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Case Report

A case of mycosis fungoides-like lesions developing after levetiracetam therapy

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ABSTRACT

Levetiracetam is a relatively new antiepileptic drug that has previously not been associated with severe dermatological side effects. We report the case of a 31-year-old male treated with levetiracetam for seizures who subsequently developed a mycosis fungoides-like drug reaction that resolved upon dosage reduction.

1. Introduction

Levetiracetam (LEV) is a new antiepileptic drug that is effective in adults and children with partial-onset seizures or idiopathic or symptomatic generalized seizures. Levetiracetam is a derivative of S-enantiomer pyrrolidone and is chemically similar to piracetam, preventing excitatory or inhibitory neurotransmitters from binding to the receptor. The effects of LEV on high-voltage neuron-specific Ca^{2+} influx through Ca^{2+} channels, gated GABA, and glycine are suggested to inhibit or reverse currents. Na^{+} or T-type Ca^{2+} does not have an effect on the channels. Levetiracetam-related side effects were observed at a rate of 17.2–51.3% and usually occurred within the first 5 months of treatment [1]. Central nervous system side effects are the most common side effects but are usually mild; other common side effects are irritability, drowsiness, and dizziness [2].

Antiepileptic drug-induced skin reactions, most commonly with phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), phenobarbital (PB), lamotrigine (LTG), and zonisamide (ZNS) and sometimes with pyrimidione, valproic acid (VPA), topiramate (TPM), gabapentin (GBP), tiagabine (TGB), and LEV are rarely reported [3].

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma characterized by the malignant proliferation of T cells with phenotypic and functional properties of T-helper cells [4]. The etiology of this uncommon lymphoma is unknown. Genetic, infective, and environmental causes have all been implicated. Most patients have a severe course of the disease. Therefore, treatment should provide optimal benefits while minimizing toxicity as much as possible. Mycosis fungoides is a low-grade lymphoproliferative disorder caused by CD4+ lymphocytes [5]. Mycosis fungoides-like skin reactions resulting from PHT, CBZ, and OXC have been previously reported in the literature.

We report the case of a patient who was taking the anticonvulsant drug levetiracetam and in whom skin lesions developed that showed histological features suggestive of mycosis fungoides.

2. Case

A thirty-one-year-old male patient presented at Uludag University Medical Faculty Department of Neurology Epilepsy Clinic with generalized seizures. Once asleep, the patient, who had no history of systemic diseases, was given JTKN twice in a 10-month period. After neurological examination, routine blood tests, and MRI (Fig. 1) of the patient, all of which were normal, LEV (500 mg/day) was started. During the wakefulness and sleep portions of the patient's EEG, left frontal theta- and sharp-wave activities were observed (Fig. 2). Approximately 2 months after LEV initiation, a pale, pinkish, macular erythema with unclear borders was observed at the sides of the abdomen (Fig. 3).

On physical examination, there was no cervical lymphadenopathy or hepatomegaly. Laboratory test results revealed no peripheral blood eosinophilia, normal renal and liver enzymes, and negative vasculitic parameters (ANA, anti-nDNA). A skin punch biopsy revealed mild infiltration of perivascular mononuclear inflammatory cells in the dermis. Immunohistochemical staining was positive for CD3–CD4–CD7 and CD8 lymphocytes (Figs. 4a–d). Mycosis fungoides, as a reaction to

