Drug induced pseudolymphoma secondary to ethosuximide

Ethosuximide is an antiepileptic succinimide, widely used in the treatment of absence seizures. Haemopoietic complications associated with the administration of this drug have included leucopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and eosinophilia.¹ We report a patient with pseudolymphoma induced by ethosuximide, a complication never reported previously.

Case report

A 12 year old boy presented with a two months history of fever, weight loss (3 kg), and non-painful swellings on the neck, axillae, and both inguinal regions. The patient had been on ethosuximide for three months for childhood absence epilepsy. It was being given at a dose of 30 mg/kg/day, in three divided doses, and the seizures had been under reasonable control.

Physical examination on presentation revealed enlarged lymph nodes on the both sides of the neck, axillae, and inguinal regions. All the nodes were non-tender, firm, measuring 1 to 2 cm in diameter, and freely mobile. The liver and spleen were not palpable and all other systems were normal.

A full blood count revealed a leucopenia of $3.6 \times 10^3/\mu\text{l}$ (48% neutrophils, 3% eosinophils, 40% lymphocytes, and 9% monocytes) and a decreased platelet count of $119.0 \times 10^3/\mu\text{l}$. Studies for serological markers revealed no acute or chronic infection with cytomegalovirus, Epstein-Barr virus, herpes simplex virus, or toxoplasmosis.

An excisional biopsy of a 2 cm cervical node was done. Frozen section diagnosis was consistent with lymphoma. Permanent sections showed a diffuse polymorphic lymphoid hyperplasia with effacement of the normal architecture; there was an admixture of lymphoid cells, including small and large lymphocytes and plasma cells (fig 1). Leucocyte phenotyping, using the ABC immunohistochemical method, showed heterogeneous T cell and B cell populations: T cell subsets included CD45RO and CD30. B lymphocyte markers included CD20.

One day after ethosuximide discontinuation the fever disappeared. The lymph nodes were noticed to have decreased in size on the second week and completely regressed on the end of the second month. The leucocyte and platelet counts normalised after two weeks of ethosuximide withdrawal. Positive

rechallenge resulted in drug induced fever and enlargement of the lymph nodes after one week of ethosuximide administration.

Comment

Lymphadenopathy has been recognised as a complication of drug treatment, particularly with antiepileptic drugs, since the first report of phenytoin-induced pseudolymphoma in 1940.² Since then, this idiosyncratic reaction has also been described with carbamazepine, lamotrigine, nifedipine, thioridazine, atenolol, amiloride/hydrochlorothiazide, mexiletine, penicillamine, captopril, enalapril, and methotrexate.³ Most of these are associated with cutaneous pseudolymphomas, but the antiepileptic drugs are more likely to precipitate cervical lymphadenopathy.

Pathologically, the term "pseudolymphoma" has been used to describe lymphoid cell proliferation with effacement of nodal architecture, so that there is a false appearance suggestive of malignancy. Although the precise pathogenesis of this drug reaction is unknown, pseudolymphoma may develop as a hypersensitivity reaction when a drug or one of its structural ligands acts as an antigen, triggering an immune reaction. Alternatively, the drug in question may promote a dysregulated immune response to another drug or non-pharmacological antigen.⁴

Ethosuximide is widely used in the treatment of absence seizures. On the basis of more than a decade of studies on its cellular effects, the mechanisms of action are thought to include blockade of the low threshold, T-type Ca^{2+} current and a reduction in both the non-inactivating Na^+ current and the Ca^{2+} activated K^+ current in thalamic and cortical neurones.⁴

The most common dose related side effects are gastrointestinal complaints (nausea, vomiting, and anorexia) and central nervous system (CNS) effects (drowsiness, lethargy, euphoria, dizziness, headache, and hiccup). Some tolerance to these effects develops. Parkinson-like symptoms and photophobia have been also reported. Urticaria and other skin reactions, including Stevens-Johnson syndrome, as well as systemic lupus erythematosus, eosinophilia, leucopenia, thrombocytopenia, pancytopenia, hepatic dysfunction, and aplastic anaemia, also have been attributed to ethosuximide.¹

In this case, the disappearance of lymphadenopathy with withdrawal of the drug, and its prompt reappearance when the drug was reintroduced, suggests a strong cause-effect association between ethosuximide and lymphadenopathy. To our knowledge, this is the first case report of ethosuximide induced pseudolymphoma and the second to report lymphadenopathy as an adverse effect of ethosuximide.⁵

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BOOK REVIEW

Imitators of Epilepsy, Second Edition

Edited by Peter W Kaplan, Robert S Fisher. New York: Demos Medical Publishing, 2004, \$99.00 (hardcover), pp 296. ISBN 1-888799-83-8

This 300 page hardcover work encompasses four sections: one on general considerations relevant to the topic with specific focus to epileptic versus non-epileptic diagnostic dilemmas; the second section presents different types of non-epileptic spells according to age of presentation; the third section describes other disorders that resemble epileptic seizures such as migraine, vestibular problems, movement disorders, hyperreflexia, and startle disorders; and the fourth section focuses on encephalopathies, neuro-endocrine, metabolic and toxic conditions imitating epilepsy. Parasomnias, sleep disorders and narcolepsy as well as cerebral vascular imitators of epilepsy are also well described. The last section is relevant to psychological psychiatric imitators of epilepsy such as hyperventilation syndrome, psychogenic non-epileptic seizures, and panic attacks. Most chapters contain a review of the basic definitions and physiology of the respective differential diagnoses imitating epilepsy followed by the clinical characteristics and case vignettes. Some authors of this co-authored work provide a personal perspective regarding diagnosis and treatment. This book is of particular interest to any clinician working with epilepsy patients as it is to medical students on one side and general neurologists and specialised epileptologists on the other side. The fact that imitators of epilepsy are frequently encountered in non-neurological populations or patients presenting outside neurological services makes this book a useful addition to libraries of non-neurologists as well.

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Figure 1 Lymph node biopsy resembles lymphoma, but leucocyte phenotyping shows heterogeneous cell population typical of lymphoid hyperplasia.