Distinguishing reactive inflammatory dermatoses from lymphoma: 2 cases of severe drug reactions to phenytoin/phenobarbital and rosuvastatin mimicking lymphoma

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INTRODUCTION

Cutaneous pseudolymphomas (CPL) are benign lymphoproliferative processes secondary to factors such as drug and arthropod reactions, infections, and inflammatory dermatoses that clinically and histologically mimic lymphoma.[1,2] Similarly, severe cases of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome or drug-induced hypersensitivity syndrome (DIHS) are reported to mimic systemic lymphoma due to blood count abnormalities, lymphadenopathy, and atypical peripheral blood smears. Although challenging at times, distinguishing lymphoma from CPL or a severe drug reaction is critical to avoid potentially unnecessary treatment and assign an appropriate favorable prognosis. We present 2 cases of lymphoma mimickers, initially diagnosed as lymphoma.

Abbreviations used:

CPL:	cutaneous pseudolymphomas
CTCL:	cutaneous T-Cell lymphoma
DRESS:	drug rash with eosinophilia and systemic symptoms
MF:	mycosis fungoides
PTCL:	peripheral T-cell lymphoma

CASE 1

A 54-year-old man presented with a pruritic and burning eruption, fever, weight loss, and night sweats of several months' duration. The patient had been treated continuously for a seizure disorder with phenytoin and phenobarbital for 20 years.

On physical examination he had erythematous-to-violaceous patches and indurated plaques on his head, trunk, and extremities. Thicker erythematous to brown nodules and tumors were noted on the head and neck accompanied by diffuse lymphadenopathy (Fig 1, *A*). Laboratory findings were notable for pancytopenia. Diffuse, tumor-stage cutaneous T-cell lymphoma was suspected.

Punch biopsies of the neck and inguinal fold found a non-necrotizing granulomatous dermatitis with eosinophils and an atypical lymphoid infiltrate without evidence of infection (Fig 1, *B*). On immunohistochemical staining, the infiltrate was predominately $CD3^+$ with an increased CD8/CD4 ratio of 1:1. Positron emission tomography/computed tomography found hypermetabolic foci in multiple lymph nodes. Peripheral blood flow cytometric analysis found lymphopenia without definitive aberrancy of T cells. Bone marrow examination and left groin lymph node biopsy found no evidence of lymphoma, and T-cell receptor γ and β gene arrangement studies performed on multiple skin biopsies did not find a monoclonal T-cell population. All 9 biopsies (6 skin, 2 lymph node, and 1 bone marrow) reviewed at our cutaneous lymphoma tumor board and the National Institute of Health were

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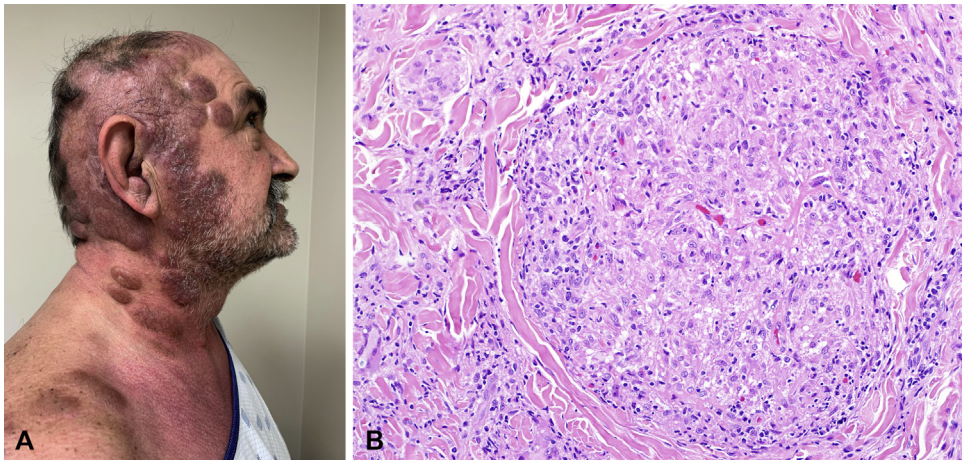

Fig 1. A, Scattered, erythematous-brown indurated plaques, nodules, and tumors with overlying telangiectasias were seen on the patient's face, scalp, trunk and extremities in addition to widespread erythematous patches with scaling. **B**, Punch biopsy from the left inguinal fold shows non-necrotizing granulomatous dermatitis with eosinophils and atypical lymphocytic infiltrate. (Original magnification: ×200) On immunohistochemical staining, the infiltrate was predominately $CD3^+$ with an increased CD8/CD4 ratio of 1:1.

negative for lymphoma and were thought to represent a granulomatous and inflammatory process.

