated by only a few degrees on a clinicopathologic spectrum, is the gradual histopathologic differences between the two entities, reflecting intermediate degrees of severity (Fig 4).[12,18,50,55,56] Also, the presence of "acute"-type histopathologic findings in patients with PLC and "chronic"-type findings in patients with PLEVA is not uncommon.[14] Table III lists the histopathologic findings in PLEVA, febrile ulceronecrotic Mucha-Habermann disease, and PLC.

IMMUNOHISTOCHEMISTRY

Immunohistochemical studies for both PLEVA and PLC lesions have shown that T cells predominate in both the dermal and epidermal inflammatory infiltrates. Admixed in the infiltrate are variable numbers of macrophages and CD1a+ epidermal dendritic cells (Langerhans or indeterminate cells). There has been much interest in comparing the various subpopulations of T cells in both PLEVA and PLC lesions, namely CD8+ and CD4+ T cells. Most studies indicate that CD8+ T cells predominate in PLEVA lesions[50,57-59] and CD4+ T cells predominate in

Table IV. Predominant lymphocyte populations in the inflammatory infiltrate of PLEVA and PLC

		Epidermis			Dermis		
Study	**No. of Specimens***	**PLEVA**	**FUMHD**	**PLC**	**PLEVA**	**FUMHD**	**PLC**
Muhlbauer et al[57]	11 (4)	CD8[139]	...	...	CD8[139]	...	...
Wood et al[50†]	5 (3)	CD8	...	...	Eq[139]	...	...
	3 (3)	...	...	CD4	...	...	CD4
Giannetti et al[59†]	5 (5)	CD8	...	...	CD4[139]	...	...
	6 (6)	...	...	CD4[139]	...	...	CD4[1]
Varga et al[58]	6 (6)	NR[139]	...	...	CD4[139]	...	...
Tsai et al[37]	1	...	CD8	...	...	CD4	...
Yanaba et al[40]	1	...	CD8	...	...	CD8	...
Yang et al[43]	1	...	Eq[139]	...	...	Eq[139]	...
Ito et al[44]	1	...	NR	...	...	CD8	...
Cozzio et al[45]	2 (2)	...	Eq	...	...	CD8	...

Eq, Equivocal evidence; *FUMHD*, febrile ulceronecrotic Mucha-Habermann disease; *NR*, not reported; *PLC*, pityriasis lichenoides chronica; *PLEVA*, pityriasis lichenoides et varioliformis acuta.

*Numerals in parentheses in this column represent numbers of patients.

†First row of data represents PLEVA patients. Second row of data represents PLC patients.

PLC[49,59] (Table IV). Epidermal keratinocytes and dermal endothelial cells are often human leukocyte antigen—D-related subtype positive (HLA-DR+), especially in areas where the infiltrate is at its densest[50,56,57] and staining is more diffuse and strong in PLEVA in comparison with PLC.[57] HLA-DR+ keratinocytes are markers for diseased skin, and their occurrence is often linked to the presence of a lymphocytic infiltrate that contains numerous activated T cells. Dermatoses that lack significant lymphocytic infiltration also consistently lack HLA-DR+ keratinocytes.[60]

In the study of lesions of febrile ulceronecrotic Mucha-Habermann disease, immunohistochemical staining has shown that infiltrating lymphocytes are predominantly composed of T lymphocytes as well. Most often, these are CD8+ cytotoxic lymphocytes.[37,40,43,44,45] In most circumstances, immunohistochemical staining shows infiltrating lymphocytes to be CD30−,[40,43] although Rivera et al[42] detected a group of CD30+ lymphocytes in early biopsies.

PATHOGENESIS

There are 3 major pathogenic theories of pityriasis lichenoides: an inflammatory reaction triggered by infectious agents; an inflammatory response secondary to a T-cell dyscrasia; and an immune complex—mediated hypersensitivity vasculitis.

Infectious etiology

Characteristics of pityriasis lichenoides that are consistent with an infectious model include young age at onset, an acute eruptive manifestation, and reports of familial outbreaks.[61,62]

