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〔Case Report〕

Diphenylhydantoin hypersensitivity syndrome without skin rash

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SUMMARY

A 17-year-old woman developed high fever, lymphadenopathy and elevated liver enzymes 4 days after the initiation of diphenylhydantoin (DPH) for seizure prophylaxis. There was no skin rash. The extensive tests for infectious sources were negative. After the discontinuation of DPH, the fever and lymphadenopathy rapidly resolved, and the elevated liver enzymes reverted to normal.

It is important to recognize anticonvulsant hypersensitivity syndrome, even in the absence of skin rash, and to withdraw the medication promptly to avoid otherwise potentially life-threatening complication.

Key words : diphenylhydantoin (DPH), lymphadenopathy, skin rash, hypersensitive syndrome

Ⅰ. Introduction

The manifestatiens of drug-induced diseases frequently resemble those of other diseases, and anticonvulsant is unique in that it causes lymphadenopathy.

We describe a case of DPH hypersensitivity reaction comprised with an onset of spiking fever, cervical adenopathy and hepatitis mimicking infectious mononucleosis. Skin rash was not observed throughout the course.

Ⅱ. Case Report

A 17-year-old girl was well until June 25, 1997 when she developed a headache. Aspirin did not alleviate her symptom and she came to the hospital the following day. There was no nausea or vomiting.

Examination showed the body temperature 36. 7℃, and the blood pressure was 100／60. There was tenderness in the shoulder muscles, otherwise the physical examination was completely normal. Nuchal rigidity was not

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present. The initial impression was either tension headache or migraine. Mefenamic acid 250 mg 6 tablets a day and clotiazepam 5 mg 3 times a day were prescribed, and the patient was sent home. The medication did not appear to relieve her headache, but she still went to school when she felt better. She returned to the hospital on July 1, a week later, still complaining of the headache. Physical examination again was not remarkable. The patient was oriented to time, place and person. The cranial nerve examination did not show abnormalities. There was no peripheral motor or sensory disturbance. Signs of cerebellar dysfunction were not present. The peripheral blood count, serum chemistries and CRP were all normal. Because of persisting headache, brain CT was performed which showed a large high density mass lesion in the right parieto-occipital region measuring 4.0×4.5cm in 4 slices, consistent with intracerebral bleeding (Fig. 1).

The patient was admitted to the hospital. Cerebral angiogram was performed on the same day which revealed no abnormalities. There was no evidence of arterio-venous malformations, angioma nor aneurysms, and the diagnosis by the neurosurgeons was idiopathic intracerebral bleeding. 10% glycerin (Glyceol) was administered twice daily to reduce intracranial pressure. Diphenylhydantoin DPH (Aleviatin) was started initially, 125 mg intravenously twice daily for 2 days, then 200mg orally twice a day for seizure prophylaxis.

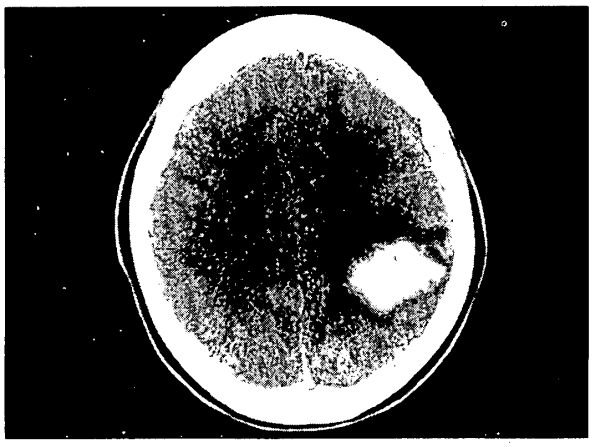

Fig.1 Brain CT showed a large high density mass lesion in the right parieto-occipital region.

Her headache improved drastically and she was well till July 6, the 6th day of hospitalization, when her body temperature rose to 38.6℃. There was no sore throat, cough or arthralgia.

On July 8th, small tender cervical adenopathy was felt bilaterally. There was no enlargement of the liver and spleen.

The laboratory values showed the peripheral WBC count $5.6\times10^3/mm^3$ with 68% neutrophils, 1% eosinophils, 23% lymphocytes, 8% monocytes. The serum chemistries showed elevated liver enzymes with GOT 68 (10-40IU/L) and GPT 89 (5-45IU/L). The rest of the chemistries were not remarkable. Her urinalysis was normal. The erythrocyte sedimentation rate was 12 mm/hr and CRP negative. ANA, C_3, C_4 and anti-DNA antibodies were all within normal ranges.

HBsAg, HCV antibody and hepatitis A antibody were negative.

EB virus VCA-IgM, IgG were negative and there was no evidence of recent infection of cytomegalovirus or mumps. Antibodies to streptococcus and toxoplasma were negative. The cultures of the throat swab and the bloood were negative.

Fever spiked daily, occasionally reaching to 40℃. The patient was lethargic during pyrexia. The fever fairly well responded to diclofenac sodium 50 mg suppository. The cervical lymph nodes were enlarging, the largest measuring approximately 3×3×2cm. Lymph node swellings were also felt in the post-auricular area but not in the axilla or inguinal regions. The abdominal echography showed mild hepatomegaly with normal-sized spleen. The peripheral blood lymphocyte subset studies using flowcytometry showed CD3 78.0% (59.5-87.9), CD4 37.2 (28.3-56.7), CD8 41.3% (19.7-40.1),

CD10 0.4% (5.7-14.6), CD13 6.8% (<0.5), CD14 2.2% (<4.6), CD19 8.3% (6.3-19.6).

