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Review article

Drug induced pseudolymphoma

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ABSTRACT

Atypical lymphocytic infiltrates of the skin comprise a broad spectrum of entities ranging from benign infiltrates to those that are malignant. Many of these infiltrates are in fact reactive lymphomatoid ones related to drug therapy falling under the general category of drug associated pseudolymphoma. Within this nosologic umbrella are nodular and diffuse infiltrates resembling low grade T and B cell lymphoma consistent with lymphocytoma cutis, drug associated reversible T cell dyscrasias which draw a strong morphologic and phenotypic parallel with mycosis fungoides and the various pre-lymphomatous T cell dyscrasias, and angiocentric CD30 positive infiltrates mirroring lymphomatoid papulosis. The implicated drug classes are quite varied and include antidepressants, antihistamines, calcium channel blockers, statins, anticonvulsants, and various biologic drugs. The drugs from these various drug classes exert certain effects on lymphoid function including evoking overzealous responses to other antigenic stimuli. As the adverse effect on lymphocyte function may be cumulative over years and or reflect the interplay of other drugs, a temporal association may not exist between the onset of the rash/lesion and the initiation of the drug. In certain lymphomatoid reactions however such as DRESS syndrome the drug may function as both an antigen as well as an immune dysregulating agent. It is critical that the pathologist works carefully with the clinician in the evaluation of all atypical cutaneous lymphoid infiltrates where the distinction between pseudolymphoma versus lymphoma cannot be reliably made based on pathologic analysis alone.

Introduction

The spectrum of atypical cutaneous lymphocytic infiltrates of the skin is broad especially in regard to the various subtypes of primary cutaneous lymphoma. A common cause of atypical cutaneous lymphoid infiltrates that can resemble B and T cell lymphoma is the drug induced pseudolymphoma. In routine dermatopathology practice, most biopsies showing atypical lymphocytic infiltrates are not neoplastic in nature but instead represent a lymphomatoid state that often reflects underlying iatrogenic and endogenous immune dysregulation.

The intent of this review is to address the clinical and pathologic aspects of drug induced pseudolymphoma by examining the two main categories, namely: lymphocytoma cutis and those atypical T cell lymphocytic infiltrates that resemble varied forms of T cell lymphoproliferative disease, for which we have coined the term *drug associated reversible T cell dyscrasia*. While lymphocytoma cutis has a uniform clinical and histomorphologic appearance, the drug associated reversible T cell dyscrasias show wide variation in their clinical and histologic presentations.[1]

Examples of drug induced reversible T cell dyscrasias comprise the following entities: the pseudo-mycosis fungoides-like drug reaction including the drug associated reversible granulomatous T cell dyscrasia which can masquerade as interstitial granulomatous mycosis fungoides, the CD30 positive angiocentric lymphomatoid drug reaction as a mimic of lymphomatoid papulosis, drug associated reversible erythrodermic T cell dyscrasia (i.e. pseudo-Sezary syndrome), the pityriasis lichenoides-like drug reaction and drug induced atypical pigmented purpuric dermatosis.[2–4]

Many of the clinical, histologic and phenotypic features that we encounter in endogenous T cell lymphoproliferative disorders can be observed in drug induced pseudolymphomas. At times the distinction is so difficult that we make treatment recommendations similar to those applied to endogenous T cell dyscrasias, such as light therapy, along with a trial of drug modulation. In theory, if the process is truly a reversible state induced by drug therapy, resolution of the rash should occur with the aforesaid interventional therapy and should not recur. Recurrent and/or persistent disease is the hallmark of endogenous T cell lymphoproliferative disease.[5]

In drug induced reversible T cell dyscrasias, the temporal association between the initiation of the drug and the development of the

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atypical cutaneous infiltrate may be difficult to discern, as the role of the drug in immune dysregulation may be a cumulative, long term effect. In conventional drug eruptions, where a new drug functions as a triggering antigen, the patient and the clinician often recognize an immediate temporal association.[3]

Nevertheless there are drug reactions that show both features of hypersensitivity and an excessive immune response, suggesting that the drug manifests combined allergic and immune dysregulating properties, best exemplified by the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. The distinctive features of DRESS syndrome are drug associated peripheral blood eosinophilia, systemic symptoms, and skin rash.[6] When one addresses the literature precedent on drug induced pseudolymphoma, the first reported cases were examples of DRESS syndrome whereby the inciting drug triggers were from the anticonvulsant class.[7]

It was not until the 1990s that it became apparent that drugs other than those from the anticonvulsant class could be associated with a cutaneous pseudolymphomatous response. One of the first series addressing atypical lymphocytic infiltrates associated with non-anticonvulsant drug therapy was in the context of antidepressant therapy.[8] This series was also novel in that atypical cutaneous lymphocytic infiltrates could present exclusively in the skin without other clinical stigmata typical of DRESS syndrome. In fact, if we fast forward to 2017, a review of the literature indicates that the majority of T-cell rich pseudolymphomatous responses to drug are not in the context of DRESS syndrome, but instead are cutaneous infiltrates that resemble low grade B cell lymphomas such as T cell rich marginal zone lymphoma and primary cutaneous CD4+ small/medium sized pleomorphic T cell lymphoma, or epidermotropic infiltrates as seen within the spectrum of mycosis fungoides (MF) and the prelymphomatous T cell dyscrasias.