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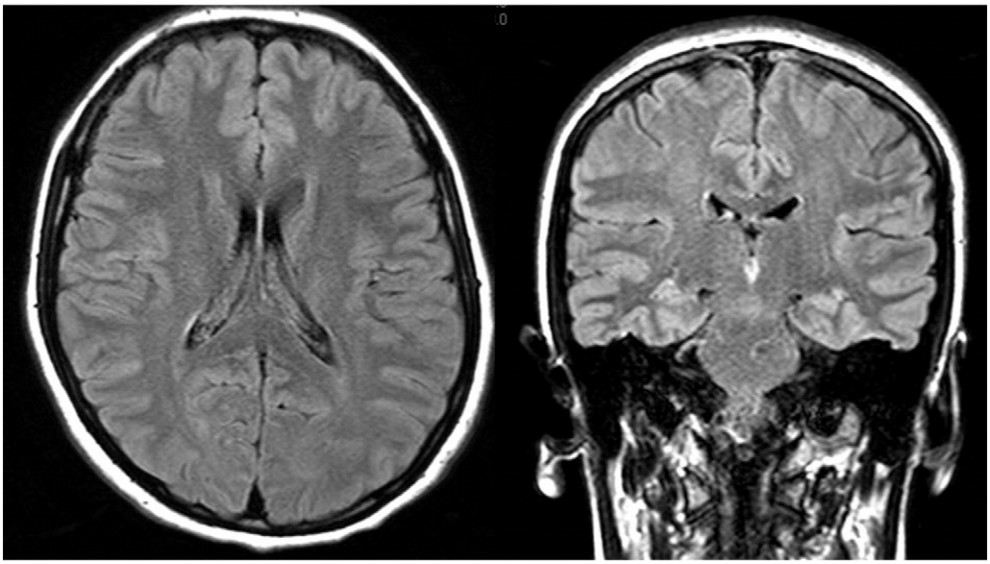

Fig. 1. Cranial MRI was unremarkable.

drug administration, was thought to be the cause. The patient recovered by reducing his dosage of LEV and of other medications capable of causing rare skin reactions; the patient was subsequently started on VPA 500 mg/day p.o.

We concluded that a mycosis fungoides-like drug reaction was the cause. The patient recovered by reducing his dosage of LEV and of other medications capable of causing rare skin reactions; VPA and topical corticosteroid treatments were started. The patient was seizure-free and recovered from the skin lesions.

3. Discussion

Although antiepileptic drug-induced skin reactions, including maculopapular rash, are very rare, cases such as Stevens–Johnson