Toxoplasma gondii. Nonspecific skin manifestations due to *Toxoplasma gondii* were first described by Pinkerton and Weinman[63] in 1940 and then 1 year later by Pinkerton and Henderson.[64] They reported extensive macular, papular, and hemorrhagic eruptions in 2 patients with acute and fatal toxoplasmosis. In 1969 Andreev et al reported a patient with pityriasis lichenoides—like lesions and systemic symptoms who had strongly positive results of serologic and immunologic tests for toxoplasmosis.[65] Furthermore, treatment with pyrimethamine resulted in prompt and marked improvement in the systemic symptoms and the skin lesions. In 1972 Zlatkov and Andreev demonstrated that in 6 of 11 (54.5%) patients with clinically diagnosed pityriasis lichenoides, results of the complement fixation test, the intradermal toxoplasmin test, and the Sabin-Feldman test were strongly positive for toxoplasmosis.[66] All 6 patients were also shown to have had continuous animal contact. These 6 patients, as well as 3 pityriasis lichenoides patients with negative results of toxoplasmosis testing, underwent treatment with pyrimethamine. Fifty percent or greater clearance of skin lesions was achieved in all 6 of the toxoplasmosis-positive patients. None of the patients with negative results of toxoplasmosis tests had improvement with pyrimethamine.

In 1987 Rongioletti et al reported a patient with PLEVA who was enzyme-linked immunosorbent assay—positive for IgG and IgM antibodies against toxoplasmosis, although the result of Giemsa stain of the biopsy specimen was negative.[67] Empiric treatment with spiramycin resulted in clearing of the cutaneous lesions within a few weeks. In 1997 Nassef and Hammam compared 22 patients clinically and

histopathologically diagnosed with PLC with 20 healthy control subjects.[68] Eight of 22 PLC patients (36%) had serologic results positive for toxoplasmosis by means of indirect hemagglutination, as compared with 2 of the 20 (10%) control subjects. All of the PLC patients subsequently underwent treatment with pyrimethamine and trisulfapyrimidine, and 5 of the 8 patients (62.5%) with seropositivity had complete clearance within 2 months, whereas none of the seronegative patients had a response. In 1999 Rongioletti et al reported a patient with clinically and histopathologically confirmed pityriasis lichenoides with positive IgG and IgM for *T gondii*.[69] Treatment with spiramycin led to complete resolution of skin lesions.

Despite this evidence, Ceilley and Zuehlke failed to find significantly elevated *Toxoplasma* titers in 13 pityriasis lichenoides patients in a part of Iowa that is endemic for toxoplasmosis.[70]

Epstein-Barr virus. It is unclear whether a recent infection with the Epstein-Barr virus (EBV) can trigger PLEVA or whether PLEVA can lead to an immune dysregulation that reactivates a preexisting EBV infection. In 1978 Boss et al described a patient with PLEVA and highly elevated EBV titers that fell as the eruption resolved.[71] A retrospective survey of 9 other PLEVA patients, as well as 11 control subjects (with various dermatoses that ranged from erythema multiforme to guttate psoriasis), showed that 4 of the 10 PLEVA patients had very high levels of IgG complement fixing antibodies to EBV, as compared with 1 of 11 control subjects. In 1989 Edwards et al reported a 12-year-old girl who presented with a 3-week history of migratory arthralgias, monoarticular arthritis, pharyngitis, otitis media, high fever, and a cutaneous eruption consistent with PLEVA.[72] The result of a Monospot test was positive, and serologic results were consistent with reactivated EBV infection. In 2000 Almagro et al reported a 43-year-old man who presented with an eruption that was both clinically and histopathologically consistent with PLEVA and who had serologic results indicative of acute primary infection with EBV. The rash disappeared within 7 days of the initiation of oral acyclovir treatment.[73] In 2003 Klein et al[74] reported a 23-year-old woman who presented with a 3-day history of fever, sore throat, jaundice, dark urine, and clay-colored stools, as well as a cutaneous eruption clinically and histopathologically consistent with PLC. Results of laboratory studies indicated acute infectious mononucleosis, and as her serologic results for EBV, results of hepatic function tests, and constitutional symptoms improved, her cutaneous lesions resolved. In 2001 Jang et al performed in situ hybridization on 12 persons with PLEVA by using fluorescein-conjugated oligonucleotide probes for EBV early regions.[75] All 12 cases were negative, suggesting that EBV was not operative in these cases of PLEVA.

HIV. It is thought that HIV infection, with its inherent immune dysregulation, could lead to pityriasis lichenoides by means of either an immune-complex or a cell-mediated mechanism.[76,77] The first association between pityriasis lichenoides and HIV was reported in 1992 by Ostlere et al.[76] Six months after HIV infection was diagnosed in a 48-year-old man, he developed a rash that was clinically and histopathologically consistent with PLEVA. At the time of the eruption, he had a CD4+ count of 208 cells per microliter and had stopped taking azidothymidine treatment. Other case reports that link HIV with pityriasis lichenoides have also been described. In 1997 Smith et al reported on 5 early-stage HIV-positive patients, all of whom had histologically confirmed PLEVA.[77] In 1998 Griffiths reported an HIV-positive patient who developed a severe erythematous, papular rash, which was histopathologically consistent with PLC, as her CD4+ count fell from 200 to 20 cells per microliter.[78] Antihistamines, ultraviolet light therapy, and systemic steroids offered no relief, but cyclosporine therapy led to dramatic improvement. Any attempt to wean the cyclosporine led to worsening of the PLC. Maintenance therapy with cyclosporine was necessary to keep the PLC under control. In addition, antiretroviral treatment resulted in an increase in her CD4+ count and complete remission of the PLC lesions.

