Title
Pityriasis lichenoides-like drug reaction: A clinical histopathologic study of 10 cases

Journal
Dermatology Online Journal, 23(11)

Authors
Magro, Cynthia
Guo, Ruifeng
Nguyen, Giang Huong
et al.

Publication Date
2017

DOI
10.5070/D32311037249

Pityriasis lichenoides-like drug reaction: A clinical histopathologic study of 10 cases

Cynthia Magro[1] MD, Ruifeng Guo[2] MD PhD, Giang Huong Nguyen[3] MD PhD, Hamilton Tsang[4] MD, Shabnam Momtahen[5] MD

Affiliations: [1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York, [2]University of Florida Health Pathology Laboratories, Gainesville, Florida, [3]Department of Dermatology, University of Colorado, Aurora, Colorado, [4]Department of Laboratory Medicine, University of Washington, Seattle, Washington, [5]Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Corresponding Author: Cynthia M. Magro M.D., Professor of Pathology and Laboratory Medicine, Professor of Dermatopathology in Dermatology, Director of Dermatopathology, Weill Cornell Medicine, Department of Pathology & Laboratory Medicine, 1300 York Avenue, F-309, New York, NY 10065, Tel: 212-746-6434, Fax: 212-746-8570, Email: cym2003@med.cornell.edu

Abstract

Background: Lymphomatoid drug reactions can mimic endogenous T and B cell lymphoproliferative diseases. Objectives: We present a novel form of cutaneous drug reaction with features of pityriasis lichenoides (PL), a recognized form of T cell dyscrasia. Methods: Ten cases were studied where a cutaneous eruption exhibiting semblance to PL within a few weeks to months after starting a particular drug. Results: The patient cohort comprised 7 females and 3 males with the mean age of 60 years. Widely distributed erythematous cutaneous lesions were present in 6 cases whereas a more localized distribution was seen in three cases. The most frequently implicated drugs associated with the eruption were antidepressants and statins. Histologic examination showed a morphologic picture identical to PL including marked epitheliotropism of mildly atypical lymphocytes, psoriasiform epidermal hyperplasia, dyskeratosis, hemorrhage, and a thick parakeratotic scale. There was a significant reduction in the expression of CD7 and CD62L amid the T cells. Regression of the eruption occurred in all cases excluding one. Conclusion: The findings conform the categorization of this process as a form of T-cell dyscrasia albeit one that is reversible, dependent on the drug withdrawal. The limitation of our study includes the retrospective design of the study.

Keywords: cutaneous drug eruption, T cell dyscrasia, pityriasis lichenoides-like drug reaction

Introduction

Cutaneous drug eruptions define a common adverse effect of drug therapy [1-5]. Although most drug eruptions are mild, life-threatening reactions are common. These include Stevens-Johnson syndrome, toxic epidermal necrolysis, erythroderma, and angioedema [6-9]. Most drug eruptions are immunologically mediated, although non-immunological drug eruptions are known to occur [10]. Clinical and histopathological features of drug eruptions are extremely variable and they can mimic most types of dermatoses including eczema, lupus erythematosus, lichen planus, and psoriasis. The most important clues for diagnosis of drug eruption are the onset of skin lesions within a few weeks of the causative drug use and alleviation of the rash with drug modulation [1-4, 9].

There are certain drugs that dysregulate immune function and lead to the emergence of cutaneous infiltrates which mimic lymphomas/lymphoproliferative disease (i.e. low grade B cell lymphoma, mycosis fungoides, and lymphomatoid papulosis) and/or pre-lymphomatous T-cell dyscrasias (pigmented purpuric dermatosis). Unlike the classic drug hypersensitivity reaction, there is characteristically no temporal association between the onset of the lymphomatoid response and the initiation of the drug therapy [11-15]. We present a novel form of cutaneous drug reaction with features of pityriasis lichenoides (PL) that has not been systematically studied. Since de novo PL represents a low-grade T-cell dyscrasia with an undefined but presumed small risk of evolution into mycosis fungoides [17-19], differentiating between the PL-like