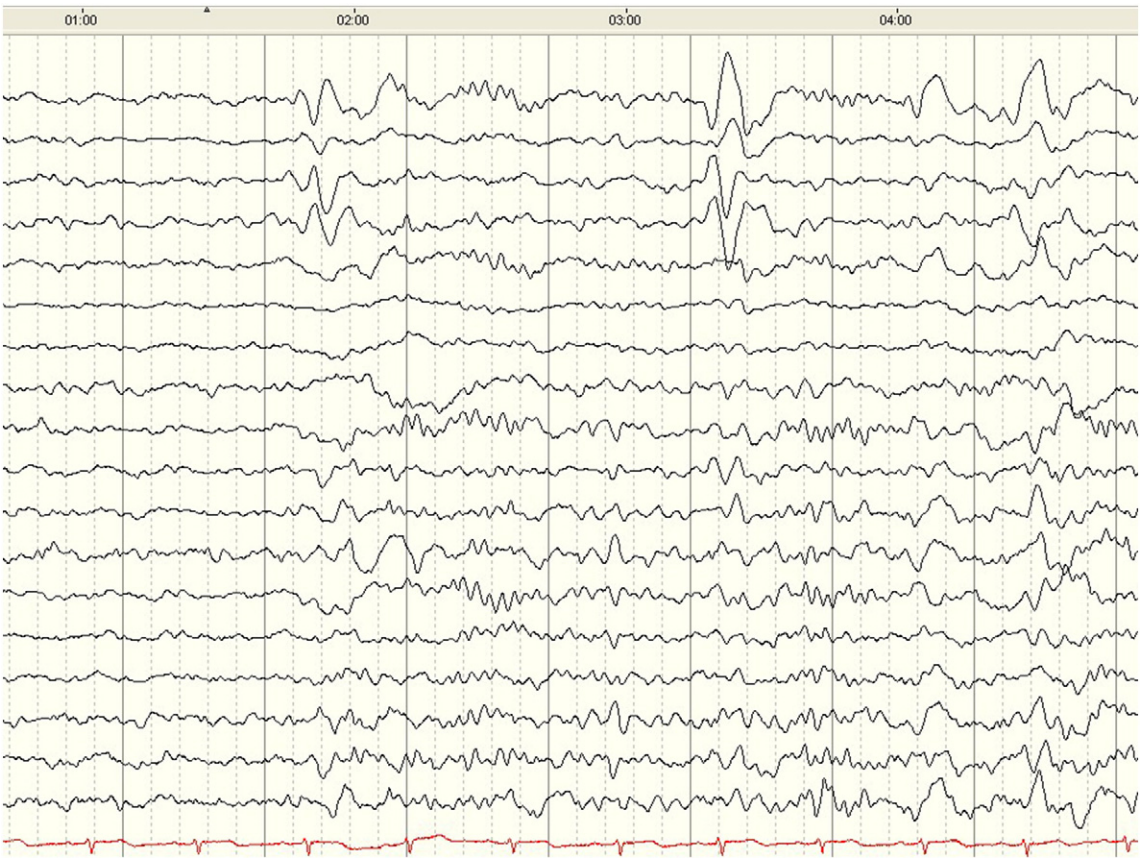

Fig. 2. Spike–wave and theta activities were observed over the left frontotemporal area in the EEG.

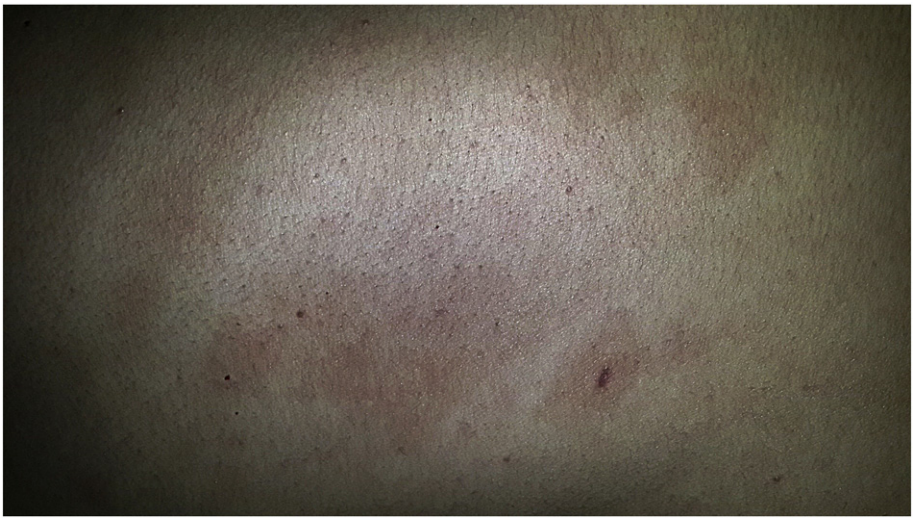

Fig. 3. Abdomen with pale, pinkish, macular, erythematous borders.

syndrome and toxic epidermal necrosis have been reported. Mycosis fungoides is a peripheral non-Hodgkin's T-cell neoplastic process, representing the most common type of primary cutaneous malignant lymphoma. Anticonvulsant-induced pseudolymphomas usually develop within 2 to 8 weeks of drug use. Although skin lesions usually resolve within 3 to 4 weeks after discontinuing the offending agents, long-term follow-up is needed to assure the absence of lymphoproliferative malignancy [6]. Our patient developed a pale, pinkish, erythematous, macular lesion on both sides of the abdomen approximately 3 months after LEV initiation.

There are two main groups of drug-induced pseudolymphomas: those that clinically and histological simulate cutaneous lymphomas and those known as hypersensitivity syndromes. Pseudolymphomas cannot be differentiated from true lymphomas through clinical, pathological, or molecular findings. A definitive test for diagnosis is the resolution of the lesions after the medication involved is suspended [7].

Mycosis fungoides-like skin reactions to PHT, PB, CBZ, and OXC have been previously reported in the literature. Rosenthal et al. reported patients showing histological features suggestive of MF who were taking the anticonvulsant drug diphenylhydantoin [8]. After using LEV, our patient, upon histopathological examination, exhibited mild perivascular mononuclear inflammatory cells in the papillary dermis suggestive of an anticonvulsant-induced pseudolymphoma. Clinical and histopathological differential diagnosis included skin manifestation of connective tissue diseases. However, a detailed history along with dermatological examinations failed to reveal a connective tissue disease.