After an extensive workup to exclude malignancy, CPL secondary to phenytoin was suspected, although phenobarbital as the offending agent could not be excluded. Both phenobarbital and phenytoin were discontinued, and the patient was started on levetiracetam, 1000 mg twice a day, with effective control of his epilepsy. Doxycycline, 100 mg twice a day, topical triamcinolone 0.1% ointment, and oral prednisone, 80 mg/d, were initiated and was slowly tapered over 7 months with close monitoring of the patient's clinical response. Significant improvement was seen after 1 to 2 months of therapy followed by near-complete resolution 7 months after treatment initiation.

CASE 2

A 54-year-old man presented to an outside institution with an erythematous eruption, fever, facial swelling and diffuse lymphadenopathy (Fig 2, *A*). A generalized rash had started just before hospitalization, and a skin punch biopsy showed findings consistent with a drug reaction. Laboratory studies found leukocytosis, transaminitis, hyperbilirubinemia, and hypereosinophilia (6.2 mg/L). The patient had acute, progressively worsening renal failure, transaminitis, hyperbilirubinemia, and disseminated intravascular coagulopathy. He was eventually transferred to the intensive care unit where he required hemodialysis. Imaging found fluorodeoxyglucose-avid lymphadenopathy. Left inguinal lymph node biopsy found atypical lymphocytes, histiocytes, and plasma cells with frequent mitotic figures and apoptotic bodies. There was no evidence of monoclonality on gene rearrangement, but because there were larger lymphocytes with prominent nucleoli, open chromatin pattern, and amphophilic cytoplasm on the lymph node biopsy, anaplastic lymphoma kinase–negative anaplastic large cell lymphoma was diagnosed, and the patient reported that he was told he had a poor prognosis. Two rounds of chemotherapy, including cyclophosphamide followed by doxorubicin and vincristine, as well as steroids, were given before transfer to our institution for further management of the lymphoma.

At our institution, the dermatology service was consulted for a rash. On our initial examination, there was a mild, resolving morbilliform eruption. Punch biopsy found a vacuolar interface dermatitis consistent with a drug eruption (Fig 2, *B*). Rosuvastatin therapy initiated 1 month before presentation to the outside hospital was elicited on further questioning. No other medications or supplements had been started for several years before patient's onset of the rash. Given this medication history, DRESS syndrome was highly suspected. We calculated a RegiSCAR score of 8 (definite DRESS) based on his workup done at the outside hospital (fever, enlarged lymph nodes, eosinophilia, skin rash >50% body surface area, biopsy consistent with DRESS, >2 organs involved, and resolution delay >15 days). The likelihood of DRESS syndrome and lymphoma starting at the exact same time seemed very unlikely, which prompted multiple discussions

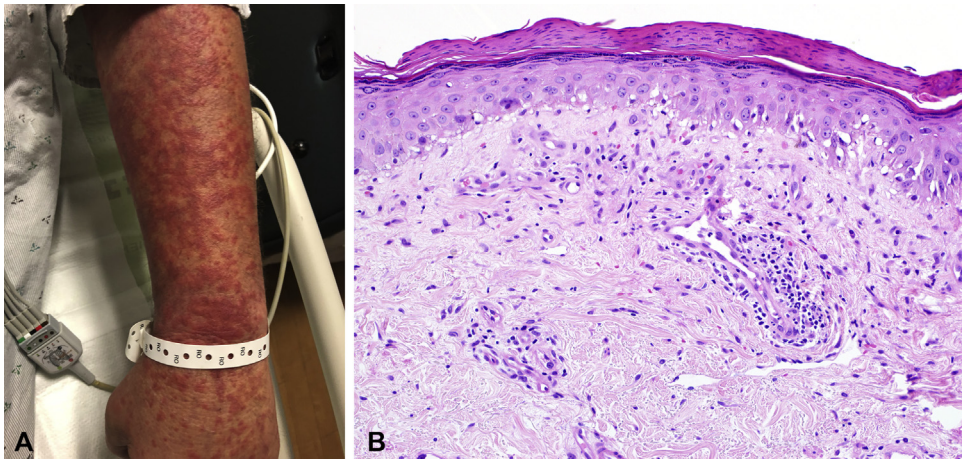

Fig 2. A, On initial presentation to an outside hospital, there were scattered purpuric and petechial lesions on the upper and lower extremities with an erythematous, morbilliform eruption on the trunk (not pictured). **B**, At our institution, punch biopsy of a scaly macule on the right forearm found a vacuolar interface dermatitis with foci of parakeratosis. There also were superficial perivascular lymphocytic infiltrates containing eosinophils with extravasated red blood cells. (Original magnification: ×100.)

with the hematology/oncology team. The hematology/oncology team eventually confirmed that there was no evidence of systemic lymphoma on re-examination of the patient's bone marrow and lymph node biopsies. Bone marrow biopsy re-examination found no evidence of lymphoma, and T-cell receptor γ and β gene rearrangement tests were negative. A reread of the lymph node biopsy results also found no definitive evidence of lymphoma. No further chemotherapy treatments were given at our institution. The patient was treated with prednisone, 60 mg/d, which was slowly tapered over 7 months, with close monitoring of his laboratory values and symptoms. He had normalization of laboratory values, including eosinophils, creatinine, liver transaminases, and urinalysis within 2 months of presentation to our institution.