Other infectious agents. Other pathogens have also been implicated in the cause and pathogenesis of pityriasis lichenoides. Mechanisms for viral pathogens that lead to pityriasis lichenoides may include an initial vasculitis caused by the infection, which leads to further cutaneous effects or a cutaneous immune response to the virus-infected cells.[37] In 2001 Tsai et al reported the detection of IgG titers to cytomegalovirus (CMV) in a patient with febrile ulceronecrotic Mucha-Habermann disease.[37] Immunohistochemical staining allowed identification of the expression of CMV late antigen in endothelial cells, and expression of CMV early gene was verified by means of in situ hybridization. The presence of CMV in the skin lesions was also confirmed with polymerase chain reaction (PCR). In 2003 Boralevi et al investigated the presence of varicella zoster virus in 13 patients with histologically confirmed pityriasis lichenoides, as well as in 22 control subjects.[79] Twelve of the 13 pityriasis lichenoides patients and 19 of 22 control subjects had a history of chickenpox. PCR methods were used to identify genomic sequences of varicella zoster virus in skin samples from

8 of the 13 pityriasis lichenoides patients (61.5%) and none of the control subjects ($P < .0001$). Antiviral therapy was given to the 12 pityriasis lichenoides patients with a history of chickenpox; eight had improvement of at least 50%.

In 1996 Sabarthe et al reported a patient who presented with pityriasis lichenoides with lingual ulcerations that appeared during a seroconversion for parvovirus B19.[80] Tomasini et al demonstrated parvovirus B19 genomic DNA in lesional skin from 9 of 30 patients with histologically confirmed PLEVA.[81] The authors suggested that the incorporation of the virus into the host cell might have introduced novel keratinocyte antigenicity, subsequently leading to a cytotoxic reaction against antigenic epidermal targets.

In 1974 Piamphongsant reported the finding of coagulase-positive staphylococci in throat swab cultures in 4 of 10 patients with histologically confirmed pityriasis lichenoides, with improvement of skin lesions in all 4 of these patients with tetracycline therapy.[82] Takahashi and Atsumi reported the resolution of histologically confirmed PLC after tonsillectomy in a patient with chronic tonsillitis.[83] Cultures of the excised tonsillar tissue grew *Staphylococcus aureus*, as well as group A β-hemolytic streptococci. English et al reported a husband and wife with histologically confirmed PLEVA.[84] Group A β-hemolytic streptococci were isolated from a PLEVA lesion of the husband, and a Gram stain of a lesion from the wife revealed Gram-positive cocci. Both patients' PLEVA resolved with antibiotic therapy.

Pityriasis lichenoides has also been linked to vaccination. In 1992 Torinuki reported the occurrence of PLEVA in a 2.5-year-old boy 5 days after an injection of freeze-dried live attenuated measles vaccine.[85] To our knowledge, this is the only reported case of pityriasis lichenoides in association with virus vaccination.

Lymphoproliferative etiology

Some experts believe that pityriasis lichenoides is a primary lymphoproliferative process because of the similarities between PLEVA and lymphomatoid papulosis. The purposes of this particular ideology are twofold: first, to address the pathogenesis of pityriasis lichenoides lesions and, second, to address the prognostic concern for malignant transformation of pityriasis lichenoides. Characteristics of T cells with possible malignant transformation include the loss of certain T-cell antigens (especially CD5 and CD7), expression of CD30, presence of large atypical T cells, and clonal rearrangement of the T-cell receptor (TCR) gene.

