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Clinical and Laboratory Investigations

Clinicopathological and genotypic aspects of anticonvulsant-induced pseudolymphoma syndrome

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Summary

Background Pseudolymphoma syndrome (PLS) is relatively rare but can lead to death if there are extensive skin lesions, severe hepatitis, agranulocytosis and neutropenia. PLS may also give rise to harmful effects if misdiagnosed as malignant lymphoma and patients with PLS are treated unnecessarily with chemotherapy, because it may mimic histologically other lymphomas, including mycosis fungoides (MF).

Objectives To examine the clinicopathological and genotypic features of anticonvulsant-induced PLS.

Patients and methods We retrospectively reviewed clinical, laboratory and histological findings for eight cases of anticonvulsant-induced PLS, and performed T-cell receptor gene rearrangement using polymerase chain reaction with paraffin-embedded specimens from each case.

Results The causative agents were carbamazepine (four cases), phenytoin (two cases), phenobarbital (one case) and valproic acid (one case). A cross-reaction between phenobarbital and phenytoin was observed in one case. The duration from the start of anticonvulsant therapy to skin eruption was 3–24 weeks (mean 7 weeks). The skin lesions were generalized maculopapular eruptions in all cases, including one case accompanied by vesiculopustular lesions. The frequencies of the associated features were as follows: facial oedema (88%), fever (75%), lymphadenopathy (63%), and hepatomegaly (25%). Laboratory findings revealed leukocytosis, atypical lymphocytes, eosinophilia, monocytosis, neutrophilia, lymphocytosis and abnormal liver function. Histopathologically, there was similarity between PLS and MF in that epidermotrophism of atypical lymphocytes (100%) and Pautrier's microabscess-like structures (38%) were observed. However, PLS has some differences from MF that include moderate to marked spongiosis (75%), necrotic keratinocytes (63%), and infiltration of eosinophils (25%) in the epidermis and, in the dermis, papillary dermal oedema (100%), extravasated erythrocytes (100%), lymphocytes within the dermis larger than those within the epidermis (63%), and infiltration of various inflammatory cells including neutrophils (50%). Genotypic analysis demonstrated a rearrangement of the T-cell receptor-γ gene in one of eight cases studied. There were no deaths and all cases were improved at 2–9 weeks (mean 6 weeks), after the cessation of causative agents, systemic and topical corticosteroid therapy, and symptomatic therapy. There were no significant differences in clinical, laboratory and histological findings between the causative agents.

Conclusions PLS may show histopathological findings similar to MF and take a prolonged course even after the cessation of causative agents. Thus, a clear understanding and diagnosis of this disease is considered to have an important effect on treatment and prognosis.

Key words: anticonvulsant, clinicopathological findings, genotypic features, pseudolymphoma syndrome

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Pseudolymphoma syndrome (PLS) was first reported by Chaiken *et al.* in 1950.[1] Its pathogenesis has not been clearly understood, but it has been described as a hypersensitivity reaction due to anticonvulsants.[2,3] Clinically it is characterized by findings such as erythematous patch, maculopapular eruption or nodules developing within 2–3 weeks after administering causative agents, and systemic fever of 38–39 °C, lymphadenopathy, arthralgia, hepatosplenomegaly, abnormal liver profile and eosinophilia. Histopathologically it is characterized by the infiltration of atypical lymphocytes into the epidermis and dermis that requires differentiation from other lymphomas, especially mycosis fungoides (MF).[4,5] Thus, along with the histopathological findings, clonality testing of infiltrative cells using polymerase chain reaction (PCR) has been widely used in discrimination from lymphomas.[6,7]

PLS not only shows different clinical features from a usual drug eruption but also may lead to death if accompanied by extensive skin lesions, severe hepatitis, agranulocytosis, leukopenia, or if it is not clearly recognized and the causative agents continue to be administered.[8] It is important clearly to understand and diagnose PLS because serious harm may be caused to the patient if it is misdiagnosed as malignant lymphoma histopathologically. We have carried out a retrospective review of clinicopathological features and T-cell receptor (TCR)-γ gene rearrangement studies for eight cases of PLS.

Patients and methods

Patients

The present study was done with the patients who visited our clinic between February 1993 and March 2001 and were diagnosed as having PLS on the basis of clinical, laboratory and histological findings. Eight patients with PLS were registered, five males and three females, age range 49–72 years (mean 60 years).

