Differential Diagnosis of Fever and Generalized Lymphadenopathy: An Interesting Case Report

Ateş ve Jeneralize Lenfadenopatinin Ayırıcı Tanısı: İlginç Bir Olgu Sunumu

Eda DEMİR ÖNAL, MD,[a]
Mine DURUSU TANRIÖVER, MD[a]
İbrahim Koral ÖNAL, MD[a]
Yeşim ÇETİNKAYA ŞARDAN, MD[b]

Departments of
[a]Internal Medicine,
[b]Infectious Diseases,
Hacettepe University
Faculty of Medicine, Ankara

Geliş Tarihi/*Received:* 29.10.2008
Kabul Tarihi/*Accepted:* 03.01.2009

Yazışma Adresi/*Correspondence:*
İbrahim Koral ONAL, MD
Türkiye Yüksek İhtisas Education and Research Hospital,
Gastroenterology Clinic, Ankara,
TÜRKİYE/TURKEY
koralonal@yahoo.com

ABSTRACT Generalized lymphadenopathy is defined as enlargement of more than two noncontiguous lymph node groups. Sometimes it can be a real diagnostic challenge to the physician because the associated diseases clinically and pathologically may mimic each other. The differential diagnosis is important because each cause necessitates a different therapeutic approach. Associated diseases include infections, malignancies, autoimmune diseases, benign hyperplasia, storage diseases, and drug reactions. Here we presented a patient who developed fever and lymphadeopathy after phenytoin use but whose clinical presentation was later found to be secondary to Epstein-Barr virus (EBV) infection. We discussed the differential diagnosis between drug reaction and EBV infection as a cause of generalized lymphadenopathy.

Key Words: Epstein-Barr virus infections; phenytoin; lymphoproliferative disorders

ÖZET Jeneralize lenfadenopati, birbirine komşu olmayan ikiden fazla lenf düğümü grubunun büyümesi şeklinde tanımlanır. Bazen hekim için gerçek bir tanısal zorluk teşkil edebilir; çünkü ilişkili hastalıklar birbirini klinik ve patolojik olarak taklit edebilir. Ayırıcı tanı önemlidir; çünkü her neden farklı bir tedavi yaklaşımı gerektirir. İlişkili hastalıklar enfeksiyonlar, maliniteler, otoimmün hastalıklar, benin hiperplazi, depo hastalıkları ve ilaç reaksiyonlarını kapsar. Burada fenitoin kullanımı sonrası ateş ve lenfadenopati gelişen, fakat daha sonra, klinik görünümünün Epstein-Barr virüs (EBV) enfeksiyonuna ikincil olduğu anlaşılan bir hasta takdim edilmekte ve jeneralize lenfadenopati nedeni olarak ilaç reaksiyonu ve EBV enfeksiyonu arasında ayırıcı tanı yapılmaktadır.

Anahtar Kelimeler: Epstein-Barr virüsü enfeksiyonları; fenitoin; lenfoproliferatif hastalıklar

Turkiye Klinikleri J Med Sci 2009;29(4):1032-4

Generalized lymphadenopathy is defined as enlargement of more than two noncontiguous lymph node groups. Causes include infections, malignancies, autoimmune diseases, benign hyperplasia, storage diseases, and drug reactions. Although the etiology can be uncovered by simple diagnostic algorithms, sometimes it can be a real diagnostic challenge to the physician because the associated diseases may mimic each other clinically and pathologically. The differential diagnosis is important because each cause necessitates a different therapeutic approach. For example, misdiagnosis of an EBV infection as lymphoma is a disaster, which results in inconvenient chemotherapy.

Here we presented a patient who developed fever and lymphadeopathy after phenytoin use but whose clinical presentation was later found to be secondary to EBV infection. We discussed the differential diagnosis between drug reaction and EBV infection as a cause of generalized lymphadenopathy.

CASE REPORT

An 18-year-old man was referred to our hospital with a fever of 2 months duration and multiple lymphadenopathies. He had a history of subdural hemorrhage following trauma 2 months ago. The hemorrhage was drained and phenytoin was started for seizure prophylaxis. He developed fever two weeks after treatment was initiated. Phenytoin was changed to carbamazepine and empirical amoxicillin-clavulanic acid treatment was started. Then the fever disappeared for ten days. However, the fever reappeared with spikes of 40°C. His medical history was unremarkable otherwise.

During admission, he had no complaint except for fever. The physical examination revealed bilateral posterior cervical and inguinal lymphadenopathies. The cervical ones were 2 x 2 cm on the right and 1 x 1 cm on the left while the inguinal ones were both 2 x 2 cm. The patient had mild splenomegaly and hepatomegaly. In the initial laboratory examination, the positive findings were as follows: Hemoglobin 10.4 g/dL (13-17 g/dL), white blood cell count 3200/mm^3 (4000-10000/mm^3), platelet count 187,000/mm^3 (140,000-400,000/mm^3), erythrocyte sedimentation rate 45 mm/hr and gamma glutamyl transferase 174 U/l (5-36 U/l). Differential revealed atypical lymphocytes and lymphocytosis (85%). Since the leukocyte count had a decreasing trend and the absolute neutrophile count was 650/mm^3, piperacillin-tazobactam was started empirically for neutropenic fever. Neither drug induced fever nor lymphoproliferative malignancy could be excluded, so the patient was hospitalized for further workout.

Blood, urine and cerebrospinal fluid cultures were negative. The fever regressed one day after the initiation of piperacillin-tazobactam. Viral serological tests revealed acute EBV infection (Table 1). Serum iron, ferritin, transferrin saturation, cobalamin, folic acid and ß$_2$ microglobulin levels were within normal limits.