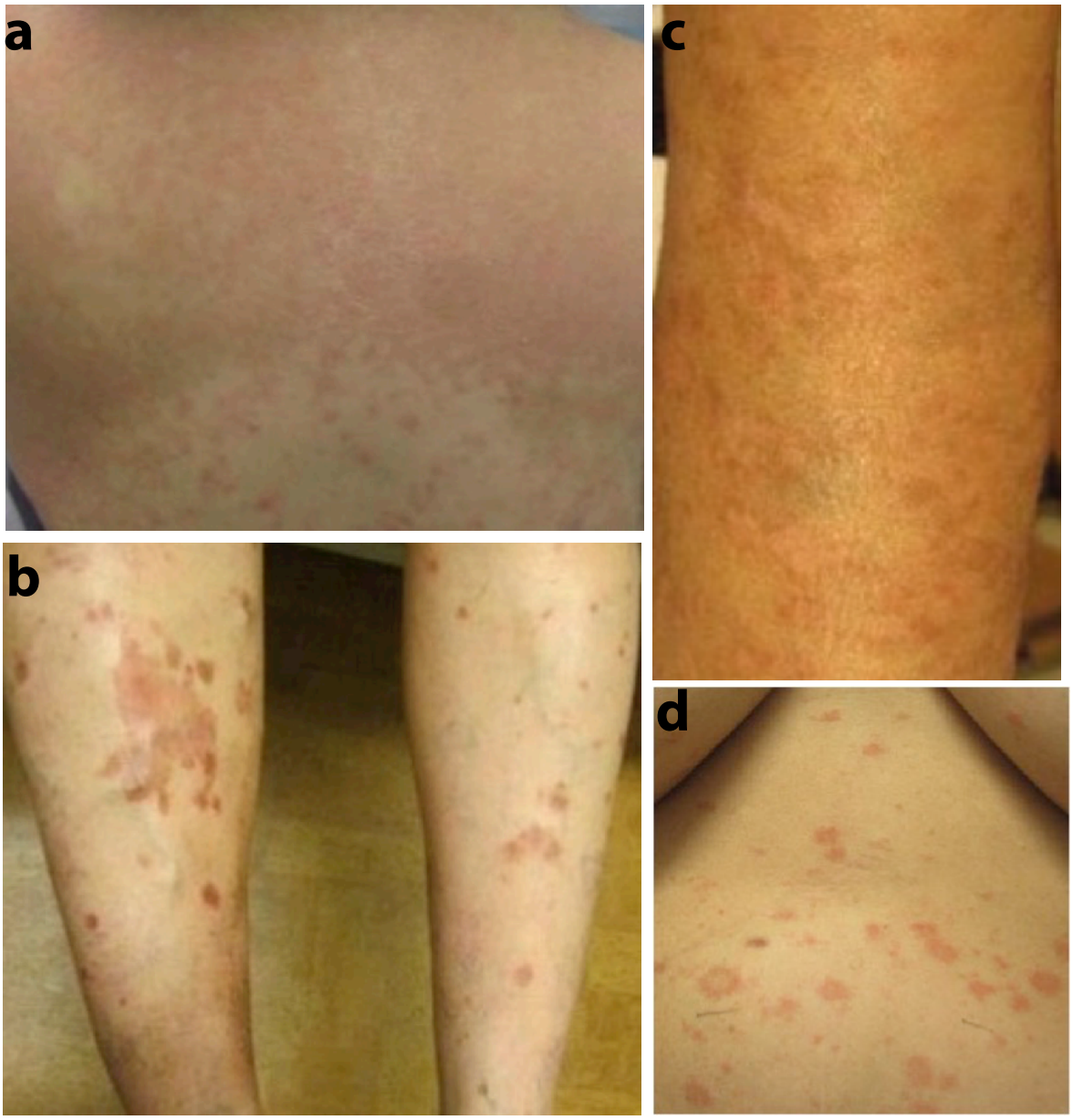

Figure 1. *A) Case 2 developed a hypopigmented scaly eruption involving the lower extremities within 2 weeks of starting duloxetine. B), C) Case 3 developed a more generalized erythematous scaly rash involving the extremities and trunk 18 months after starting cyclobenzaprine. D) Case 10 developed generalized erythematous papules on the trunk and extremities. Illustrated are erythematous papules involving the abdomen.*

drug reaction and PL is important prognostically with regard to patient management [17-19]. Although the pityriasis lichenoides-like drug reaction is self-limited with complete regression occurring upon drug withdrawal, pityriasis lichenoides is a recalcitrant dermatosis that follows a waxing and waning course over years and can eventuate into mycosis fungoides in a minority of cases. The fact that drug therapy can lead to local cutaneous microenvironment that exactly recapitulates pityriasis lichenoides sheds some insight into the pathophysiologic events associated with the development of pityriasis lichenoides.

Case Synopsis

Methods:

Thirty one archived cases bearing a diagnosis of pityriasis lichenoides chronica (PLC), pityriasis lichenoides et varioliformis acuta (PLEVA), or PL-like drug reaction from 2005 to 2016 were identified and reviewed retrospectively from one of the author's dermatopathology practice. The basic