Clinical, laboratory and histopathological studies

The period of onset after administering causative agents, pattern and distribution of skin rashes, systemic symptoms (e.g. fever, lymphadenopathy, pharyngitis, and hepatosplenomegaly, etc.), laboratory findings (e.g. peripheral blood smear and chemistry, liver function test, renal function test, and urinalysis, etc.), response to therapy and improvement period after cessation of causative agents were examined. Eight cases of PLS were evaluated histologically, using paraffin blocks and haematoxylin and eosin-stained slides, for similarities to or differences from MF.

Genotypic analysis

Paraffin-embedded tissue from eight patients with PLS was tested for the presence of monoclonal TCR-γ gene rearrangements. Paraffin-embedded tissue from 14 patients with MF served as control. DNA from the formalin-fixed paraffin-embedded tissues was obtained from one to three 10–20-μm tissue sections, depending on the size of biopsies. Sections were dewaxed with xylene at 60 °C for 10 min twice, treated with absolute and 70% ethanol, dried and digested overnight at 56 °C in distilled water containing proteinase K (200 μg mL^{-1}) and 5% Chelex® 100 Resin (BioRad, Hercules, CA, U.S.A.). The samples were heated for 10 min at 95 °C to destroy proteinase K activity, and 2–3 μL were added to the PCR mixture containing 50 mmol L^{-1} KCl, 10 mmol L^{-1} Tris–HCl pH 8·3, 10 pmol L^{-1} of each primer, 200 mmol L^{-1} of each dNTP, 1 U Taq polymerase (Promega, Madison, WI, U.S.A.), and 1·5 mmol L^{-1} $MgCl_2$ in a final volume of 25 μL. A nested protocol involving two rounds of PCR was used for amplification. Each amplification product was loaded onto 8% polyacrylamide gel, stained in ethidium bromide solution after electrophoresis at 150 V for 2 h, and photographed under ultraviolet illumination.

Results

Clinical and laboratory findings

Clinical and laboratory results are summarized in Tables 1–3. The causative agents were carbamazepine in four cases, phenytoin in two cases, and phenobarbital and valproic acid in one case each. None of the patients was on any other anticonvulsants before taking the above drugs. Cross-reaction between aromatic anticonvulsants was observed in one case in which the substitution of phenobarbital by phenytoin was followed by a recurrence of PLS. The time from administration of anticonvulsant drug to onset of skin eruption was 3 weeks in two cases, 4 weeks in three cases, and more than 5 weeks in three cases. Of these, onset was observed at 6 months after carbamazepine administration in one case.

On physical examination, morbilliform maculopapular eruptions accompanied by pruritus were observed

Table 1. Clinical features of eight patients with pseudolymphoma syndrome

Case	Age (year)/ sex	Drug	Skin lesion	Onset time[a] (weeks)	Fever	Facial oedema	Lymphadeno-pathy	Hepato/ splenomegaly	Resolution time[b] (weeks)
1	49/M	CBZ	MP	3	+	+	+	–/–	3
2	58/F	PT	MP	7	+	+	–	–/–	6
3	59/M	CBZ	MP	24	+	+	+	+/+	6
4	65/M	CBZ	MP	5	–	+	+	–/–	6
5	61/M	CBZ	MP, VP	4	+	+	+	–/–	9
6	72/M	PT	MP	4	+	+	–	+/–	4
7	66/F	PB(r)PT	MP	4	+	+	+	–/–	8
8	50/F	VPA	MP	3	–	–	–	–/–	2

[a]Time between start of drug therapy and the eruption. [b]Time between withdrawal of causative drug and the clinical remission. CBZ, carbamazepine; MP, maculopapular eruption; PB, phenobarbital; PT, phenytoin; VP, vesiculopustule; VPA, valproic acid.

Table 2. Laboratory findings of eight patients with pseudolymphoma syndrome

Case	WBC (cells mm^{-3})	Seg. (%)	Lymph. (%)	Mono. (%)	Eos. (%)	Atypical lymphocyte	AST/ALT[a] (U L^{-1})	ALP[a] (U L^{-1})	γ-GTP[a] (U L^{-1})
1	10 700	44	48	6	2	–	3·5/4·5	1	1
2	28 000	66	22	3	9	–	3·5/2	1	1
3	15 210	40	47	3	3	+ (5%)	9/23	2·5	9·5
4	10 000	63	27	6·2	3·8	–	1/5	1	6
5	9700	46	4	8	31	+ (5·6%)	1/1	1	1
6	20 160	35	33	10	0·2	+ (10·9%)	1/3	1·5	4·5
7	11 480	28·5	52	13	6·5	–	1/1	1	1
8	28 000	30·8	34	16	13	+ (5·2%)	1/1	1	1

[a]Expressed as number of times the normal value, e.g. 3·5 indicates 3·5 times the normal value. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Eos., eosinophil; γ-GTP, γ-glutamyl transferase; Lymph., lymphocyte; Mono., monocyte; Seg., segmented neutrophil; WBC, white blood count.