Since extensive studies did not disclose any infectious sources, it was thought that the fever, lymphadenopathy and hepatitis were reaction to DPH and this was discontinued. Glyceol was maintained. On the 2nd day after stopping DPH, the fever drastically subsided (Fig. 2). Lymph node pain and swelling improved gradually. On July 17th, the lymph node swellings could not be felt. By July 25th, all liver function test results normalized, and she was discharged. Commertially available drug-induced lymphocyte stimulation test performed on July 11 showed negative reaction to phenytoin.

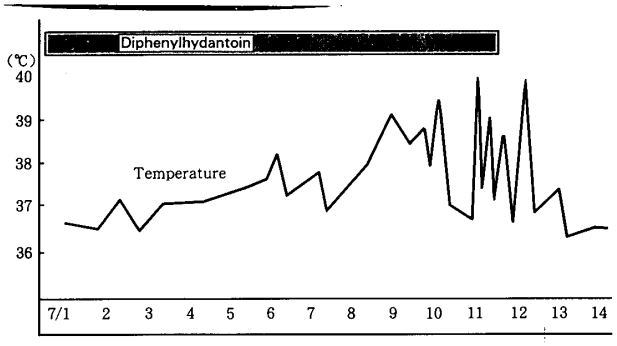

Fig. 2 Clinical Course : Diphenylhydantoin administration and the development of fever.

Ⅲ. Discussion

Hypersensitivity reaction due to diphenylhydantoin (DPH) has been described from the early days of its use [1]. Its hallmark clinical features are fever, rash, lymphadenopathy and hepatitis. The incidence is estimated to be between one in 1,000 and one in 10,000 exposures [2]. An identical reaction was also reported in carbamazepine and phenobarbital therapy [3]. It is now generically termed anticonvulsant hypersensitivity syndrome [4]. In addition to fever, rash, lymphadenopathy and hepatitis, various hematologic abnormalities such as eosinophilia, leukocytosis or leukopenia [5, 6] are reported. The onset is usually within 3 months of treatment initiaion, most often within 2 to 4 weeks [7].

Our patient developed high fever on the 6th day of the drug administration followed by cervical lymph node swelling which became prominent as the days went by. An elevation of liver enzymes was also present, but skin rash was not seen throughout the course. In DPH hypersensitivity reaction, it usually heralded by the fever and rash [8, 9]. A comprehensive review by Power et al [10] of 17 pediatric patients including 4 of their own showed all patients had skin manifestation at time of admission or during hospitalization. In another series of 38 cases reported by Haruda [11], lymphadenopathy occurred in nine patients, and was associated with a rash in all nine. Eosinophilia suggestive of allergic reaction is a frequent finding [8]. In the absence of rash or eosinophilia, it may easily be mistaken with other diagnosis such as infections mononucleosis. Failure to recognize DPH hypersensitivity as the offending drug will be life-thretening [12].

We did not perform lymph node biopsy. Lymph node histology usually shows benign hyperplasia with preservation of architectures, but might show pseudolymphoma pattern with loss of normal architectures [13]. Development of frank lymphoma has been reported with long-term use of DPH [14, 15].

The mechanism to develop anticonvulsant hypersensitivity syndrome is unknown. A form of allergic hypersensitivity [12], acute graft-vs-host disease [16] or enzymatic deficiencies [17] are proposed.

The results of lymphocyte stimulation tests to antiepileptic drugs so far showed variable results [13, 18]. Our test result of blastogenesis to DPH was negative.

Anticonvulsant hypersensitivity with fever, rash, lymphadenopathy is a rare syndrome.

Fatal outcomes are most often associated with liver failure. Overall mortality rate when the liver is involved is between 18% and 40% [4]. Prompt withdrawal of the drug when rash or other reactions occurred is advocated [19], but without rash, one may be in a diagnostic puzzle. It is important to recognize the characteristic constellation to avoid a serious outcome from this widely used drug.

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要　旨

抗痙攣剤過敏症候群 anticonvulsant hypersensitivity syndrome は，熱発，皮疹，リンパ節腫脹を伴なう稀な症候群で，発症頻度は1,000名から10,000名に1人位と推定される。患者はしばしば重篤となり，ことに肝障害をきたした場合，致死率は18%から40%と高率である。本症候群はジフェニルヒダイトインによるものがまず報告されたが，その後カルバマゼピン，フェノバルビタール投与によっても，同様の症候群が起こることが報告された。治療は本症候群に気付き，薬剤をすみやかに中止することである。

我々は17歳の女性で，原因不明の脳内出血で入院し，痙攣予防のためジフェニルヒダントイン投与を受けた患者に本症候群が発症した例を経験した。薬剤開始約1週間後に，著名な熱発，頸部リンパ節腫脹，肝機能異常が出現し，患者は急速に疲弊した。当初，伝染性単核症など感染症を疑ったが，臨床的に否定的で，症状が入院後に起り，また脳内出血との関連が病因的に同一に説明できないことから，ジフェニルヒダントインによる過敏症を疑い薬剤を中止したところ，症状は劇的に改善した。本症候群は，薬剤過敏を示唆する皮疹の出現によってまず疑われることが多いが，本症例では経過中皮疹の出現は認められず，そのような場合でも抗痙攣剤服用患者に熱発，リンパ節腫脹が出現した例では，本症候群を念頭に入れておく必要がある。

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