The choice of treatment for patients with MF varies depending on the stage involved and the site of the lesions. Treatment should be considered in all patients, irrespective of staging, as it has been shown to improve the prognosis even in the early stage of disease [9]. PUVA, topical nitrogen mustard, and topical corticosteroids are the main options for early-stage disease. The patient was diagnosed with a drug-induced pseudolymphoma, and topical corticosteroid therapy was initiated.

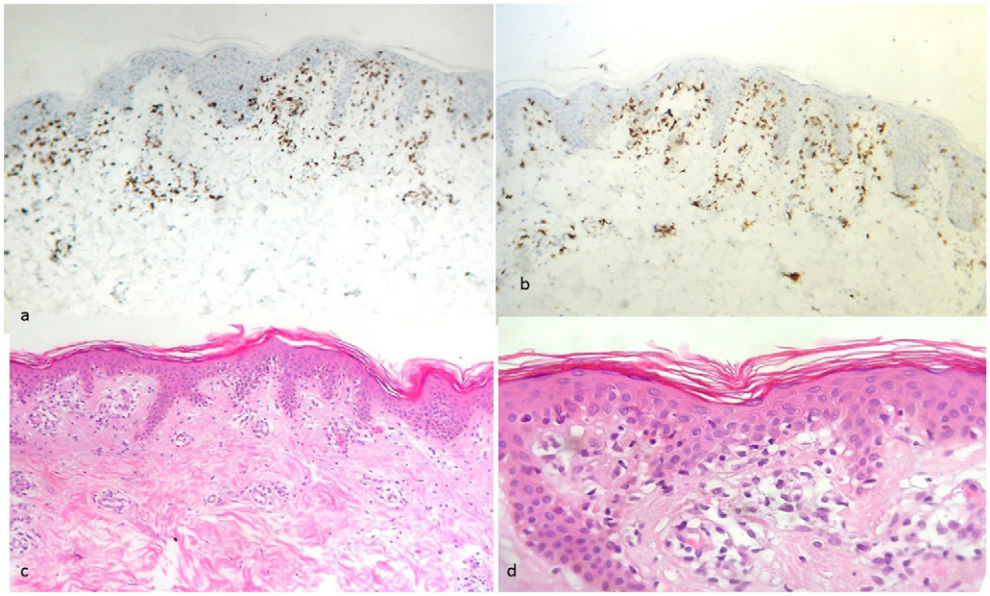

Fig. 4. a–d. Immunohistochemical staining was positive for CD3–CD4–CD7 and CD8 lymphocytes.

Antiepileptic drugs, especially PHT and CBZ, can produce pseudolymphoma, and PHT, CBZ, and OXC can induce MF-like skin reactions. Mycosis fungoides-associated pseudolymphoma was first mentioned in the literature in 1982 as a result of the use of diphenylhydantoin [8] and has been referred to by different names, such as, in 1985, phenytoin-related MF-like lesions and, in 1997, also caused by phenytoin, pseudomycosis fungoides syndrome. In recent years (1990 and 2001), in cases of CBZ use, MF-associated pseudolymphoma has been referred to as mimicking mycosis fungoides; in 2003, it was termed pseudomycosis fungoides [10–14].

In 2011, Navarro and his colleagues reported a 45-year-old female patient who used OXC for 2 months and developed a mycosis fungoides-like syndrome, as evidenced by a skin biopsy [15].

4. Conclusions

In our case, cutaneous lesions were evaluated by a dermatologist after approximately 3 months of taking LEV. After making the differential diagnosis of MF disease, it was decided that it was compatible with MF histopathologically. It has been observed in the literature that drugs such as CBZ, OXC, PHT, and PB have an MF-like impact mechanism. However, our case involved LEV, which is a different drug than those referenced in the literature.

There have been no prior reported cases of MF-like disease associated with LEV. We think that this could be the first appearance in the literature of MF-like disease associated with LEV and a different mechanism of action that causes an MF-like skin reaction.

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