DISCUSSION

In anticonvulsant-induced pseudolymphoma, histopathology of lymph nodes may mimic lymphoma, with features including atypical lymphoid hyperplasia, focal necrosis, and destruction of lymph node architecture by eosinophilic and histiocytic infiltrates; however, resolution of lymphadenopathy occurs after cessation of the offending drug.[3] Similarly, cutaneous histopathology mimics lymphoma with a band-like to superficial and deep lymphoid infiltrate, frequent epidermotropism, and lymphocyte atypia. Eosinophils and sometimes histiocytes and granulomas may be present. Anticonvulsant-induced pseudolymphomas are well known but have not been reported to occur after decades of use and are usually more mild in presentation.[1,4] The most common drugs implicated in pseudolymphoma include anticonvulsants, calcium channel blockers, antidepressants, H1 and H2 antagonists, statins, and angiotensin converting enzyme inhibitor.[1]

DRESS syndrome can occasionally mimic lymphoma, and, conversely, acute onset of lymphoma can mimic DRESS syndrome.[5,6] Although statins have not been reported to cause DRESS-like pseudolymphoma, they have been implicated in the causation of DRESS syndrome occasionally.[7] The most common drugs implicated in DRESS include sulfonamides, minocycline, dapsone, vancomycin, tyrosine kinase inhibitors, anticonvulsants (eg, lamotrigine, carbamazepine, phenytoin), febuxostat, and allopurinol.[1] An expanded T-cell population on bone marrow biopsy, seen in cutaneous T-cell lymphomas, can also occur in DRESS syndrome.[5] Neither patient was rechallenged with either medication due to the serious nature of the initial reactions.

These cases highlight the difficulty in distinguishing between severe drug reactions, including cutaneous pseudolymphoma and DRESS syndrome from true cutaneous or systemic lymphoma. Differentiation must be based on careful examination of clinical and histopathologic findings (Fig 3).[3] Close follow-up is warranted, as cases of pseudolymphoma have rarely been reported to progress to lymphoma.[2]

CPL and severe hypersensitivity reactions must be carefully excluded before rendering a definitive