The concept of CD8 lymphocytes exerting cytotoxic properties on neoplastic T lymphocytes was demonstrated by Wood et al in 1994,[86] as cited by Magro et al.[11] Magro et al cited this fact to support their observation that a predominance of CD8 lymphocytes in the epidermis of early-stage mycosis fungoides (MF) lesions correlated with a more indolent course. They further suggested that a cellular cytotoxic response directed against the aberrant lymphocyte population might lead to a spontaneous resolution of lesions, consistent with the typical clinical course of pityriasis lichenoides. Wood et al in 1987 suggested that for PLEVA and PLC to be T-cell lymphoproliferative disorders, it may not be necessary to detect morphologically and antigenically atypical large T cells.[50] They believed that even infiltrates with normal T cells might contain clonal T-cell populations and thus cause PLEVA and PLC to fall in the spectrum of T-cell lymphoproliferative disorders. Wood et al also suggested that if PLEVA and PLC are T-cell lymphoproliferative disorders, it might be host immune responses that determine either the regression of the lesions or the progression of the lesions into a true cutaneous lymphoma. These authors were among the first to suggest that an effective host immune response might be represented by a greater predominance of cytotoxic CD8+ cells in PLEVA, citing the fact that a decrease of this subset in lymphomatoid papulosis is evidence for a less effective host immune response in a more malignant condition. Varga et al suggested that activated CD8+ cells liberate cytokines, which are responsible for epidermal damage, and that even CD4+ cells might play a role in the cytotoxic damage and expression of HLA-DR by epidermal keratinocytes.[58] This theory is supported by evidence that a subset of CD4+ cells releases cytotoxic factors analogous to those of CD8+ cytotoxic T cells,[87] including interferon-γ, which can induce HLA-DR expression by epidermal keratinocytes in vitro.[88]

PLEVA. Weiss et al reported 3 persons with histologically confirmed PLEVA whose biopsy results showed clonal rearrangement of the β-TCR gene.[89] In 2 of these persons, 2 separate lesions were subjected to biopsy, and both showed identical rearrangements. All 3 patients, however, also had cellular infiltrates that lacked cytologic atypia and were shown immunohistologically to contain T cells with normal patterns of antigen expression. Panhans et al reported a 7-year-old boy with histologically confirmed PLEVA whose biopsy showed large CD30+ cells in the intradermal infiltrate.[90] PCR analysis of the TCRγ gene showed minor biallelic clonal rearrangement. Although this patient may have had lymphomatoid papulosis, the inflammatory

Table V. Immunofluorescence of lesional skin in pityriasis lichenoides

Study	Study details			Biopsy specimens (%) with immunofluorescence at						
				Dermoepidermal junction			Vessel wall			DEJ and vessel wall
	Skin disorder	No. of patients	No. of biopsies	IgM	C3	IgM and C3	IgM	C3	IgM and C3	IgM and C3
Clayton et al[94]	PLEVA	2	23	26	48	26	35	57	26	13
	PLC	14								
Clayton and Haffenden[95]	PLEVA	2	43	NR	NR	21	NR	NR	26	12
	PLC	25								
Hayashi[96]	PLEVA	2	2	100	100	100	100	100	100	100
Hayashi and Kawada[97]	PLC	9	9	22	22	22	67	78	67	22
	PLEVA	1	1	100	100	100	100	100	100	100
Thivolet et al[98]	PL	NR	21	0	5	0	0	14	0	0
Nieboer and Kalsbeek[99]	PL	NR	15	NR	NR	NR	NR	NR	NR	NR
Faber and van Joost[100]	PLC	3	3	33	67	33	0	33	0	0
	PLEVA	5	9	11	56	11	0	56	0	0
Warshauer et al[23]	FUMHD	1	1	NR	NR	NR	NR	NR	NR	NR

DEJ, Dermoepidermal junction; *FUMHD*, febrile ulceronecrotic Mucha-Habermann disease; *NR*, not reported; *PL*, pityriasis lichenoides; *PLC*, pityriasis lichenoides chronica; *PLEVA*, pityriasis lichenoides et varioliformis acuta.

infiltrate was much more indicative of PLEVA, leading the authors to suggest that PLEVA may represent a CD30+ lymphoproliferative disorder. Dereure et al echoed these findings in 2000, when they reported that 13 of 20 biopsies of PLEVA revealed the presence of a dominant T-cell clone detected by means of PCR and heteroduplex analysis targeted on the TCRγ gene.[91] They suggested that PLEVA might represent a cytotoxic defense against the assault of a T-cell clone, thus preventing the development of a cutaneous lymphoma until the clone acquires enough genetic alterations to overwhelm the body's immune system. Weinberg et al demonstrated that 8 of 14 PLEVA patients had monoclonal TCRγ gene rearrangements. They subsequently suggested that the single entity of pityriasis lichenoides might result from a host immune response to a variety of pathogenic factors, but what determines a specific outcome of PLEVA versus PLC may be a matter of the different stage of evolution of this immune response.[92] The authors also propose that a PLEVA monoclonal T-cell population itself may arise from a subset of T cells in PLC lesions, and the subsequent host immune response to this clone then determines the clinical and histopathologic characteristics of PLEVA.