Table 3. Clinical and laboratory summary of eight patients with pseudolymphoma syndrome

Feature	($n = 8$)
Mean age (years)/sex (M : F)	(60 ± 7·86)/(5 : 3)
Mean onset time, weeks	7
Mean resolution time, week	6
Mortality, *n* (%)	0 (0%)
Clinical manifestation, *n* (%)	
Maculopapular eruption	8 (100%)
Fever	6 (75%)
Facial oedema	7 (88%)
Lymphadenopathy	5 (63%)
Hepatomegaly	2 (25%)
Laboratory findings, *n* (%)	
Leukocytosis	8 (100%)
Lymphocytosis	1 (13%)
Monocytosis	3 (38%)
Eosinophilia	3 (38%)
Neutropenia	3 (38%)
Atypical lymphocyte	4 (50%)
Abnormal liver function	5 (63%)

Figure 1. Confluent maculopapular eruption on the trunk and upper extremities.

in all cases (Fig. 1). In one case, vesiculopustular lesions with maculopapular eruption were observed on the whole body except for the palm and sole. Systemic fever (38–40·1 °C) was present in six cases. Facial oedema was noted in seven cases, enlarged lymph nodes in five cases and hepatosplenomegaly in one case. Haematological abnormalities were common, including eight cases of leukocytosis (≥ 9000 mm^{-3}), three cases of eosinophilia (≥ 8%), three cases of

monocytosis (≥ 10%), one case of lymphocytosis (≥ 50%), three cases of neutropenia (≤ 35%) and four cases of atypical lymphocyte (≥ 5%). Liver function tests showed increased alanine aminotransferase and/or aspartate aminotransferase in five cases, and increased alkaline phosphatase or γ-glutamyl transferase together with transaminase in three cases.

Histopathological findings

Histological features are summarized in Table 4. All biopsies were characterized by lymphocytes displaying exocytosis, resembling MF (Fig. 2). Similar involvement of follicular epithelium and Pautrier's microabscess-like structures were present in three biopsies. Eosinophils formed a component of exocytic cells in two biopsies and neutrophilic microabscess was revealed in three biopsies (Fig. 3). Variable spongiosis and scattered necrotic keratinocytes were present in six and five biopsies, respectively. Papillary dermal oedema and extravasated erythrocytes were seen in all biopsies; however, the blood vessels were not involved. A moderate dense band-like infiltrate that contained atypical lymphocytes with hyperchromatic cerebriform nuclei characterized most biopsies (Fig. 4). Some lymphocytes in the dermis were larger than those in the epidermis in five biopsies. The infiltrate also contained blast-like cells and atypical mitoses. Eosinophils and neutrophils were additionally present in

Table 4. Histopathological findings of eight patients with pseudolymphoma syndrome

Histopathological findings	*n* (%)
Epidermis	
Epidermotrophism	8 (100)
Epidermotrophism in the infundibulum	3 (38)
Spongiosis	6 (75)
Pautrier's microabscess-like structure	3 (38)
Necrotic keratinocyte	5 (63)
Neutrophilic microabscess	3 (38)
Eosinophilic infiltration	2 (25)
Dermis	
Pattern	
Nodular	2 (25)
Band-like	6 (75)
Papillary dermal oedema	8 (100)
Extravasation of erythrocytes	8 (100)
Eosinophilic infiltration	3 (38)
Neutrophilic infiltration	4 (50)
Atypical cells with hyperchromatic cerebriform nuclei	8 (100)
Blast-like cells	7 (88)
Mitoses	4 (50)
Some lymphocytes in the dermis larger than those in the epidermis	5 (63)

