

# Lymphomatoid Drug Reaction Secondary to Methylphenidate Hydrochloride

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*Lymphomatoid drug reactions are relatively rare, with no gender, race, or age predilection. The condition generally may be divided into 2 broad categories with some overlap: (1) drug-induced pseudolymphoma and (2) anticonvulsant-induced pseudolymphoma syndrome, marked by the triad of papular to nodular skin lesions, fever, and lymphadenopathy. While a vast array of pharmacologic agents has been linked to lymphomatoid drug reactions, our case represents the first reported incidence of methylphenidate hydrochloride—a ubiquitously prescribed medication for attention deficit hyperactivity disorder—causing a pseudolymphoma.*

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## Case Report

A 22-year-old Chinese woman with a medical history of attention deficit disorder presented with a 4-month complaint of recurrent, mildly pruritic crops of painless lesions generally localized to the face and proximal upper extremities. Prior to each eruption, the patient developed a fever (maximum fever, 104°F [40°C]). The patient had begun methylphenidate hydrochloride for her attention deficit disorder in October 2005, but the drug was discontinued by her psychiatrist 2 months later secondary to periodic spiking fevers. Methylphenidate hydrochloride was reinstated in January 2006 but summarily discontinued in late February 2006 because of the development of her rash. She denied any further systemic symptoms

(ie, no chills, weight loss, night sweats), allergies, or unusual travel history.

Examination revealed few erosions and excoriated 0.2-cm pink papules on the scalp, as well as multiple 0.2- to 0.6-cm indurated, red, excoriated papulonodules (few with central crust) on the face, right upper arm, and right buttock. There was no palpable lymphadenopathy. At follow-up, the scalp erosions had healed and there was no visible crusting or excoriation, but the patient continued to manifest multiple 0.2- to 0.6-cm indurated, red, excoriated papulonodules on the face (Figure 1) and bilateral upper arms (Figure 2).

Laboratory workup consisting of a complete blood count with peripheral smear, complete metabolic panel, lactate dehydrogenase, serum/urine protein electrophoresis, and computed tomographic scan was essentially negative.

A 4.0-mm punch biopsy from the patient's right arm revealed an intense perivascular infiltrate of mononuclear cells (Figure 3) admixed with a population of cells that contained fragmented nuclear material (Figure 4). There were rare CD20<sup>+</sup> and CD56<sup>+</sup> cells; CD45 cells showed diffuse positive staining within the infiltrate, with many CD68<sup>+</sup> and CD43<sup>+</sup> cells. Myeloperoxidase was markedly positive, especially in cells with fragmented nuclear material, and lysozyme showed a similar staining pattern. The stain for Epstein-Barr virus and CD30 was essentially negative, while most of the cells were beta-1 positive. The biopsy also showed equal numbers of cells positive for CD4 and CD8.

A diagnosis of lymphomatoid drug reaction was made, and upon final discontinuation of the drug in February 2006, the patient reported a slow resolution of existing nodules with no additional lesions or fever.

## Comment

Over the past 2 decades, the US Drug Enforcement Administration production quotas for methylphenidate hydrochloride have undergone a 6-fold increase.<sup>1</sup>

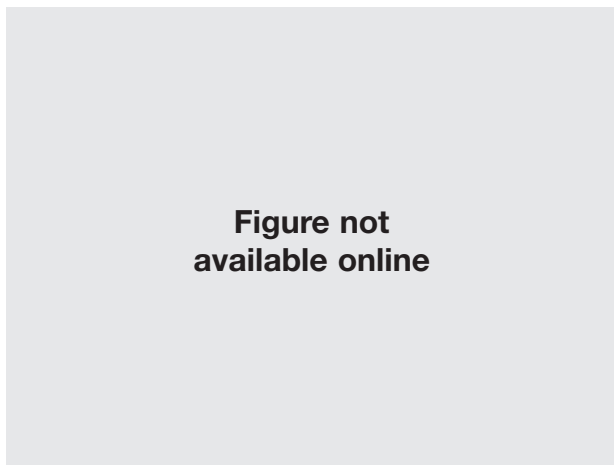
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The authors report no conflict of interest.