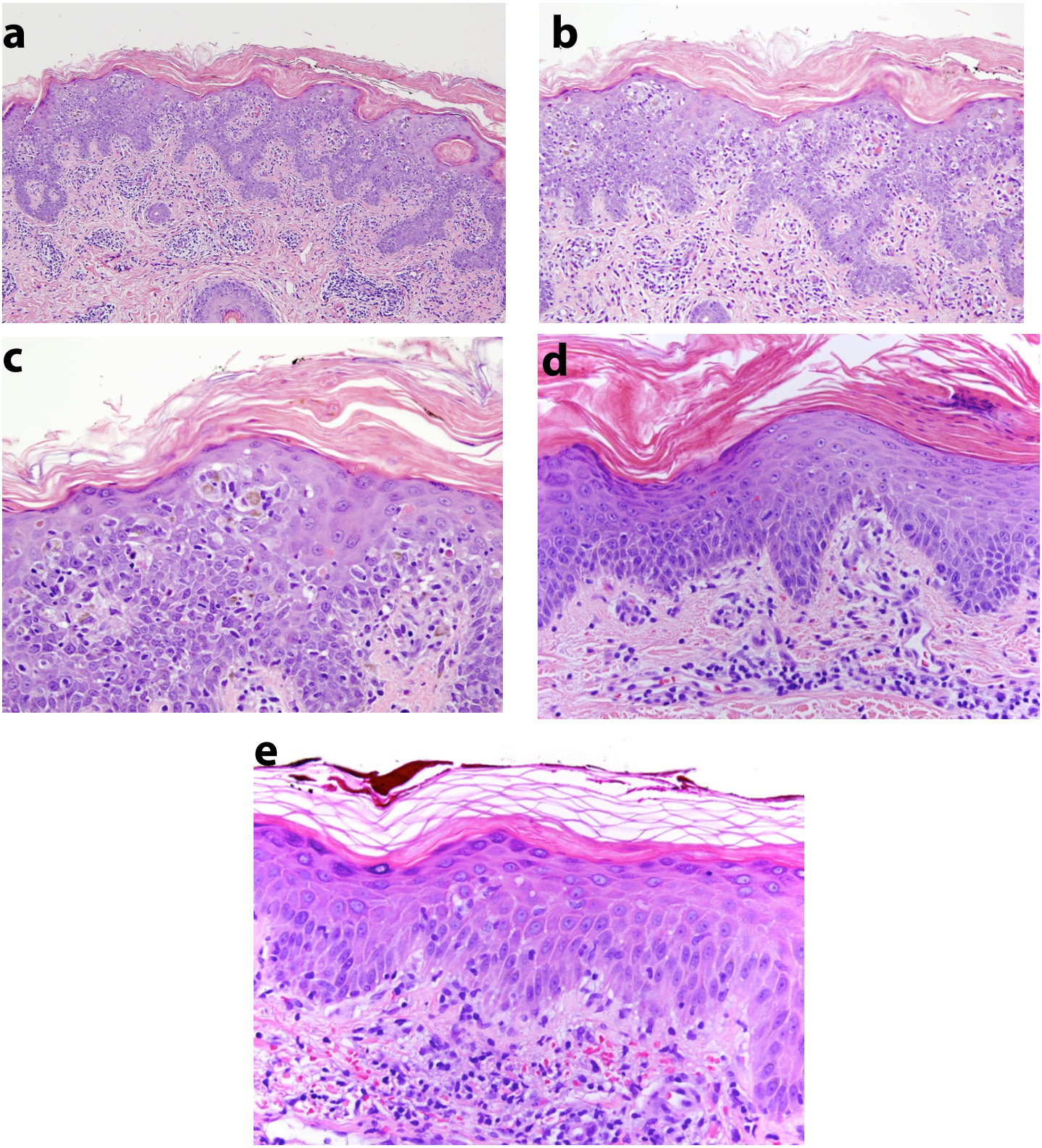

Figure 2. *A) The typical findings in this drug reaction include a psoriasiform epidermal hyperplasia with a striking thick parakeratotic scale at low power (100%). B) Higher power magnification shows significant infiltration of the epidermis by lymphocytes. The pattern of lymphocyte migration is haphazard (200%). C) Scattered necrotic keratinocytes are noted in this image (400%). D), E) A concomitant lymphocytic vascular reaction confined to the superficial dermis associated with prominent red cell extravasation completes the picture (400%).*

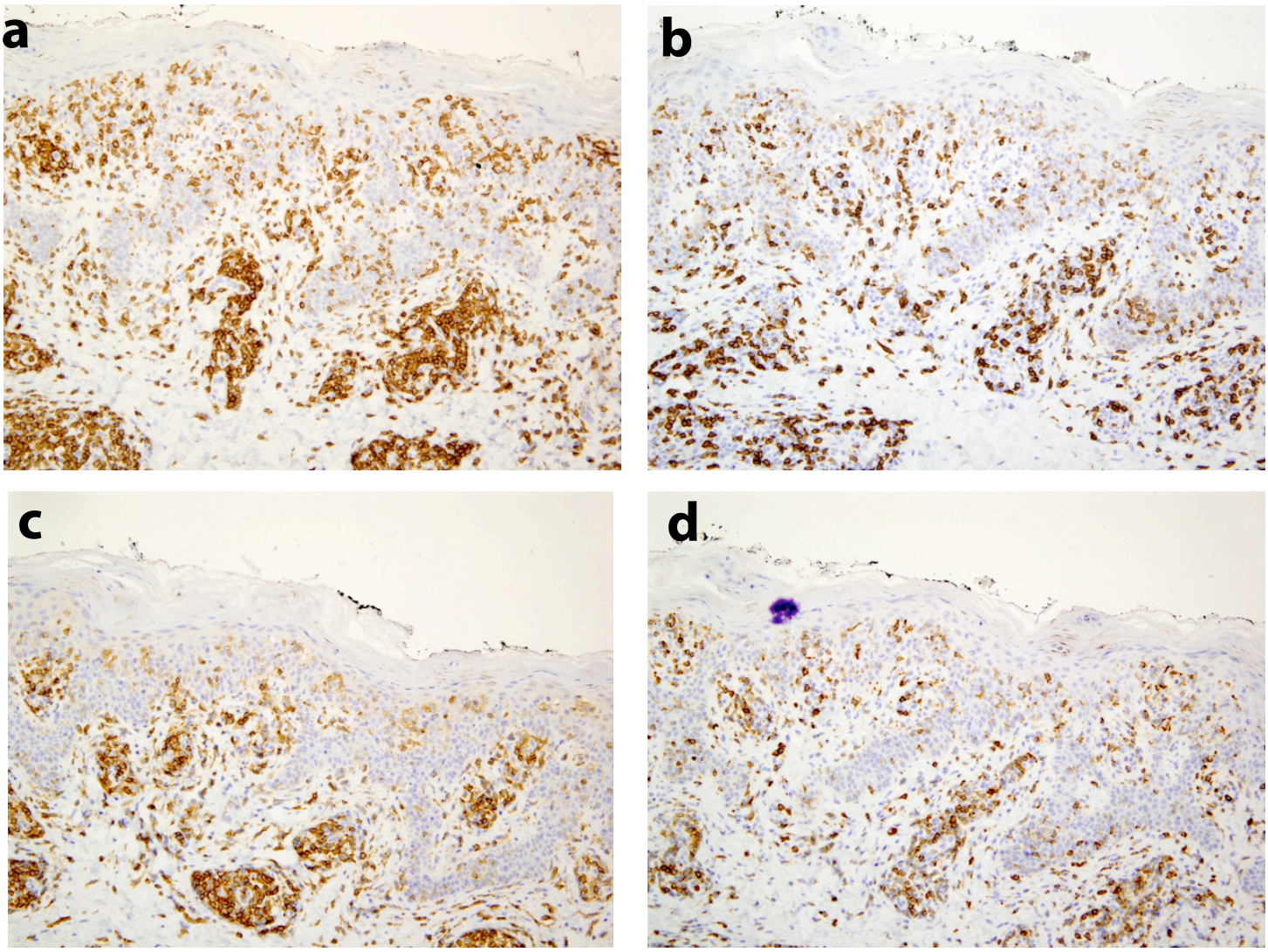

Figure 3. *A) Phenotypic studies highlighting the infiltrate by the CD3 pan T-cell marker (200%). There is a predominance of B) CD8, (200%), to C) CD4, (200%). D) There is a marked reduction in the expression of CD7 (200%).*