In addition to PLEVA, clonality has also been detected in cases of febrile ulceronecrotic Mucha-Habermann disease. Though most DNA analyses indicate no monoclonality or T-cell receptor gene rearrangement,[28,44] Miyamoto et al and Cozzio et al both detected a group of lymphocytes that were monoclonal in 1 and 2 patients, respectively.[41,45]

PLC. Clonality has also been detected in cases of PLC. Shieh et al found that 3 of 6 persons with histologically confirmed PLC had monoclonal TCRγ gene rearrangements in their biopsy specimens.[93] Magro et al in 2002 reported T-cell clonality in 33 of 35 pityriasis lichenoides patients.[11] Twenty-one of 32 biopsies had CD7 deletions, and these CD7-negative cells were typically the largest and most atypical of the T cells and, most often, CD4+ cells. The CD8-positive cells were usually small, round, and CD7-positive, and often showed satellitosis around the CD4+/CD7− atypical lymphocytes, indicating a possible cytotoxic immune response against these atypical cells. Weinberg et al, however, detected monoclonal TCRγ gene rearrangements in only 1 of 13 patients with PLC.[92]

Immune-complex-mediated vasculitis theory. The final major theory of the etiology and pathogenesis of pityriasis lichenoides is that it is a primary immune-complex-mediated hypersensitivity vasculitis (Table V). Black and Marks were among the first to investigate this hypothesis, but they were unable to find any evidence of immunoglobulin or complement deposition in their biopsies from 6 patients with pityriasis lichenoides.[56] Clayton et al, however, detected immunofluorescence in biopsy specimens of fresh purpuric lesions obtained from 16 patients with pityriasis lichenoides.[94] Fifteen specimens from 8 patients also showed circulating immune complexes, which were detected 71% of the time when IgM was positive at either the dermoepidermal junction or vessel wall and only 18% of the time when IgM was negative at both the

Table VI. Distinguishing characteristics of lymphomatoid papulosis and pityriasis lichenoides

Area of distinction	Lymphomatoid papulosis	Pityriasis lichenoides
Lesion characteristics	Papules can develop into nodules, tumors, and large plaques[12]	Papules do not develop into nodules, tumors, and plaques
Average age of onset (y)	29[12]	45[12]
Duration	Years[12,102]	PLEVA, weeks to months; PLC, months to years
Histologic findings	Type A: large, atypical nonlymphoid cells with bizarre-shaped nuclei, multinucleated cells that resemble Reed-Sternberg cells, many neutrophils and few lymphocytes, late involvement of epidermis, little to no necrotic keratinocytes, minimal to no vacuolar degeneration of the basal layer[12] Type B: hyperchromatic cerebriform mononuclear cells in infiltrate, minimal vacuolar degeneration of basal layer, and few necrotic keratinocytes[12]	PLEVA: lymphocytic infiltrate, rare presence of large atypical cells, early involvement of epidermis with many necrotic keratinocytes and vacuolar degeneration of basal layer PLC: mild lymphocytic infiltrate, absence of atypical cells, few necrotic changes, minimal vacuolar degeneration of basal layer
CD30 cells	Present[58,75,102]	Absent[58,75,102]
Concomitant disease	Occasional[12*,103†,104‡]	Rare[12]
Potential for malignancy	Occasional[12§,105-107‖]	Rare[12,19,129-139]

*Willemze and Scheffer noted no concomitant disease in any PLEVA patients, whereas 2 lymphomatoid papulosis patients had concomitant parapsoriasis en plaques and 1 such patient had had classic plaque-stage mycosis fungoides.
†The Dutch Cutaneous Lymphoma Group revealed that 23 of 118 patients (19%) with lymphomatoid papulosis had associated lymphomas before, after, or concurrent with the development of the lymphomatoid papulosis.
‡Various types of malignancies seen before, after, or concurrent with lymphomatoid papulosis include mycosis fungoides, Hodgkin disease, CD30+ large T-cell lymphoma, and various non-Hodgkin lymphomas.
§Willemze and Scheffer noted that 3 of 26 lymphomatoid papulosis patients developed a malignant lymphoma.
‖Incidence of malignant lymphoma in lymphomatoid papulosis has been shown to range from 10% to 20%.