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**Figure not available online**

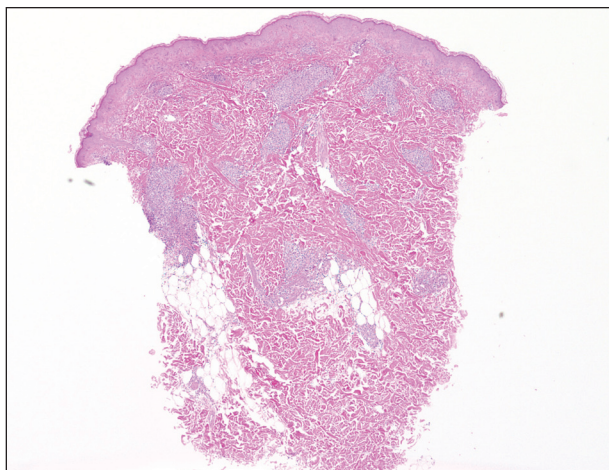
**Figure 1.** Multiple 0.2- to 0.6-cm indurated, red, excoriated papulonodules on the face.



**Figure 2.** Papulonodules (few with central crust) on the right upper arm.

With approximately 1.5 million Americans aged 5 to 18 years (2.8% of the population)<sup>1</sup> and a similar percentage of their Canadian counterparts on methylphenidate hydrochloride, it is obvious that this pharmacologic option has become the preferred treatment modality for attention deficit hyperactivity disorder.<sup>1,2</sup> While attention deficit hyperactivity disorder is the most common psychiatric syndrome in the pediatric population, many adults also are turning to the medication as a means of ameliorating symptoms associated with the condition, such as difficulty concentrating. The medication also has garnered media attention as a large number of college students have been illicitly using the drug as a stimulant and study aid. Given the increased prevalence of methylphenidate hydrochloride, it is important for all physicians to be aware of its potential adverse effects.

Case reports and information in postmarketing research link methylphenidate hydrochloride with

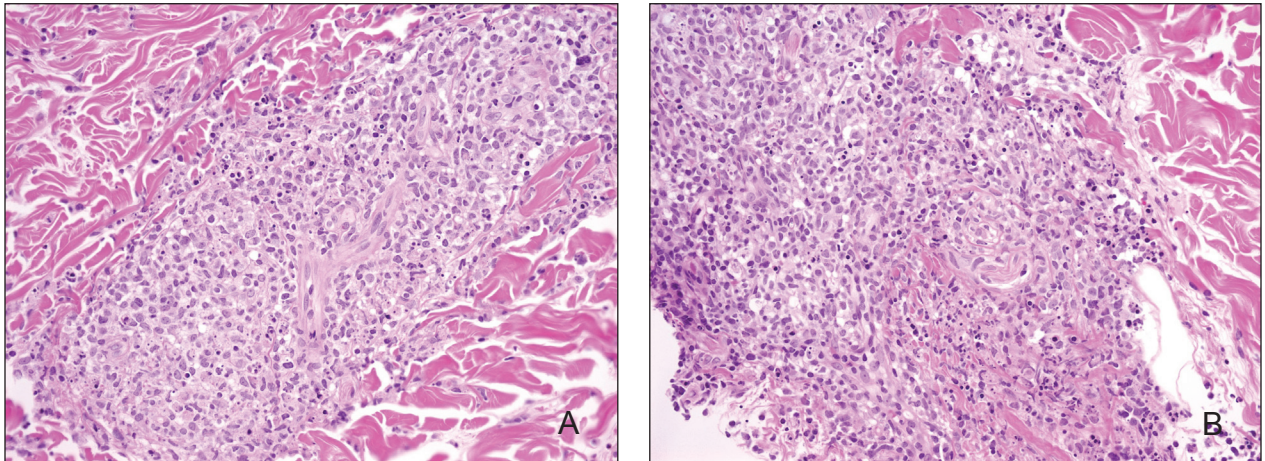


**Figure 3.** Punch biopsy revealed an intense nodular perivascular infiltrate of mononuclear cells (H&E, original magnification  $\times 10$ ).