morphology of pityriasis lichenoides-like reactions include striking icthyotic parakeratosis, extensive infiltration of the epidermis by lymphocytes characteristically with a proclivity to involve the superficial layers of the epidermis, focal dyskeratosis, and a superficial purpuric lymphocytic vascular reaction with prominent red cell extravasation and variable lymphoid atypia although characteristically low grade; fibrin deposition was not a consistent feature. Medical records and histologic sections were analyzed in detail for all cases with a suspicion of drug reaction. After screening, the most up-to-date clinical follow-up was conducted by the patients' dermatologists. Ten cases in which a possible drug trigger was suggested and cessation of the drug led to regression of the skin rash without any recurrence defined the patient cohort. In each case the phenotypic assessment as part of the routine work up comprised CD2, CD3, CD4, CD5, CD7, and CD8. In a few cases CD62L testing were conducted. The methodologies have been previously described [19]. Molecular studies to assess for T cell receptor gene rearrangement were performed on paraffin embedded formalin fixed tissue on cases 1 and 4.

Results

Clinical Presentations

The patient cohort comprised 7 females and 3 males ranging in age from 24 to 83 years of age (**Figure 1**A, 1B).

Of the 10 cases studied, a widely distributed eruption was present. A combined papular and plaque-like morphology was present in 6 cases (cases 1, 3, 4, 6, 8 and 9) of which three exhibited a trailing scale

(cases 1, 2, 6). In case 10 the generalized eruption was papular in nature.

A hypopigmented scaly eruption involving the lower extremities was present in case 2 (**Figure 1**C). In three cases, the eruption was more limited in distribution. In particular Case 5 and case 7 had a limited eruption of the thigh, whereas case 9 had a limited involvement of the abdomen.

In each patient the eruption had been present for weeks to months before the patient presented to a dermatologist and underwent a diagnostic biopsy procedure. All patients have been receiving multiple drugs for different medical conditions, including mood disorders, depression, hypertension, and hypercholesterolemia. After carefully screening all the medications used by the patients, possible triggering agents were identified for each individual and drug modulation was suggested (**Table 1**). The eruption underwent regression following drug cessation in all cases. In case 8, patient had been diagnosed with HTLV positive adult T cell lymphoma and was receiving anti CCR4 antibody. Owing to the critical role of the medication it could not be discontinued and the rash was remitting and recurring upon each infusion. It was not indicated that any additional therapy either topically and or systemically was implemented except in case 8 in which topical steroids were also administered.

Histopathologic Findings

All cases showed histopathological features reminiscent of pityriasis lichenoides. In each case there was a psoriasiform epidermal hyperplasia, interface dermatitis as well as striking infiltration of the epidermis by lymphocytes (**Figure 2**A). A prominent feature was the presence of a thick ichthyotic-like parakeratotic scale (**Figure 2**B). Superficially disposed collections of Langerhans cells and lymphocytes were noted in the upper layers of the epidermis (**Figure 2**C). Scattered necrotic keratinocytes independent of lymphocyte satellitosis were noted in each case (**Figure 2**D, 2E). In each case there was a concomitant mild lymphocytic vascular reaction associated with red cell extravasation including intraepidermal erythrocyte entrapment but largely unaccompanied by fibrin deposition. The lymphocytes showed low-grade atypia including a few cells manifesting a cerebriform outline. There was a paucity of other inflammatory cell elements, and eosinophils were only noted in one case.

Immunophenotyping and TCR Gene Rearrangement Assay

The epidermotropic T-cells were positive for the pan T-cell markers including CD2, CD3, and CD5 (**Figure 3**a). The dominant cell population in the epidermis was CD8+ in two cases (cases 1 and 3), and CD4+ in five cases (cases 4, 6- 9, **Figure 3**B, 3C).

There was a reduction in the expression of CD7 with a greater extent of CD62L reduction (>90% reduction) compared to CD7 reduction (30-50%, **Figure 3**D). T-cell receptor gene rearrangement assays were performed on case 1 and case 4, and clonality was not identified in either case.

Drug Modulation and Outcome

All patients were receiving certain drugs at the time of the development of the eruption. The implicated pharmaceutical agents for each case are listed in **Table 1**; in certain cases the patient could be on more than one drug. Anti-depressants, including sertraline HCl, duloxetine HCl, bupropion, and paroxetine were implicated in four cases (cases 1, 2, 5 and 9). Cholesterol reducing medications (atorvastatin and rosuvastatin) were the putative agents in three cases (cases 4, 6, and 7). Other agents included a topical antibiotic (doxycycline, case 2), muscle relaxant (cyclobenzaprine, case 3), beta-blocker (metoprolol, cases 6, 7), diuretic (bumetanide, case 6), and a tumor necrosis factor(TNF) inhibitor (adalimumab, case 10). Case 8 was receiving anti-CCR4 antibody. The skin lesions appeared from 2 weeks to a few months after the initial administration of the drug, with the exception of case 3. Notably, this patient did not seek immediate dermatological examination when the skin rash first developed. Therefore the actual onset of the rash was probably earlier than listed in **Table 1**. With the clinical suspicion of drug reaction, the listed agents were discontinued permanently or temporarily in all cases. In 8 of the 10 cases only one drug was discontinued whereas in two cases all drugs of which there were two in each case were stopped as outlined in Table I. The time of drug modulation varied from a few months to a year and