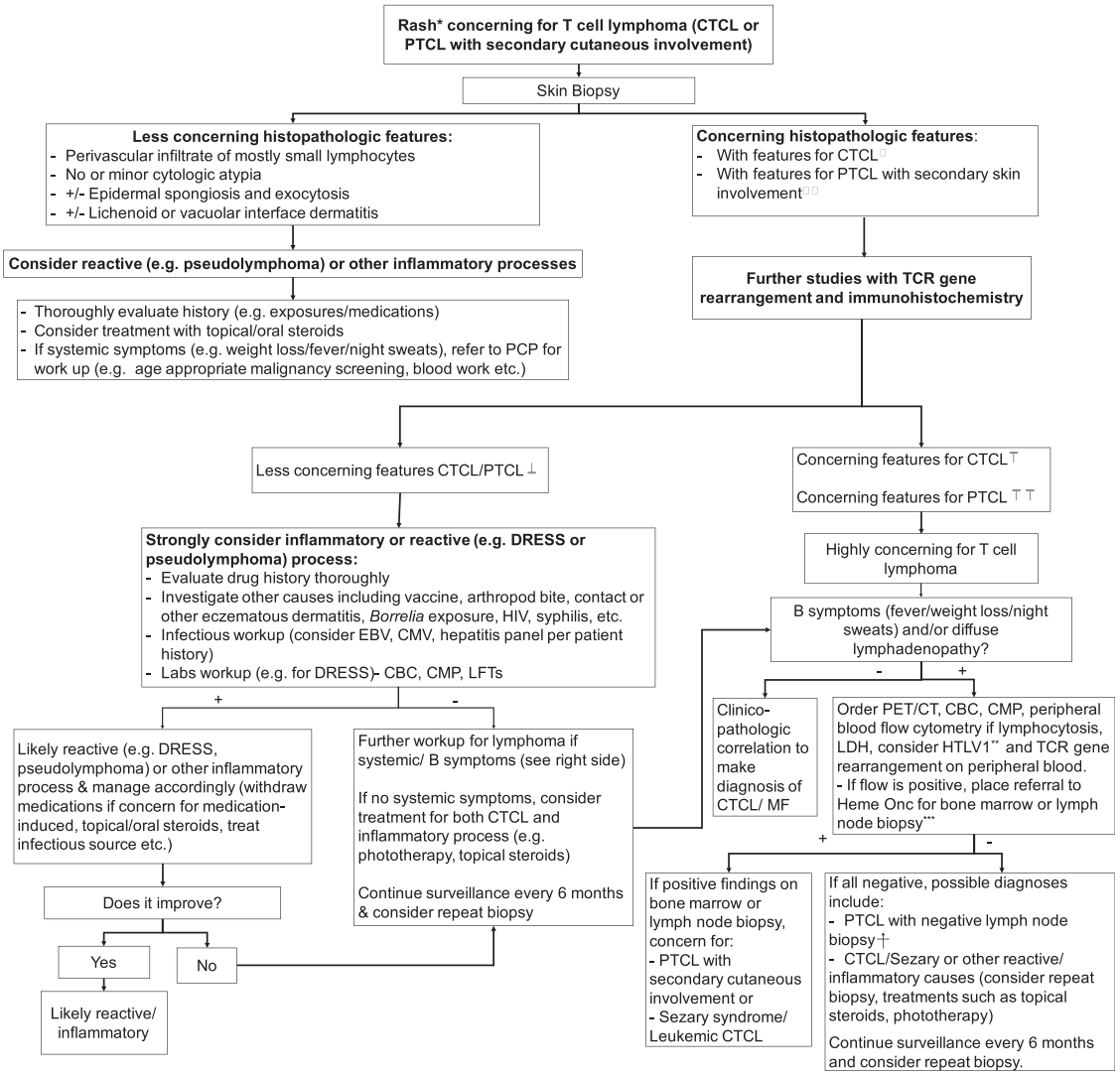

Figure Legend:

* For CTCL, clinical features of rash include persistent and/or progressive patches, plaques, nodules, tumors and erythroderma; more concerning clinical features for MF include non-sun exposed location, size/shape variation and poikiloderma. Rash may also be morbilliform or cutaneous-lymphoma like

□ **Concerning histopathologic features for cutaneous T-cell lymphoma**: Atypical lymphoid cells with irregular nuclear contours, enlarged nuclei, nuclear hyperchromasia (may be few in number); positive epidermotropism; absent spongiosis with a passive epidermis; folliculotropism; syringotropism. Sezary syndrome may show subtle or non-diagnostic histopathologic features. If Sezary syndrome is clinically suspected, immunohistochemical and gene rearrangement studies may be helpful in the absence of overt histopathologic features of T-cell lymphoma.

□□ **Concerning histopathologic features for PTCL with secondary skin involvement:** Many patterns are possible; may see atypical, enlarged lymphoid cells, often replacing much of the dermis and subcutis

⊥ **Less concerning features for CTCL/PTCL on immunohistochemistry/TCR gene rearrangement**: T-cells retain expression of CD2, CD5, CD7. Mixed T-cell infiltrate with no marked predominance of CD4+, CD8+ or CD4-/CD8- T-cells (the CD4:CD8 is often ≤ ~4-5:1; sometimes CD8+ epidermal cells predominate in reactive processes such as drug reactions, pityriasis lichenoides, etc); Polyconal; Negative TCR gene rearrangement

⊤ **Concerning features for CTCL on immunohistochemistry/TCR gene rearrangement**: Loss or dim expression of CD2, CD5, CD7, CD3; CD4:CD8 ≥~7-10:1 (rare cases may be CD8+, or CD4-/CD8-); Monoclonal; positive TCR gene rearrangement, >1 anatomic site with same T-cell clone (different sites on skin, bone marrow, lymph node and/or blood)

⊤⊤ **Concerning features for PTCL with secondary skin involvement on immunohistochemistry/TCR gene rearrangement**: Loss or dim expression of CD2, CD5, CD7, CD3; with a predominance of CD4 (rare cases may be CD8+, or CD4-/CD8-); Monoclonal; positive TCR gene rearrangement, >1 anatomic site with same T-cell clone (different sites on skin, bone marrow, lymph node and/or blood)

** Get Human T-lymphotrophic Virus Type I (HTLV1) labs in populations for which HTLV-1 is endemic (e.g. Japanese, Caribbean)

*** Under NCCN guidelines, bone marrow biopsy is useful in selective cases with unexplained hematologic abnormalities

† Sometimes, lymph node biopsy can be negative due to partial treatment (e.g. steroid); in such case, repeat lymph node biopsy may be needed

Fig 3. Flowchart guideline on how to approach a rash concerning for T-cell lymphoma as a dermatologist.

diagnosis of cutaneous lymphoma. Dermatologic hospital consultation is invaluable in the evaluation and correct diagnosis of these patients to avoid serious overtreatment, including chemotherapy.

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