both a hypersensitivity syndrome marked by fever and rash, most frequently urticaria or erythema multiforme, and fixed drug eruption, but there is no reported incidence of the drug causing a lymphomatoid variant.<sup>3,4</sup>

Clinically, lymphomatoid drug reactions may present with variable morphology, from a solitary plaque to widespread nodules to Sézary-like erythroderma.<sup>5,6</sup> Histologically, these reactions reveal an atypical infiltrate of lymphocytes in the dermis, which is most often bandlike or nodular. The infiltrate contains atypical cerebriform nuclei and is frequently accompanied by a substantial histiocytic component, especially in the nodular lesions, as well as a relative absence of eosinophils or plasma cells.<sup>7</sup> The lymphomatoid reaction pattern has been seen with a vast array of pharmacologic agents. A review of the literature has been summarized in the Table.<sup>8-18</sup>

While debate has historically raged as to whether drug-induced pseudolymphoma and hypersensitivity syndrome were 2 distinct clinical entities or merely the same condition existing on a spectrum, studies have shown them to be separate conditions. Callot et al<sup>19</sup> revealed that patients with drug-induced pseudolymphoma possessed subacute, papulonodular, infiltrated plaques, without visceral involvement, that histologically mimicked lymphoma and resolved with discontinuation of the offending medication. In contrast, the researchers' patients with hypersensitivity syndrome had a widespread eruption with fever, palpable lymphadenopathy, and multivisceral involvement, including hepatitis, lymphocytosis, eosinophilia, and elevated lactate dehydrogenase, as well as variable nonspecific histology that only occasionally simulated lymphoma and frequent relapses upon cessation of the drug.<sup>19</sup> Our case, therefore, is



**Figure 4.** Infiltrate composed of mononuclear cells admixed with cells that contained fragmented nuclear material; immunohistochemistry was negative for lymphoma (H&E, original magnification  $\times 40$  for both)(A and B).

### Reported Etiologic Causes of the Lymphomatoid Drug Reaction<sup>8-18</sup>

Drug Class	Implicated Etiologic Agents
Antiarrhythmics	Mexiletine, procainamide hydrochloride
Antibiotics	Cefuroxime, dapsone, nitrofurantoin, penicillin
Anticonvulsants	Butobarbital, carbamazepine, ethosuximide, lamotrigine, mephenytoin, methsuximide, phenobarbital, phensuximide, phenytoin, primidone, sodium valproate, trimethadone
Antidepressants	Amitriptyline hydrochloride, bupropion hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, lithium
Antifungal	Griseofulvin
Antihistamines	Cimetidine, diphenhydramine hydrochloride, ranitidine
Antihypertensives	ACE inhibitors, atenolol, clonidine hydrochloride, diltiazem hydrochloride, labetalol hydrochloride, losartan, thiazides, verapamil
Antimetabolites	Cyclosporine, methotrexate
Antipsychotics	Phenothiazines
Antirheumatics	Allopurinol, D-penicillamine, gold, NSAIDs
Miscellany	Bromocriptine, hydroquinone, lovastatin, menthol, silicone
Sex hormones	Estrogen, progesterone
Vaccines	Hepatitis A and B

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.



best classified as a methylphenidate hydrochloride–induced pseudolymphoma, though the patient did have spiking fevers.

Lymphomatoid drug reactions are uncommon. There is no gender, race, or age predilection. Symptoms may occur anywhere from weeks to months after exposure to the offending agent and generally resolve spontaneously after weeks to months upon discontinuation of the drug. However, several cases of malignant transformation (pseudopseudolymphoma) do exist; thus, patients should be monitored for the development of true malignancy, especially those cases secondary to anticonvulsants.<sup>5</sup>

While our patient's clinical and histologic presentation had features consistent with lymphoma, the diagnosis of methylphenidate hydrochloride–induced pseudolymphoma was largely based on the resolution of the patient's lesions with discontinuation of the offending agent and negative workup. The other helpful clue in this patient that mitigated against the diagnosis of a true lymphoma was the presence of a mixed cellular infiltrate on histology that included not only lymphocytes but also histiocytes and neutrophils. Our case emphasizes the need to always consider a drug-related reaction, even in patients on a medication such as methylphenidate hydrochloride with few reported cutaneous adverse effects.

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