dermoepidermal junction and vessel wall. This result suggested to the authors that the complexes are deposited in the skin and thus play a role in the pathogenesis of pityriasis lichenoides. To further support this theory, 16 biopsy specimens from normal skin of healthy control subjects were also investigated: faint immunofluorescence of IgM and C3 was seen in the superficial dermal vessels of only 1 specimen, and circulating immune complexes were found in only 4% of specimens. These investigators also reported the detection of immunofluorescence in 31 of 43 biopsies (72%) of fresh purpuric lesions in a later study.[95] Studies by Hayashi[96] and Hayashi and Kawada[97] also demonstrated immunofluorescence in lesions of pityriasis lichenoides, as did Warshauer et al in a specimen of PLEVA.[23]

Other investigators have not been able to detect significant amounts of immune complexes in pityriasis lichenoides.[98-100] Furthermore, Nieboer and Kalsbeek[99] cited the fact that granular IgM/C3 deposits were found in normal sun-exposed skin of more than 50% of healthy persons in a study performed by Baart de la Faille-Kuyper er al,[101] suggesting that controlled studies are needed to validate this hypothesis.

DIFFERENTIAL DIAGNOSIS

Among the various dermatoses that are clinically confused with PLEVA and PLC, lymphomatoid papulosis is by far the most common. The relationship between pityriasis lichenoides and lymphomatoid papulosis has long been debated. Although a thorough discussion of lymphomatoid papulosis is beyond the scope of this manuscript, Table VI lists the characteristics that are useful in differentiating the 2 disorders, such as lesion characteristics,[12] duration of disease,[12,102] histologic findings,[12] immunopathologic results,[58,75,102] concomitant disease,[12,103,104] and potential for malignancy.[12,104-108]

In addition to lymphomatoid papulosis, pityriasis lichenoides may clinically resemble arthropod bite reactions, varicella, other viral exanthems, Gianotti-Crosti syndrome, erythema multiforme, pityriasis rosea, guttate psoriasis, vasculitis, and secondary syphilis. Characteristics that help to differentiate these disorders from pityriasis lichenoides are listed in Table VII.

DIAGNOSTIC TESTS

The most important diagnostic test for pityriasis lichenoides is histologic assessment of lesional skin.

Table VII. Characteristics of conditions that can clinically resemble pityriasis lichenoides

Disorder	Distinguishing feature
Arthropod bite	Intense pruritus with bites, notable dermal edema and high prevalence of eosinophils in dermal infiltrate, common presence of capillary proliferation[48]
Varicella	Tzanck-positive clear vesicles, constitutional symptoms, common involvement of mucous membranes and face, extensive vesiculation in infiltrate, presence of balloon cells and multinucleate giant cells
Gianotti-Crosti syndrome	Lack of necrotic lesions, predominantly acral distribution, frequent occurrence with lymphadenopathy and acute hepatitis, no significant erythrocyte exocytosis or epidermal necrosis at histologic study
Erythema multiforme	Presence of target lesions, predominantly acral distribution, common involvement of mucous membranes, infiltrate often sparing epidermis, and uncommon erythrocyte extravasation
Pityriasis rosea	Solitary microvesicles less than 50 μm in diameter with minimal adjacent spongiosis[49]

Additional tests that may also be helpful in the differential diagnosis include immunopathologic evaluation, antistreptolysin O titers, throat cultures, EBV IgM-IgG viral capsid antigen and nuclear antigen antibody, monospot or heterophil antibody, toxoplasma Sabin-Feldman dye, enzyme-linked immunoassay, indirect immunofluorescence antibody (IFA), and indirect hemagglutination (IHA) for serodiagnosis of toxoplasmosis, hepatitis B surface antigen, antisurface antibody and anticore IgM, HIV screening, rapid plasma regain, and venereal disease research laboratory test.

TREATMENT

The several different therapeutic modalities that have been used for pityriasis lichenoides range from natural ultraviolet light exposure[13,109,110] to chemotherapeutic agents. Interpretation of results from formal evaluations of therapy is limited by the frequency of spontaneous remissions of pityriasis lichenoides.

Topical agents

Topical corticosteroids are often the first-line therapy for pityriasis lichenoides, though no studies have specifically compared the efficacy of such agents with that of either placebo or other treatments. However, concerns about their side-effect profile have led to the increased utilization of nonsteroidal topical immune-modulating therapies. Topical tacrolimus has been reported to work in some patients. Simon et al reported complete clearance in 2 patients with PLC who underwent treatment with 0.03% ointment twice daily for 14 and 18 weeks, respectively.[111] Mallipeddi and Evans also reported the successful use of twice-daily tacrolimus 0.1% ointment in a patient with refractory PLC.[112]