In the thoracic computerized tomography (CT) there was no significant finding except for bilateral axillary lymphadenopathies, which had a maximum size of 10 mm. In the neck CT, there were bilateral jugulary lymphadenopathies, the largest one being 18 x 9 mm. The abdominal CT revealed paraaortic and bilateral inguinal lymphadenopathies maximally 13 x 7 mm and hepatomegaly (total vertical length of 20 cm). The patient had no fever during follow-up in the ward and the lymphadenopathies regressed as well. Antibiotic treatment was stopped after 5 days. The clinical picture was considered compatible with infectious mononucleosis although phenytoin induced benign lymphoproliferative disease could not be ruled out. One week after discharge, no lympadenopathy was left to be excised for pathological examination. Leukocyte count increased to 6200/mm^3. Thrombocytosis of 429,000/mm^3 was present indicating bone marrow activation. The patient was followed-up with carbamazepine thereafter for seizure prophylaxis.

DISCUSSION

Anticonvulsant hypersensitivity syndrome is a clinical entity characterized by fever, lymphadenopathy, hepatomegaly and cutaneous eruptions.[1] These features of the syndrome led to its designation as pseudolymphoma syndrome. The associati-

TABLE 1: An 18-year-old patient with fever and lymhadenopathy. The viral serology tests.

Test	Result	Normal limits
EBV EBNA IgG	149.8 RU/mL	0-20
EBV VCA IgM	1.3 RU/mL	0-1.1
EBV VCA IgG	88.5 RU/mL	0-20
EBV EA IgG	Negative	0-20
Anti-CMV IgM	0.33 AU/mL	0.0-0.9
Anti-CMV IgG	80 IU/mL	0.0-6.0

EBV: Epstein-Barr virus, NA: Nuclear antigen, VCA: Viral capsid antigen, EA: Early antigen, CMV: Cytomegalovirus, Ig: Immunglobulin.

on of phenytoin treatment and lymphadenopathy (which may be generalized) has been reported soon after the introduction of the drug.[1] Lymphocytosis, neutropenia, atypical lymphocytes and abnormal liver function tests may be a part of this syndrome.[1] The clinical picture may be acute and life threatening, especially in cases of severe hepatitis. The onset is variable, changing between 1-8 weeks after the initiation of anticonvulsant therapy. Although the mostly accused antiepileptic is phenytoin, other antiepileptics including carbamazepine and new generation antiepileptics may also cause hypersensitivity reaction.[2,3] Treatment consists of early recognition of the syndrome, drug cessation and close follow-up of the patient.[4] The T-cell mediated drug reaction may persist despite discontinuation of the drug.[4] Corticosteroids may be used if the symptoms are very severe.

Clinical features of the anticonvulsant induced hypersensitivity syndrome are very similar to those seen in infectious mononucleosis; fever, atypical lymphocytosis, erythematous throat with white exudate, tender lymphadenopathies, elevated liver enzymes may confound the differential diagnosis of the two entities.[4]

Anticonvulsant induced pseudolymphoma syndrome may mimic lymphoma, particularly mycosis fungoides, with its clinical and histopathological features.[5] Misdiagnosing this entity may lead to unnecessary treatment options. However, it should be kept in mind that cutaneous lymphoma may develop years after antiepileptic induced hypersensitivity. Hence, close follow-up of the patients is mandatory.

Infectious mononucleosis is a heterophile antibody positive infection caused by EBV.[6] It is characterized by fever, lymphadenopathy and atypical lymphocytosis. EBV has been shown to cause several malignancies including nasopharyngeal cancer, Burkitt lymphoma, Hodgkin's disease and B-cell lymphoma. Moreover, the clinical picture of infectious mononucleosis itself may mimic lymphoma and necessitates the exclusion of malignancy.

Our patient was diagnosed to have acute infectious mononucleosis regarding the positivity of EBV VCA IgM. Hypersensitivity or pseudolymphoma syndrome was excluded with the lack of skin eruptions, which are present in all patients with antiepileptic hypersensitivity syndrome, and with complete resolution of the clinical picture. This patient suggests that other causes of lymphadenopathy should also be explored before making a final diagnosis of drug reaction. Differential diagnosis may prevent unnecessary diagnostic and therapeutic approaches.

REFERENCES

1. Korem M, Hiller N, Ackerman Z, Chajek-Shaul T, Abramowitz Y. Spleen rupture secondary to anticonvulsant hypersensitivity syndrome. Eur J Intern Med 2006;17(7):517-9.
2. Misra UK, Kalita J, Rathore C. Phenytoin and carbamazepine cross reactivity: report of a case and review of literature. Postgrad Med J 2003;79(938):703-4.
3. Karadağ AS, Güngör E, Gönültaş M, Ekşioğlu M. [Carbamazepine hypersensitivity syndrome]. Turkiye Klinikleri J Dermatol 2004; 14(3):166-71.
4. Subbannan K, Gujral JS. Necrotizing lymphadenitis associated with the phenytoin-induced hypersensitivity syndrome. South Med J 2005;98(9):937-9.
5. Ferahbaş A. [Mycosis fungoides, clinical variants and subtypes]. Turkiye Klinikleri J Dermatol 2007;17(4):242-51.
6. Topkaya AE, Aksungur FB, Özakkaş F. [An infectious mononucleosis case]. Turkiye Klinikleri J Med Sci 2007;27(2):279-81.