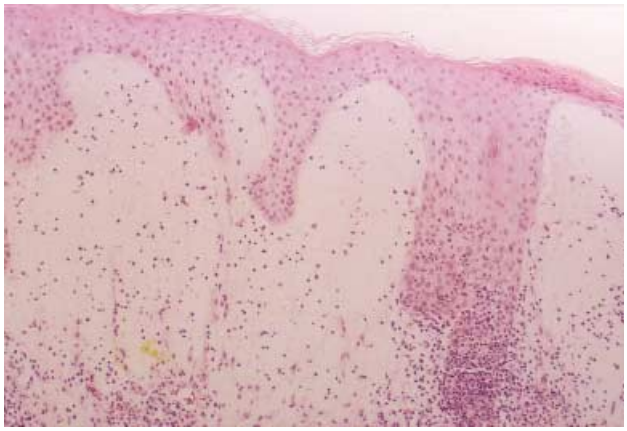

Figure 2. A lymphocytic infiltrate with focal migration into the epidermis and severe oedema in the papillary dermis (haematoxylin and eosin, original magnification ×100).

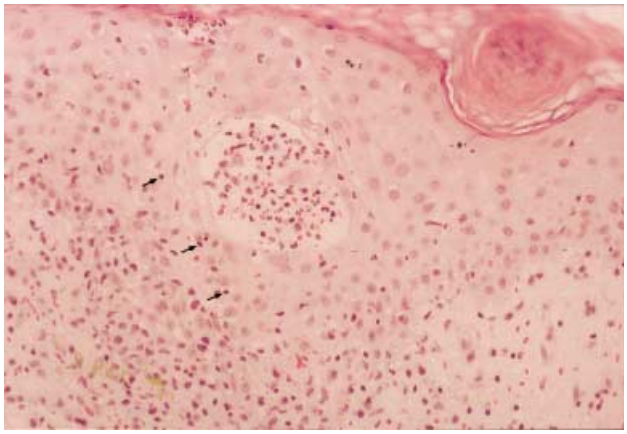

Figure 3. Atypical cells (arrows) and a neutrophilic microabscess are noted (haematoxylin and eosin, original magnification ×200).

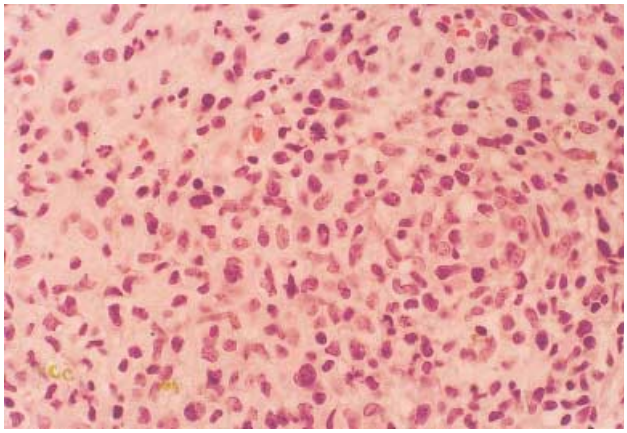

Figure 4. A dermal infiltrate containing hyperchromatic pleomorphic lymphocytes, neutrophils and some blast-like cells (haematoxylin and eosin, original magnification ×400).

Histological findings	Pseudolymphoma syndrome	Mycosis fungoides
Epidermis		
Spongiosis	Moderate to severe	Absent to minimal
Necrotic keratinocytes	Common	Rare
Dermis		
Papillary dermal oedema	Very common	Rare
Extravasation of erythrocytes	Very common	Rare
Mixed cell infiltration	Common	Uncommon
Mitosis	Many	A few
Size of lymphocyte	Dermal ≥ epidermal	Dermal ≤ epidermal

Table 5. Differential histological features of pseudolymphoma syndrome and mycosis fungoides

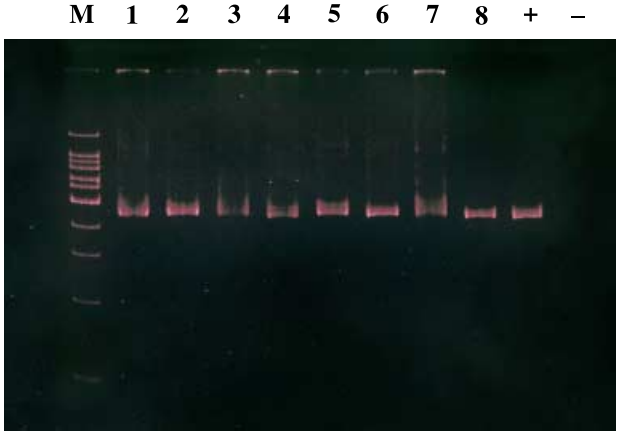

Figure 5. Polymerase chain reaction T-cell receptor-γ/polyacrylamide gel electrophoresis. Photograph demonstrates distinct clonal band in one (lane 8) of the eight cases of pseudolymphoma syndrome (lanes 1–8). Lane M, marker DNA; lane +, positive control (Jurkat T-cell line); lane –, negative control (no DNA).

three and four biopsies, respectively. Although the histological features might be highly suggestive of MF, there were some differences (Table 5).