Table 1. *Clinical features of the 9 10 cases described in this study.*

Case	Age/Sex	Clinical Presentation	Triggering drug(s)	Onset post- drug initiation	Intervention	Outcome post-drug modulation
1	58/M	Multiple well-demarcated erythematous papules with trailing scale, on trunk, chest, abdomen, extremities	Sertraline, Gabapentin	2 months	Sertraline, Gabapentin discontinued	Resolved
2	53/F	Hypopigmented scaly eruption involving the lower extremities	Topical Doxycycline, Duloxetine	2 weeks	Doxycycline, Duloxetine discontinued	Resolved
3	59/F	Generalized rash on trunk and extremities	Possible Cyclobenzaprine	Few months	Cyclobenzaprine discontinued	Resolved
4	79/F	Diffuse erythematous rash on trunk and extremities	Atorvastatin	Few months	Atorvastatin discontinued	Resolved
5	26/F	Pityriasiform eruption on the thigh	Sertraline, Bupropion, Citalopram	3 weeks	Sertraline discontinued	Resolved
6	73/M	Numerous erythematous papules with central brown macule some trailing brown ring on back, chest, scalp	Lisinopril, Metoprolol, Rosuvastatin, Bumetanide	2 weeks	Bumetanide discontinued	Resolved
7	72/M	Pityriasiform eruption on the lower extremities	Atorvastatin, Metoprolol	2 weeks	Metoprolol discontinued	Resolved
8	83/F	Generalized erythematous papules and plaques on the trunk and extremities	CCR4 antibody	1 year	Triamcinolone	Resolved and recurred upon each infusion
9	41/F	Pityriasiform eruption on the abdomen	Paroxetine	5 weeks	None	Resolved
10	72/F	Generalized erythematous papules and plaques on the trunk and extremities	Adalimumab	2 weeks	Adalimumab discontinued	Resolved

Table 2. *Drug-associated pityriasis lichenoid-like eruptions reported in the literature to date.*

Ref.	Age/Sex	Drug	Period initiation of drug to onset of symptoms	Histologic impression	Skin presentation	Therapy/outcome
[35]	72/F	Pemetrexed	13 days	PLEVA	Pruritic papular eruption on the entire body except the face	Discontinuation of the drug. Topical corticosteroid and phototherapy/ Complete resolution
[36]	61/M	Chemotherapy regimen including Vincristin	Unknown	Pityriasis lichenoides-like dermatitis	Erythematous papules and macules on the trunk	Unknown
[37]	59/M	Tegafur	7 months	PLEVA	Papulonecrotic eruption on trunk and extremities	Unknown
[38]	40/M	Astemizole	Unknown	PLEVA	Generalized eruption	Unknown
[39]	35/M	Adalimumab	Few months	PLC	Papular eruption on the trunk, buttocks, and extremities	Discontinuation of the drug and methotrexate/ Complete resolution
[39]	29/F	Adalimumab	12 months	PLC	Pruritic papules on the trunk, buttocks, and proximal extremities, progressing rapidly to vesicles and hemorrhagic crusts	Discontinuation of the drug and methotrexate/ Complete resolution
[40]	53/M	Infliximab	4 months	PLC	Erythematous Papules on the trunk, arms, buttocks and legs	Discontinuation of the drug and methotrexate/ Complete resolution
[41]	24/M	Human immunoglobulin	1 month	PLEVA	Generalized violaceous papules on the torso and upper extremities	Discontinuation of the drug, corticosteroid and phototherapy / Complete resolution
[42]	62/M	Simvastatin and Pravastatin	12 months	PLC	Generalized papular eruption on the limbs	Discontinuation of the drug/Complete resolution
[42]	70/M	Pravastatin	36 months	PLC	Maculopapluar eruption on the entire trunk and limbs	Discontinuation of the drug/Complete resolution
[42]	79/F	Pravastatin and Rosuvastatin	Unknown	PLC	Papular eruption	Discontinuation of the drug/Complete resolution

- Pityriasis lichenoides et varioliformis acuta (PLEVA), Pytyriasis lichenoides chronica (PLC)

initial follow-up examination showed moderate to significant improvement of the lesions. Ultimately, all cases showed complete regression of the skin rashes following drug cessation. In one patient the eruption recurred with worsening features upon each infusion of the anti-CCR4 antibody (case 8).

Case Discussion

Pityriasis lichenoides is a group of uncommon skin disorders that are often challenging to diagnose and treat [17, 20, 21]. Based on the clinical features, PL is subdivided into PLEVA and PLC; the former encompasses a variant exhibiting constitutional symptoms falling under the designation of febrile ulceronecrotic Mucha-Habermann disease (FUMHD). PLEVA and PLC are considered to be the two extremes of a continuum and it is common to observe both lesions in the same specimen [17, 20, 21]. The variant of PLEVA designated as FUMHD is noteworthy for its aggressive clinical presentation [22-24]. Although the etiology of disease in PL spectrum was speculative for many years with hypotheses ranging from infection-related inflammation, lymphoproliferative disorder, to immune complex mediated hypersensitivity vasculitis, it would appear that its most reasonable categorization is in the context of an indolent T cell lymphoproliferative disease [17-19, 23, 25, 26]. In fact it can be difficult to reliably distinguish PL from type B lymphomatoid papulosis and papular mycosis fungoides. The evolution of PL into mycosis fungoides occurs when the counter-regulatory cells represented by regulatory T cells and reactive cytotoxic CD8 T cells are sufficiently diminished to allow the unchecked expansion of clonally restricted T cells, oftentimes of the CD4 subset [18, 19, 27]. In PL the regulatory cells infiltrate the skin and lead to lesional regression.

