Case Report

Lamotrigine-related pseudolymphoma presenting as cervical lymphadenopathy

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Abstract

Immune-mediated drug reactions are a potentially life-threatening complication of antiseizure medications. Drug hypersensitivity syndrome (DHS) is the best recognised of these, presenting with fever, eosinophilia, rash and internal organ involvement. Isolated lymphadenopathy is a less recognized immune-mediated reaction to antiseizure drugs such as lamotrigine. We describe the case of a 24-year-old woman who developed lamotrigine-related bilateral cervical lymphadenopathy (pseudolymphoma) fifteen months following therapy initiation. This is the second such case reported in the medical literature.

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1. Introduction

Lamotrigine is a triazine-derived antiseizure drug which acts to stabilize neuronal membranes through inhibition of voltage-sensitive sodium and calcium channel opening. Drug reactions are an important consideration when prescribing this medication. Skin rashes are a worrisome side-effect, as they may signal the development of Stevens–Johnson syndrome, toxic epidermal necrolysis, or drug hypersensitivity syndrome (DHS). A less common, and less recognised reaction to lamotrigine is the development of localized lymphadenopathy (pseudolymphoma) without systemic features or rash. In contrast to DHS and severe cutaneous adverse reactions, which happen within weeks of therapy initiation, drug-induced pseudolymphoma often occurs months after initiation. In patients taking lamotrigine and other antiseizure drugs, clinicians should consider drug reactions in the differential diagnosis of isolated lymphadenopathy, especially in the setting of peripheral blood eosinophilia.

2. Case report

A 24-year-old Sri Lankan woman with drug resistant focal dyscognitive seizures experienced daily seizures despite treatment with carbamazepine 800 mg twice daily and clonazepam 2 mg twice daily. She was on no other medication and otherwise well. Lamotrigine was started with the aim of improving seizure control and slowly titrated to a dose of 150 mg in the morning and 200 mg in the evening over a period of 6 months. Her seizure frequency reduced.

Fifteen months after initiation of lamotrigine, she complained of productive cough with yellow sputum. She was afebrile. Chest examination was normal. Lymphadenopathy was detected in the right cervical chain. Other lymph nodes, tonsillar tissue and spleen were of normal size. Spirometry was within normal limits. High resolution CT chest and neck showed extensive bilateral cervical lymphadenopathy and patchy ground-glass nodules in multiple lobes but no intrathoracic adenopathy. Full blood count, serum chemistries, as well as testing for rheumatoid factor, anti-citrullinated peptide antibodies, antinuclear antibodies, human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, toxoplasma and tuberculosis were all normal or negative. Erythrocyte sedimentation rate and C-reactive protein were elevated at 95 mm/h (normal < 23 mm/h) and 16 mg/L (normal < 5 mg/L) respectively. Histology of an excisional lymph node biopsy showed reactive follicular hyperplasia with capsular thickening without malignancy or granuloma. A review of prior blood testing revealed intermittent low-grade eosinophilia since introduction of lamotrigine (see Table 1). A diagnosis of lamotrigine-related pseudolymphoma was made. Lamotrigine was gradually withdrawn and her lymphadenopathy and pulmonary findings (which also likely represented a medication toxicity) have resolved.

3. Discussion

Lamotrigine is an antiseizure drug which acts through voltage-sensitive sodium and calcium channels to reduce the release of excitatory neurotransmitters. Cutaneous adverse reactions are the most feared complication of therapy, because the presence of a rash can herald the development of devastating complications such as Stevens–Johnson syndrome, toxic-epidermal necrolysis or a drug-hypersensitivity reaction.
syndrome (DHS). Localised lymphadenopathy without systemic symptoms (pseudolymphoma) is a much less appreciated complication of therapy.

Both drug-induced pseudolymphoma and DHS represent immune reactions to medications, but differ greatly in their time-course, clinical manifestations and treatment [1]. The most commonly implicated medications are antiseizure drugs such as phenytoin, carbamazepine and lamotrigine, but also allopurinol, antidepressants and some antihypertensive medications [2].

Pseudolymphoma may present with isolated lymphadenopathy, cutaneous lesions or both [1,3]. The presence of systemic features and internal organ dysfunction is unusual and onset is generally weeks to months following therapy initiation [1,3]. Localised lymphadenopathy secondary to lamotrigine has been reported once previously [3]. In this case, as in ours, the cervical nodes were involved. The pathogenesis of this reactive ‘pseudolymphoma’, which can be B-cell, T-cell or mixed-type is incompletely understood. As in this case, medication withdrawal is generally all that is necessary to treat the condition [1,3].

In contrast, DHS (also known as drug reaction with eosinophilia and systemic symptoms [DRESS]), a well-recognised complication of antiseizure drug treatment, is characterised by a maculopapular rash, fever, leukocytosis and internal organ involvement [4]. Onset is more acute than pseudolymphoma, beginning in the first few weeks following therapy initiation. Treatment with immunosuppressive drugs, intravenous immunoglobulin and/or plasma exchange is often necessary, especially in severe cases.

Clinicians should consider drug reactions when assessing patients with localised lymphadenopathy. Drug initiation may have taken place weeks to months prior to the onset of symptoms. In our case, lamotrigine was likely the offending medication, though in both reported cases of lamotrigine-related pseudolymphoma (ours and one other previous case), patients were concurrently taking carbamazepine, a medication whose effective plasma concentration may be increased by lamotrigine [3,5]. Intermittent or low-grade eosinophilia may be a clue to the diagnosis. Discontinuation of the offending drug (e.g. lamotrigine) in these cases can lead to resolution of clinical symptoms.

References

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