Molecular biological findings

TCR gene rearrangement was performed in the eight cases of PLS, and resulted in one case of monoclonality (Fig. 5). In contrast, a monoclonal pattern was detected in 13 of 14 of the MF control group.

Treatment and course

Causative agents were immediately discontinued and oral prednisolone 0·5–1 mg kg^{-1} day^{-1} was administered, allowing for other anticonvulsants, if necessary. As a supplementary therapy, the combination of systemic antihistamines and topical steroids was prescribed. After the original lesions had improved and no new lesions had developed, the oral prednisolone dosage was reduced. Clinical symptoms were improved in 2–9 weeks after causative agents were discontinued. In one case that had occurred after phenobarbital administration, partial improvement after cessation of phenobarbital and steroid therapy was observed, but complete resolution was observed only after cessation of both drugs because the substitution of phenobarbital by phenytoin was followed by a recurrence of PLS (Table 1).

Discussion

PLS has been called phenytoin syndrome or drug eruption due to phenytoin, but because similar hypersensitivity reactions due to anticonvulsants such as carbamazepine, phenobarbital, mephytoin and a wide variety of drugs such as para-amino salicylate, allopurinol, etc., have been described in recent years, those induced by anticonvulsants may be classified into anticonvulsant hypersensitivity syndrome.[9] In addition, Bocquet *et al.*[10] differentiated hypersensitivity syndrome from drug-induced pseudolymphoma (PL) based on clinical presentation. They have called the drug hypersensitivity reaction DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and used the term drug-induced PL solely for patients with slow-onset plaques or tumours. However, because these two entities may show not only similar histological findings but also overlapping clinical features, as in our case 8, the nosological characteristics of these drug eruptions remain to be resolved.

The pathogenesis of PLS is not known, and various theories have been proposed.[11,12] Shear and Spielberg[13] have suggested that cytotoxicity and immune reaction might be triggered because of accumulated arene oxide combined with cellular macromolecules if a patient deficient in epoxide hydrolase were administered aromatic anticonvulsants, and that family members may have similar abnormalities. However, as in our case 8, cases caused by valproate, which is structurally unrelated to aromatic anticonvulsants,

were also reported,[14] where hypersensitivity syndrome was observed 6 weeks after valproate therapy. This result indicates that other mechanisms may be involved in the pathogenesis of PLS.

Clinically, PLS is characterized by the three major symptoms of fever, lymphadenopathy and skin rash, accompanied by facial oedema, hepatosplenomegaly, vomiting, headache, arthralgia, pharyngitis and conjunctivitis. The chief complaint in the eight cases studied in our series was skin rashes. The associated features were six cases of fever, five cases of lymphadenopathy, seven cases of facial oedema and two cases of hepatomegaly, which is similar to what other authors have described in PLS.[15]

The syndrome usually occurs within 3 months after starting the causative drug, although it can develop from 1 week to 2 years after exposure to the drug. It is frequently heralded by the development of systemic fever of 38–39 °C and skin rash.[2,16,17] Skin rash is one of the most common clinical symptoms and may include a morbilliform maculopapular eruption with pruritus in extremities including the palm and sole, face and trunk, and less commonly, a perifollicular papule or generalized pustular lesion, as in our case 5. Kleier *et al.*[9] reported two patients in whom pustular lesions initially involved the face or scalp, which were different from pustules following topical and systemic steroids, oral contraceptives, halogens, isoniazid or lithium, which appear mainly on the trunk, shoulder and upper arms, with less involvement of the face or scalp. As well, a wide variety of dermatological symptoms such as erythema multiforme[18] and toxic epidermal necrolysis[19] may be observed.