Clinically, PLEVA often presents with evolving multiple small erythematous macules to papules; a fine central scale is frequently formed. The central portion of the lesion can become vesiculopustular, hemorrhagic, and ulcerative. The most commonly involved areas include the trunk, extremities, and flexural areas. PLC has a much slower clinical course and initially presents with an erythematous papule, which can develop a reddish-brown hue and central adherent scale. In some instances, especially in patients of color, dyschromia with hypopigmentation can occur in PLC. The lesion can regress spontaneously but sometimes persists. Both PLEVA and PLC last for several weeks and have a waxing and waning clinical course. Unlike other forms of T cell dyscrasia, most notably pigmented purpuric dermatosis and large plaque parapsoriasis, which occur primarily in adults, PLEVA and PLC can also be seen in the pediatric setting. Histopathologically, there are some discriminating features between PLC and PLEVA. Both frequently show a spectrum of interface dermatitis including vacuolization of the epidermal basal layer, necrotic keratinocytes, prominent infiltration of the epidermis by lymphocytes, and collections of Langerhans cells and lymphocytes disposed superficially within the epidermis. The cohesive non-spongiotic appearance of these cellular collections along with mild lymphoid atypia can result in an appearance that resembles somewhat a Pautrier microabscess. A wedge-shaped dermal lymphocytic-dominant infiltrate is frequently observed. In most cases there is conspicuous red cell extravasation albeit there may not be any significant mural fibrin deposition. PLC can exhibit attenuation as opposed to the hyperplastic psoriasiform quality that is typical of PLEVA. In addition, in the acute form of the disease i.e. PLEVA, frank vasculitic changes with overt fibrin deposition in the vessel wall eventuating into epidermal necrosis can be observed [17, 21, 28-31]. Whereas there are these aforesaid morphologic differences between PLEVA and PLC, phenotypically they appear similar whereby there may be a predominance of CD8+ lymphocytes in the epidermis but most cases show a significant admixture of CD4 T cells. In fact the CD4 T cells are oftentimes the abnormal clonally restricted T cell populace that evokes the reactive robust CD8 T cell infiltrate to induce lesional regression (18, 19).

The significant reduction in the expression of CD7 and CD62L and the presence of clonality by TCR receptor gene rearrangement analysis warrants categorization of this recalcitrant dermatosis as a form of T-cell dyscrasia. Other features supporting the categorization of PL as a form of T cell dyscrasia, be it in the context of PLC or PLEVA, include the persistent nature of the eruption in the absence of a clear cut antigenic trigger and the evolution of PL cases into mycosis fungoides [18, 19]. Therefore, it is critical to accurately diagnose PL in order to initiate appropriate treatment, including topical and oral

agents and ultraviolet photo therapy [17, 32-35].

Drug reactions commonly reflect an immunologic response to the drug most commonly in the context of a Gell and Coombs type IV immune reaction triggered by a small drug protein referred to as a hapten. However, in many instances a lymphocyte rich cutaneous eruption emerges that is likely not specifically reflective of an immunologic response to the drug but rather is attributable to inherent immune dysregulating properties manifested by the drug. In particular the drug has a direct effect on the immune system, dysregulating lymphocyte function resulting in a cytokine milieu that appears to recapitulate one operational in B cell and T cell lymphomagenesis. In fact in this current era of polypharmacy many of the atypical lymphocyte mediated cutaneous eruptions are attributable to drug therapy as opposed to being reflective of endogenous lymphoproliferative disease. The most commonly implicated drug classes are the antidepressants, antihistamines, statins, calcium channel blockers, and angiotensin-converting enzyme inhibitors [11]. Among the lymphomatoid drug reactions are those that mimic low grade B-cell lymphoma and mycosis fungoides including the interstitial granulomatous variant [12-15]. A CD30 positive lymphomatoid vascular reaction closely resembling lymphomatoid papulosis can occur [16]. In addition, a variant mimicking pigmented purpuric dermatosis, a classic cutaneous T cell dyscrasia, has been described. Owing to concomitant phenotypic abnormalities and the identification of clonality in some cases, such eruptions have been designated as drug-associated reversible T-cell dyscrasias [12-15].

Drug reactions mimicking PL have not been well described. To date 11 cases of this rare entity have been reported in the literature thus far [36-43]. Among the implicated drugs were chemotherapeutic agents in three cases, TNF inhibitors in v, intravenous gammaglobulin for combined variable immunodeficiency syndrome in one case, and statins in three. Four of the cases exhibited a PLEVA- like pattern whereas the other 6 cases showed features more in keeping with a PLC-like morphology. The features that qualified the cases as being PLEVA-like were in the context of significant epithelial necrosis and vascular injury. Of the cases reported, the outcome was unknown in three; three were given methotrexate with resolution of the eruption. In three cases in which the implicated agent was a statin, discontinuing the drug led to resolution of the eruption. The time course was variable and similar to that observed in our cases. In three of the cases, however, the time course was not known. In four cases there was a defined temporal association with the onset of the skin rash within 6 months of commencing the drug. In three cases there was a significant period of latency comprising 7 months, 12 months, and 3 years.

A summary of the current literature describing the PL-like drug reaction is provided in **Table 2**. In our patient cohort the espousal regarding the basis of the eruption being drug related was based on the onset of the rash subsequent to the commencement of the drug and regression of the eruption following the drug cessation. Unlike many of the previously reported lymphomatoid drug reactions, there was more of a direct temporal association between the commencement of the drug and the onset of the eruption by a few weeks to a few months with the maximum latent period being 18 months. The most commonly implicated drug classes in our series were anti-depressants, namely sertraline HCl, duloxetine HCl, bupropion, and paroxetine and cholesterol reducing medications (atorvastatin and rosuvastatin). The histologic findings were reproducible and produced a morphologic picture that manifested a striking semblance to PL. Prominent infiltration of the epidermis by lymphocytes accompanied by a psoriasiform epidermal hyperplasia, striking confluent parakeratosis, keratinocyte necrosis, and a lymphocytic purpuric vascular reaction were fairly ubiquitous findings. Another characteristic finding and unique to reaction patterns that fall under the rubric of PL versus PL-like were superficially disposed collections of Langerhans cells and lymphocytes within the superficial layers of the epidermis reminiscent of a Pautrier microabscess. The mononuclear cell collections were different from a true Pautrier microabscess by virtue of the more superficial localization within the epidermis as opposed to the typical parabasilar Pautrier microabscess of mycosis fungoides, the greater number of admixed Langerhans cells, and an extent of lymphoid atypia that was noticeably less than the more fully evolved lymphoid atypia seen in a

