Erythroderma and Marked Atypical Lymphocytosis Mimicking Cutaneous T-Cell Lymphoma Probably Caused by Phenobarbital

Chikara Sakai, Toshiyuki Takagi, Masao Oguro, Nobuhiro Tanabe* and Susumu Wakatsuki**

A 56-year-old man had been treated with phenobarbital seven weeks prior to admission. One month after initiation of administration of phenobarbital, fever, skin rash and lymphadenopathy occurred. Nine days later, marked atypical lymphocytosis, eosinophilia and hepatic injury was noticed. The histology of the biopsied skin was indistinguishable from lymphoma. CHOP-therapy was started but the patient was followed without further treatment because of polyclonal T-lymphocytosis. Afterward, clinical and hematologic improvement ensued and he has been well until now, 52 months later. The marked T-lymphocytosis observed in this case is probably a lymphoid leukemoid reaction secondary to hypersensitivity to phenobarbital.

(Internal Medicine 32: 182–184, 1993)

Key words: skin rash, atypical lymphocytosis, lymphoid leukemoid reaction

Introduction

Phenobarbital, an anticonvulsant drug, is known to induce an exfoliative dermatitis (or erythroderma) (1–3). On the other hand, marked lymphocytoses resembling lymphoid leukemia caused by diphenylhydantoin has also been reported (4, 5). To our knowledge, however, profound lymphocytosis due to phenobarbital has yet to be documented. We present here an unusual case of marked atypical lymphocytosis and erythroderma mimicking cutaneous T-cell lymphoma probably caused by phenobarbital.

Case Report

A 56-year-old man, a public servant, was referred to Chiba Cancer Center Hospital on suspicion of suffering from cutaneous T-cell lymphoma on July 25, 1988. He had a history of a cerebral contusion in a traffic accident seven weeks earlier. Since then he had been treated with phenobarbital, 100 mg, daily, because of a convulsive episode. On July 11, one month after initiation of administration of phenobarbital, fever, pruritic skin rash and lymphadenopathy occurred suddenly. Hepatomegaly and splenomegaly was not noticed. The hematologic findings were unremarkable at this time. Immediately, phenobarbital was discontinued and then corticosteroid was administered because drug allergy was suspected. As shown in Fig. 1, however, pyrexia and lymphadenopathy persisted and the skin rash progressed to a generalized erythroderma with scales (Fig. 2a). On July 20, marked atypical lymphocytosis (Fig. 3) and eosinophilia was noticed for the first time. At this time, the leukocyte count was 44.0 × 10^9/l, with 46% atypical lymphocytes and 20% eosinophils, and the platelet count was 82 × 10^9/l. The leukocyte count increased to 50.8 × 10^9/l with 56% atypical lymphocytes two days later. The bone marrow aspirate revealed eosinophilic hyperplasia (percentage of eosinophils was 47.5%) with few atypical lymphocytes (only 4.5%) (Fig. 4). The serum lactate dehydrogenase (LDH) was 1,885 IU/l (normal: 100–450), aspartate aminotransferase (GOT) was 440 IU/l (normal: 5–40), alanine aminotransferase (GPT) was 447 IU/l (normal: 5–35), and total bilirubin was 2.6 mg/dl (normal: 0.4–0.9). A skin biopsy was performed on July 22. Microscopically, a gross lymphocytic infiltration into the dermis and epidermis was observed and eosinophilic infiltration was hardly seen (Fig. 2b). The immunohistochemical staining showed that these infiltrating lymphocytes were positive for pan T-cell antibody (MT-1, UCHL-1) but negative for pan B-cell antibody (L26). The pathological diagnosis was “atypical lymphocytic infiltration” and lymphoma could not be excluded from differential diagnoses. On admission to our hospital,
Lymphoid Leukemoid Reaction

Fig. 1. Clinical course.

the patient had a massive cutaneous lesion and slight lymphadenopathy. The leukocyte count decreased to \(18.2 \times 10^9/l\), with 47% atypical lymphocytes. The surface markers of peripheral blood lymphocytes were as follows: immunoglobulins less than 2%, CD2 76.9%, CD3 61.5%, CD4 44.8%, CD8 23.8%, and HLA-DR 80.9%. The results of serologic tests for Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, herpes simplex virus and rubella virus were unremarkable. HTLV-1 antibody was less than 1:5.

At first chemotherapy with doxorubicin, cyclophosphamide, vincristine and prednisolone (CHOP) was started because cutaneous T-cell lymphoma was strongly suspected. Thereafter, however, the patient was followed without further treatment except for a corticosteroid because of polyclonality of T-lymphocytosis. Afterward, as shown in Fig. 1, clinical and hematologic improvement ensued and the corticosteroid was tapered gradually. In February 1989, a lymphocyte stimulation test using phenobarbital was done but a positive result could not be obtained. The patient has been well without recurrence of erythroderma and atypical lymphocytosis until the time of reporting, 52 months later.

Fig. 2. a) Skin rash (erythroderma with scales). b) Histology of the biopsied skin. Massive infiltration of lymphocytes into the dermis and epidermis is seen (HE stain, \times200).
The histology of the biopsied skin of this patient was indistinguishable from lymphoma, but the lymphocytosis was composed of both CD4 and CD8 lymphocytes (CD4:CD8 ratio was 1.9:1). It is very unlikely that this case had a cutaneous T-cell lymphoma and complete remission has lasted for four years after only one course of CHOP-therapy. The present case had eosinophilia and hepatic injury in addition to T-lymphocytosis. Similarly, the case reported by Siegal and Berkowitz (4) had both eosinophilia and severe hepatic damage together with lymphocytosis caused by diphenylhydantoïn. Phenobarbital is well known to induce an allergic eruption and hepatic injury (1–3). The lymphocyte stimulation test did not confirm that phenobarbital was causative of hypersensitivity. Clinically, however, the skin rash and hepatic damage seen in our patient was strongly suspected to have been caused by phenobarbital. Therefore, the simultaneous T-lymphocytosis is probably a reactive lymphocytosis, namely lymphoid leukemoid reaction (6), associated with hypersensitivity to phenobarbital. The association of exfoliative dermatitis (7) or dermatitis herpetiformis (8) with marked lymphocytosis mimicking lymphoid leukemia has been documented. Furthermore, the reported patients with diphenylhydantoin-induced lymphocytosis also had a skin rash (4, 5). Recently, the keratinocytes of epidermis are recognized as initiators of inflammation (9, 10). The activated keratinocytes produce and release some cytokines such as interleukin (IL)-1 and GM-CSF (9–11). These cytokines are presumably responsible for proliferation and activation of T-lymphocytes associated with some cutaneous lesions regardless of their etiology. Subsequently, the activated T-lymphocytes produce IL-5 and then induce eosinophilia (12).

Aside from the mechanism of reactive T-lymphocytosis, the present case indicates that the symptomatic combination of a skin rash with lymphocytosis, eosinophilia and hepatic injury is the clue to the suspicion of drug hypersensitivity.

References