In most PLS patients, hepatic injury was reported, but this hepatic injury is not always observed by laboratory investigation, and symptoms related to hepatic dysfunction may rarely be seen at the time of diagnosis. The majority of patients have mild hepatic injury and recover within a few weeks after cessation of causative agents, but when hepatitis is severe the prognosis is poor, and in one report mortality was 10–50%.[20] Furthermore, haematological abnormalities are common in PLS, including leukocytosis, eosinophilia, and atypical lymphocytes, at times with lymphocytosis, monocytosis, aplastic anaemia, hyper- and hypo-gammaglobulinaemia, coagulation disorder and nephritis.[21,22] The outcome of the PLS depends on the severity and extent of the hepatic injury as well as the presence of other complications such as coagulation abnormalities, nephritis or sepsis.

Because there may be various clinical findings due to one drug and various histological findings according to the clinical type of the lesion biopsied, it is difficult to link histological findings with specific causative agents as the findings observed may be very similar to those seen in cutaneous T-cell lymphoma, especially MF.[4,5] Although MF has been reported to be aggravated by drugs,[23] any patient who develops an atypical lymphoid infiltrate should have a drug-based aetiology excluded before the diagnosis of cutaneous lymphoma is made. The histological features are polymorphic even if the MF pattern is frequently described, with epidermotrophism, Pautrier's microabscess-like structure, and a dermal band-like infiltrate of atypical T-lymphocytes. Crowson and Magro[24] reported that the discrete epidermotrophism and the epidermal change such as necrotic keratinocytes and spongiosis were useful in differentiation from MF. Ackerman *et al.*[25] described atypical cells forming Pautrier's microabscess-like structures that were scattered and with more spongiosis. Additionally, in our study there was similarity between the PLS and the MF in epidermotrophism of atypical lymphocytes, but PLS was different from MF in moderate or marked spongiosis, necrotic keratinocytes, and eosinophils in the epidermis and, in the dermis, papillary dermal oedema, extravasated erythrocytes, and infiltration of various inflammatory cells.

When it is difficult to differentiate histologically PLS from lymphoma, the TCR gene rearrangement has been known to be useful in discriminating between them.[6,7] Clonality was detected in only one of eight of our cases, that induced by valproate, giving a higher rate of clonality than detected in previous studies (0–6%).[7,26] This case was histologically similar to but clinically different from the others in that there were no systemic symptoms and a rapid resolution after drug withdrawal. Our literature search revealed four cases of PLS or PL due to valproate.[8] Although T-cell clonal rearrangement has been investigated in only one of these four cases, that case and our valproate-induced case showed clonal rearrangements. It should be noted that the prevalence of monoclonality in PLS associated with valproate is significantly higher in comparison with the number of case reports. It is possible that the emergence of a dominant clone is facilitated by unspecified effects or the mechanism of valproate on lymphocytes, as stated above. Recently, Brady *et al.*[27] reported 14 lymphomatoid hypersensitivity reactions in which TCR gene rearrangements showed similar clonality (14%) to our results, despite the fact that cutaneous T-cell lymphoma controls showed clonality in eight (89%) of nine cases.

TCR gene rearrangement is considered to be a good supplementary method in differentiating PLS from lymphoma, but it is necessary to evaluate TCR gene rearrangement data with appropriate clinicopathological correlation, as PLS can also show clonality.

It is very important to cease causative agents immediately in PLS treatment. Although systemic steroids are used prevalently for the acute phase of disease, it is unclear whether steroids can reduce significantly the disease process.[28] Furthermore, symptomatic therapy and local therapy are required for fever, pruritus, and skin lesions, but the use of antipyretics should be considered carefully owing to the potential risk of increased hepatotoxicity, and patients require regular liver function test and safe care. Additionally, aromatic anticonvulsants are known to cause cross-reactions with each other because they produce the same intermediate metabolites, arene oxides, but not with valproate, a nonaromatic anticonvulsant. However, Cogrel *et al.*[8] reported a case in which cross-reactivity between valproate and carbamazepine occurred. Accordingly, although there is no evidence that lamotrigine, a drug of the phenyltriazine class chemically unrelated to existing antiepileptic drugs, cross-reacts with other anticonvulsants, we must be careful in selecting alternative drugs when anticonvulsants are necessary.

Generally, most patients with PLS show improvement within several weeks after causative agents are discontinued. However, a thorough understanding of PLS is important because the combination of extensive skin lesions, hepatic failure and leukopenia in patients with PLS can lead to harmful effects and death if they are misdiagnosed as having lymphoma and subsequently receive unnecessary chemotherapeutic drugs.

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