classic Pautrier microabscess. Rare eosinophils were only observed in case 2 in the perivascular infiltrate, which indicated that the presence of eosinophils is not a sensitive marker in the diagnosis of PL-like drug reaction. The lack of tissue eosinophilia draws another parallel with PL in which the rarity of this cell type is well established (18, 19). With regard to the term lymphocytic vasculitis, at least in the context of lesions of pityriasis lichenoides/pityriasis lichenoides-like drug rash, the process is not a necrotizing lymphocytic vasculitis but rather a lymphocytic vascular reaction associated with red cell extravasation including intraepidermal erythrocyte entrapment, typically accompanied by significant lymphocytic epitheliotropism and marked parakeratosis. Although CD8 T cells defined the predominant T cell subset in the epidermis in two cases, in the other cases the main T cell subset in the epidermis was CD4 positive, which is in contradistinction to PLEVA and PLC in which the prevalent intraepidermal lymphoid population is oftentimes of the CD8 subset [19]. In all cases the positivity of CD7 and CD62L was significantly diminished. Overall the phenotypic profile was similar to that observed in PL [18, 19]. With the availability of DNA from the paraffin blocks of two cases, molecular testing was applied to investigate the clonality of the T-cell receptor gene rearrangement, which did not show evidence of monoclonality as demonstrated in some de novo PL cases.

Conclusion

Our findings conform the categorization of this process as a form of T-cell dyscrasia, albeit one that is reversible dependent on drug withdrawal, adding to the spectrum of lymphomatoid drug reactions. The mechanisms by which these specific drug classes cause this distinctive reaction is unclear but given the closer temporal association with drug exposure, the role of the drug as an antigenic trigger in concert with inherent immune dysregulating properties of the drug could be operational. The onset of lesions clinically and histologically resembling PL in an older individual should lead one to consider a drug-based trigger.

References

1. Breathnach SM. Mechanisms of drug eruptions: Part I. *Australas J Dermatol* 1995; 36: 121-7. [PMID: 7487737].
2. Breathnach SM. Management of drug eruptions: Part II. Diagnosis and treatment. *Australas J Dermatol* 1995; 36: 187-91. [PMID: 8593105].
3. McKenna JK, Leiferman K. Dermatologic drug reactions. *Immunol Allergy Clin North Am.* 2004; 24: 399-423. [PMID: 15242718].
4. Nigen S, Knowles SR, Shear NH. Drug eruptions: approaching the diagnosis of druginduced skin diseases. *J Drugs Dermatol* 2003; 2: 278-99. [PMID: 12848112].
5. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol* 2001; 137: 765-70. [PMID: 11405768].
6. Revuz J. New advances in severe adverse drug reactions. *Dermatol Clin* 2001;19: 697-709. [PMID: 11705355].
7. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; 331: 1272-85. [PMID: 7794310].
8. Wolkenstein P, Charue D, Laurent P, Revuz J, Roujeau JC, Bagot M. Metabolic predisposition to cutaneous adverse drug reactions. Role in toxic epidermal necrolysis caused by sulfonamides and anticonvulsants. *Arch Dermatol* 1995; 131: 544-51. [PMID: 7741540].
9. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. Incidence, management and prevention. *Drug Saf* 1995; 13: 56-68. [PMID: 8527020].
10. Pichler WJ. Immune mechanism of drug hypersensitivity. Immunol *Allergy Clin North Am* 2004; 24: 373-97. [PMID: 15242717].
11. Magro CM, Crowson AN. Drug-induced immune dysregulation as a cause of atypical cutaneous lymphoid infiltrates: a hypothesis. *Hum Pathol.* 1996 Feb;27(2):125-32. [PMID: 8617453].
12. Magro CM, Cruz-Inigo AE, Votava H, Jacobs M, Wolfe D, Crowson AN. Drug associated reversible granulomatous T cell dyscrasia: a distinct subset of the interstitial granulomatous drug reaction. *J Cut Pathol* 2010; 37 Suppl 1:96-111. [PMID: 20482682].
13. Magro CM, Crowson AN, Kovatich AJ, Burns F. Drug-induced reversible lymphoid dyscrasia: a clonal lymphomatoid dermatitis of memory and activated T cells. *Hum Pathol* 2003; 34: 119-29. [PMID: 12612879].
14. Crowson AN, Magro CM, Zahorchak R. Atypical pigmentary purpura: a clinical, histopathologic, and genotypic study. *Hum Pathol* 1999; 30: 1004-12. [PMID: 10492033].
15. Magro CM, Crowson AN, Schapiro BL. The interstitial granulomatous drug reaction: a distinctive clinical and pathological entity. *J Cut Pathol* 1998; 25:72-8. [PMID: 9521495].
16. Magro CM, Olson LC, Nguyen GH, de Feraudy SM. CD30 Positive Lymphomatoid Angiocentric Drug Reactions: Characterization of a Series of 20 Cases. *Am J Dermatopathol*. 2017 Jul;39(7):508-517. [PMID: 27655118].
17. Khachemoune A, Blyumin ML. Pityriasis lichenoides: pathophysiology, classification, and treatment. *Am J Clin Dermatol* 2007; 8: 29-36. [PMID: 17298104].
18. Magro C, Crowson AN, Kovatich A, Burns F. Pityriasis lichenoides: a clonal T-cell lymphoproliferative disorder. *Hum Pathol* 2002; 33: 788-95. [PMID: 12203210].
19. Magro CM, Crowson AN, Morrison C, Li J. Pityriasis lichenoides chronica: stratification by molecular and phenotypic profile. *Hum Pathol* 2007; 38: 479-90. [PMID: 17239929].
20. Szymanski FJ. Pityriasis lichenoides et varioliformis acuta: histopathological evidence that it is an entity distinct from parapsoriasis. *AMA Arch Derm* 1959; 79: 7-15. [PMID: 13605272].
21. Marks R, Black M, Jones EW. Pityriasis lichenoides: a reappraisal. *Br J Dermatol* 1972, 86: 215-25. [PMID: 5018676].
22. Burke DP, Adams RM, Arundell FD. Febrile ulceronecrotic mucha Habermann's disease. *Arch Dermatol* 1969; 100: 200-6. [PMID: 5797962].
23. Weiss LM, Wood GS, Ellisen LW, Reynolds TC, Sklar J. Clonal T-cell