There is a growing list of drugs that can be incriminated in drug associated T-cell rich pseudolymphoma including those drugs that trigger DRESS syndrome. The more common classes of implicated drugs are the anticonvulsants, calcium channel blockers, antidepressants, H1 and H2 antagonists, statins, and angiotensin converting enzyme (ACE) inhibitors.[1] Table 1 summarizes the more frequently implicated drugs and their effect on lymphocyte function.

We will consider four topics in this review: lymphocytoma cutis, the drug associated reversible T cell dyscrasias including special variants, pseudolymphomas associated with biologic therapy given the emerging role of biologics in the treatment of various inflammatory and neoplastic disorders, and the pathophysiology that underlies drug induced pseudolymphoma.

Drug induced lymphocytoma cutis (Figs. 1 and 2)

Likely one of the commonest clinical presentations of drug induced pseudolymphoma is lymphocytoma cutis. It presents as solitary or few plaque-like and/or nodular lesions typically localized to the head, neck and upper trunk.[9,10]

The dense nature of the lymphocytic infiltrates along with some degree of cytologic atypia makes the distinction from low grade lymphoma difficult. Furthermore, if one examines low grade T or B cell lymphomas of the skin, underlying diffuse and nodular reactive lymphoid hyperplasia resembling lymphocytoma cutis is often seen. While one might speculate that the infiltrate is simply part of the neoplastic cytokine milieu, it could also reflect a precursor infiltrate. The multistep process of lymphomagenesis involves an intermediary step that resembles, or perhaps represents, lymphocytoma cutis. We previously reported a case of antidepressant associated pseudolymphoma that evolved into a low grade marginal zone lymphoma.[11] It can be very difficult to rule out low grade lymphomas of the skin when a small punch biopsy shows features of lymphocytoma cutis.

The basis of the reactive infiltrate is an exuberant immune response to an antigen potentially reflective of underlying iatrogenic and/or endogenous immune dysregulation. There is a role for drugs with immune dysregulating properties in the pathogenesis of at least some cases of lymphocytoma cutis. The implicated drugs are from many classes such as anticonvulsants, antidepressants, certain immunosuppressive drugs such as cyclosporine, allopurinol, and antihistamines.

A distinct subset of drug associated lymphocytoma cutis is Jessner's lymphocytic infiltrate of skin that presents as infiltrative, annular, violaceous plaques on the upper arm, upper back and face in a fashion that clinically mimicstumid lupus erythematosus. Jessner's lymphocytic infiltrate is sufficiently distinctive clinically and pathologically that it is often considered as a nosologic entity with overlapping features with, and some consider to be equated to, tumid lupus erythematosus. The authors of this review contend that it is an entity distinct and separate from tumid lupus erythematosus, more likely representing a form of lymphocytoma cutis. Cases of Jessner's lymphocytic infiltrate of skin have been described in association with bee venom sensitization shots, ramipril, leflunomide, glatiramer acetate and duloxetine ingestion.[12–15] Differentiating points from lupus erythematosus include: lack of

Table 1
Drugs with known alterations in immune/lymphocyte function.

Drugs with known alterations in immune/lymphocyte function			
	In vitro alterations in lymphocyte function	In vivo immune dysregulation	Mechanism of action of immune dysregulatory effects
Antidepressants	+	+	Histamine blockade of H1c receptors
Phenothiazines	+	+	Histamine blockade of H1c receptors
Benzodiazepines	+	+	Ligand of peripheral type benzodiazepine receptor
Lithium	+	–	Inhibits inositol − 1 phosphate in monocytes
H1 antagonists	+	–	Histamine blockade of H1c receptors
H2 antagonists	+	+	Blocking H2 receptor mediated effects of histamine on lymphocyte function
Anticonvulsants	+	+	For carbamazepine, histamine blockade of H1c receptor is possible in view of structural homology with tricyclics
Calcium channel blockers	+	+	Inhibition of potassium efflux in lymphocytes
ACE inhibitors	+	+	Unknown
Beta-blockers	+	+	Blocking immunosuppressive effects of norepinephrine on lymphocyte adrenoreceptors
Alpha-antagonists	+	–	Blocking immunosuppressive effects of norepinephrine on lymphocyte adrenoreceptors
Non-steroidal anti-inflammatory agents	+	–	Decreases IL − 2 production through inhibition of prostaglandin synthesis in monocytes
Lipid lowering agents	+	–	Unknown
Sex steroids	+	+	Unknown