Oral agents

Oral agents most often used for treatment of pityriasis lichenoides include antibiotics and methotrexate. The most common antibiotics include tetracycline and erythromycin. Piamphongsant reported success with tetracycline in 12 of 13 patients with PLC.[82] Five patients remained completely free of lesions in the 6-month period after taking a 2- to 4-week course of 2 g of tetracycline per day, whereas 7 patients needed a maintenance dose of 1g/d. Shelley and Griffith similarly noticed that a patient with PLEVA remained free of all lesions after 1 year of treatment with tetracycline.[113] In a study performed by Truhan et al, 15 children with pityriasis lichenoides (4 with PLC and 11 with PLEVA) underwent treatment with 200 mg of erythromycin 3 or 4 times daily.[20] Two of the 4 PLC patients and 9 of the 11 PLEVA patients had remission (most within 2 months), 2 others showed partial improvement, and 2 had no improvement. Romani et al also noted moderate improvements with erythromycin in 8 patients with pityriasis lichenoides.[18]

Methotrexate is an effective treatment in some patients with pityriasis lichenoides. Cornelison et al described the successful use of methotrexate, in dosages of 7.5 to 20 mg/wk, for 6 patients with pityriasis lichenoides.[114] Lynch and Saied reported the clearance of lesions in a patient with PLEVA who underwent treatment with intramuscular methotrexate.[115] No new lesions appeared after 3 weeks of treatment, but attempts to wean or discontinue methotrexate led to rapid recurrence. Two patients with PLC also did well on oral methotrexate. Also, methotrexate has often been used successfully in the treatment of febrile ulceronecrotic Mucha-Habermann disease.[18,23,28,31,34]

Table VIII. Ultraviolet therapy for pityriasis lichenoides

Study	Disease subtype and no. of patients	Type of ultraviolet therapy	No. of treatments	Total energy given (j/cm^2)	Clearance at follow-up
Gardlo et al[117]	PLEVA (1)	PUVA	NR	10	"Marked improvement"
Powell and Muller[118]	PLEVA (1)	PUVA	57	370.5	CC (18 mo.)
	PLEVA (1)	PUVA	26	189	80% (mild recurrence after discontinuation)
	PLC (1)	PUVA	35	284.5	95%
Boelen et al[119]	PLEVA (1)	PUVA	16	34.0	CC (recurrence 1 mo. after discontinuation)
			21	44.1	CC (recurrence 25 mo. after discontinuation)
	PLEVA (1)	PUVA	30	56.0	CC (20 mo.)
	PLEVA (1)	PUVA	45	344.0	None
			42	264.0	CC (36 mo.)
	PLC (1)	PUVA	41	316.5	CC (23 mo.)
Hofmann et al[120]	PLC (2)	PUVA	15–21	37–39	CC (mild recurrence 1 mo. after discontinuation)
Brenner et al[121]	PLEVA (5)	PUVA	NR	66.8 ± 46.9 (M ± 1 SD)	CC (1–8 mo.)
Thivolet et al[122]	PLEVA (1)	PUVA	41	244.5	CC
	PLEVA (1)	PUVA	17	69	>80% (recurrence after discontinuation)
Panse et al[123]	PLEVA (2), PLC (1)	PUVA	NR	NR	Acitretin and PUVA: "dramatic" clearance within a few weeks
Panizzon et al[124]	PLC (1)	PUVA	NR	NR	Etretinate and PUVA: "good response"
Hermanns-Le et al[125]	PLC (1)	PUVA	NR	NR	Acitretin and PUVA: CC (recurrence after discontinuation)
Pasic et al[126]	PLEVA (3), PLC (6)	Narrowband UVB and low-potency topical steroid	14–24 (M, 19; 3 times per week)	3.023–11.8 (M, 6.50)	No improvement, 3 PLEVA; PC, 3 PLC; CC, 3 PLC
Levine[127]	PLC (11)	UVB and emollient	10–59 (M, 29; 5 times per week in 9 patients; 3 times per week in 2)	0.806–37.077 (M, 9.24)	CC in all patients
Pinton et al[128]	PLEVA (3); PLC (5)	Ultraviolet A1 (340–400 nm) and emollient	10–30 (M, 18.8; 5 times per week)	600–1,800 (M, 1,125)	CC, 3 PLEVA, 3 PLC; PC, 2 PLC (recurrence in 4 PLC patients after 6.8 mo. ± 3.6)

CC, Complete clearance; *F*, frequency; *M*, mean; *NR*, not reported; *PC*, partial clearance; *PLC*, pityriasis lichenoides chronica; *PLEVA*, pityriasis lichenoides et varioliformis acuta; *PUVA*, psoralen ultraviolet A–range; *SD*, standard deviation; *UVB*, ultraviolet B.