populations in pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease). *Am J Pathol* 1987; 126: 417-21. [PMID: 3030116].
24. Miyamoto T, Takayama N, Kitada S, Hagari Y, Mihara M. Febrile ulceronecrotic Mucha-Habermann disease: a case report and a review of the literature. *J Clin Pathol* 2003; 56: 795-7. [PMID: 14514790].
25. Clayton R, Haffenden G, Du Vivier A, Burton J, Mowbray J. Pityriasis lichenoides, an immune complex disease. *Br J Dermatol* 1977; 97: 629-34. [PMID: 146510].
26. Clayton R, Haffenden G. An immunofluorescence study of pityriasis lichenoides. *Br J Dermatol* 1978; 99: 491-3. [PMID: 361062].
27. Vonderheid EC, Kadin ME, Telang GH. Commentary about papular mycosis fungoides, lymphomatoid papulosis and lymphomatoid pityriasis lichenoides: more similarities than differences. *J Cutan Pathol* 2016 Apr; 43(4): 303-12. [PMID: 26566599].
28. Willemze R, Scheffer E. Clinical and histologic differentiation between lymphomatoid papulosis and pityriasis lichenoides. *J Am Acad Dermatol* 1985; 13: 418-28. [PMID: 4056116].
29. Black MM, Marks R. The inflammatory reaction in pityriasis lichenoides. *Br J Dermatol* 1972; 87: 533-9. [PMID: 4567640].
30. Marks R, Black MM. The epidermal component of pityriasis lichenoides. *Br J Dermatol* 1972; 87: 106-13. [PMID: 5057378].
31. Black MM, Jones EW. "Lymphomatoid" pityriasis lichenoides: a variant with histological features simulating a lymphoma. A clinical and histopathological study of 15cases with details of long term follow up. *Br J Dermatol* 1972; 86: 329-47. PMID: 4112468
32. Simon D, Boudny C, Nievergelt H, Simon HU, Braathen LR. Successful treatment of pityriasis lichenoides with topical tacrolimus. *Br J Dermatol* 2004; 150: 1033-5. PMID: 15149526
33. Powell FC, Muller SA. Psoralens and ultraviolet A therapy of pityriasis lichenoides. *J Am Acad Dermatol* 1984; 10: 59-64. [PMID: 6693602].
34. LeVine MJ. Phototherapy of pityriasis lichenoides. *Arch Dermato*l 1983; 119: 378-80. [PMID: 6847216].
35. Cornelison RL, Jr., Knox JM, Everett MA. Methotrexate for the treatment of Mucha-Habermann disease. *Arch Dermatol* 1972; 106: 507-8. [PMID: 5079356].
36. Sabatiello M, Willemaers V, Lesuisse M, Pierard GE. Pemetrexed-induced pityriasis lichenoides-like dermatitis. *J Eur Acad Dermatol Venereol* 2012; 26: 127-9. [PMID: 22168779].
37. Isoda M. Pityriasis lichenoides-like eruption occurring during therapy for myelogenous leukemia. *J Dermatol* 1989; 16: 73-5. [PMID: 2656809].
38. Kawamura K, Tsuji T, Kuwabara Y. Mucha-Habermann disease-like eruptions due to Tegafur. *J Dermatol* 1999; 26: 164-7. [PMID: 10209923].
39. Stosiek N, Peters KP, von den Driesch P. [Pityriasis-lichenoides-et-varioliformis-acutalike drug exanthema caused by astemizole]. *Hautarzt* 1993; 44(4): 235-7. [PMID: 8482605].
40. Said BB, Kanitakis J, Graber I, Nicolas JF, Saurin JC, Berard F. Pityriasis lichenoides chronica induced by adalimumab therapy for Crohn's disease: report of 2 cases successfully treated with methotrexate. *Inflamm Bowel Dis* 2010; 16(6): 912-3. [PMID: 19821511].
41. López-Ferrer A, Puig L, Moreno G, Camps-Fresneda A, Palou J, Alomar A. Pityriasis lichenoides chronica induced by infliximab, with response to methotrexate. *Eur J Dermatol* 2010; 20(4): 511-2. [PMID: 20395191].
42. Machan M, Loren R, Fraga G, Liu D. Pityriasis lichenoides et varioliformis acuta associated with subcutaneous immunoglobulin administration. *J Am Acad Dermatol* 2012; 67(4): e151-2. [PMID: 22980275].
43. Massay RJ, Maynard AA. Pityriasis lichenoides chronica associated with use of HMGCoA reductase inhibitors. *West Indian Med J* 2012; 61(7): 743-5. [PMID: 23620974].