Other oral medications successfully used in the treatment of pityriasis lichenoides include ciprofloxacin in 1 patient with PLEVA,[84] cyclosporine in HIV-induced PLC (with a starting dose of 200 mg/d for 3 months and a maintenance dose at 100 to 200 mg/d),[78] and pentoxifylline (400 mg 2 to 3 times a day) for a patient with PLEVA.[116] There have been a few reports of successful treatment of febrile ulceronecrotic Mucha-Habermann disease with the use of oral 4,4'-diaminodiphenylsulfone (dapsone) in doses of 100 mg once to twice daily.[24,29,32]

Ultraviolet light therapy

Many reports indicate the benefits of ultraviolet therapy for pityriasis lichenoides (see Table VIII). Psoralen plus ultraviolet A (PUVA) has been used

with success both in patients with PLEVA and in those with PLC. The total amount of energy used has varied from 10 j/cm^2 to 370.5 j/cm^2.[117,118] Recurrences after cessation of therapy or after long periods of remission are not uncommon,[119,120] although complete clearing has also been documented.[108,121,122] Several reports have also noted success in the use of PUVA in conjunction with oral retinoids.[123-125] Ultraviolet B therapy and ultraviolet A without psoralen have also been used with varying degrees of success.[126-128]

Recommended therapies. From the evidence listed above, the ease of administration, and the authors' experience, first-line therapies could include oral antibiotics and topical corticosteroids or topical immunomodulators. Recommended second-line therapies include ultraviolet B or PUVA light treatments followed by third-line therapies with methotrexate, acitretin, dapsone, or cyclosporine, or a combination of these, for more resistant and severe disease.

COURSE AND PROGNOSIS

Although pityriasis lichenoides and its variants are generally regarded as benign disorders, there have been a few reports of the disease coexisting with extensive poikiloderma, with some of these cases subsequently evolving into MF.[129-132] When Rivers et al reviewed 13 patients with pityriasis lichenoides–like lesions coexistent with poikiloderma, they found that 6 of these patients had progression to MF.[130] Fortson et al reported 2 pediatric cases of PLEVA, which further evolved after several years into poikiloderma with evidence of blast transformation and patch-stage cutaneous T-cell lymphoma, respectively.[133] Tomasini et al reported a case of PLC that evolved into MF in a 17-year-old girl,[134] and Ko et al described pityriasis-like eruptions that histopathologically were determined to be MF in both a 10-year-old boy and a 5-year-old boy.[135] Thomson et al reported cutaneous T-cell lymphoma that developed in a 2-year-old boy who had had PLC since he was 8 months old,[136] and Hermanns-Le et al reported a case of medullary CD30+ T-cell lymphoma that developed 50 years after the initial onset of pityriasis lichenoides.[125] Niemczyk et al reported the case of a child with a 10-year history of PLC who subsequently developed parakeratosis variegata with clonal TCRγ gene rearrangement.[137]

PLC has also been described as a paraneoplastic condition. Dermatoses may be characterized as paraneoplastic if they occur after the development of the primary malignant tumor and if they follow a parallel course to the primary malignant tumor.[138] Lazarov et al reported a case of PLC developing concurrently with an oncocytoma of the left kidney, which subsequently resolved after a nephrectomy to remove the primary tumor.[139] Panizzon et al reported 3 paraneoplastic presentations of PLC.[124] The first was PLC in a 21-year-old woman with a low-grade malignant lymphoma of the lung that improved after chemotherapy. The second was development of PLC in a 41-year-old man with Hodgkin disease, stage IVa. The PLC eruption, which initially had responded well to PUVA and oral retinoids, eventually became recalcitrant and progressed into a pleomorphic non-Hodgkin lymphoma of the skin. The third case was that of a 44-year-old man who had had PLC for several years that subsequently transformed into a large-cell anaplastic non-Hodgkin lymphoma or atypical Hodgkin disease of the skin.

Despite these rare reports of malignant transformation, it is generally accepted that pityriasis lichenoides follows a benign course. In a 13-year follow-up of 89 children with pityriasis lichenoides, Gelmetti et al documented no evidence of malignant transformation.[19] However, because of rare reports of malignant transformation, regular follow-up of pityriasis lichenoides patients is recommended.

SUMMARY

The understanding of pityriasis lichenoides has evolved since its original description in 1894. Though there have been tremendous strides in identifying this disorder, both clinically and histopathologically, further research is needed in the areas of pathophysiology, possible malignant transformation, and potential effective treatments for this unique group of inflammatory skin disorders.

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