Int J Clin Exp Pathol 2013;6(1):100-104
www.ijcep.com /ISSN:1936-2625/IJCEP1210010

Case Report

Leukemoid reaction secondary to hypersensitivity syndrome to phenobarbital: a case report

Qinghai Zeng[1], Yuanqiang Wu[1], Yi Zhan[1], Ling Tang[1], Yangmei Zhou[1], Jun Yin[2], Fan Fan[3], Guiying Zhang[1], Qianjin Lu[1], Rong Xiao[1]

[1]Department of Dermatovenereology, Second Xiangya Hospital, Central South University, Changsha, China; [2]Department of Neurology and [3]Neurosurgery, Xiangya Hospital, Central South University, Changsha, China

Received October 21, 2012; Accepted November 7, 2012; Epub November 20, 2012; Published January 1, 2013

Abstract: The most important adverse effects of phenobarbital, an anticonvulsant drug, are behavior and cognitive alterations. Hypersensitivity syndrome caused by phenobarbital presenting with a leukemoid reaction is a rare side effect, which is rarely ever reported and needs to be known. We report on a 27-year-old Chinese woman who experienced hypersensitivity syndrome three weeks after the initiation of phenobarbital. The patient developed fever, skin rash, face swelling, lymphadenopathy, myalgia, hepatitis, eosinophilia, atypical lymphocytes and leukocytosis. Along with the pathological progress of the disease, the patient noticed a gradual exacerbation of her symptoms. And the highest leukocyte count was up to 127.2 x 10^9/L. After discontinuing of phenobarbital and administration of methylprednisolone combined with the intravenous immunoglobulin shock therapy, all initial symptoms improved and the leukocyte count normalized. This case is reported because of its rarity of the leukemoid reaction secondary to hypersensitivity syndrome to phenobarbital.

Keywords: Phenobarbital, hypersensitivity syndrome, leukemoid reaction

Introduction

Phenobarbital (PHB) is effective in a wide variety of seizures and it is still a first line drug for treatment of status epilepticus. The most important adverse effects of PHB are behavior and cognitive alterations. In developing countries, despite its adverse effects, PHB is used widely because of its cheapness [1].

Hypersensitivity syndrome (HS) is a partially understood disorder, with serious idiosyncratic drug reactions that most commonly develop 2-6 weeks after exposure to antiepileptic drugs, sulfonamides, nonsteroidal anti-inflammatory drugs, corticosteroids, and allopurinol [2]. This reaction typically presents with fever, skin rash, lymphadenopathy, hepatitis, eosinophilia and atypical circulating lymphocytes. Other clinical manifestations such as facial edema, myalgia, nephritis, and leukocytosis also may be included [3, 4]. Antiepileptic drug induced hypersensitivity syndrome is a rare side effect of aromatic anticonvulsive drugs (e.g., PHB, phenytoin and carbamazepine). The drugs implicated most frequently are carbamazepine and phenytoin [5], but the reports of hypersensitivity syndrome to PHB are uncommonly seen.

Hematological abnormalities may occur as part of PHB hypersensitivity but leukemoid reaction secondary to hypersensitivity syndrome to PHB is very rare. There was a case of hypersensitivity to PHB with the highest leukocyte count of 50.8 x 10^9/L and it was probably a leukemoid reaction secondary to hypersensitivity to PHB [6]. We report the explicit case of a 27-year-old Chinese woman who experienced hypersensitivity syndrome three weeks after the initiation of PHB associated with leukemoid reaction with the highest leukocyte count up to 127.2 x 10^9/L.

Case present

A 27-year-old woman presented to the dermatology department with a 1-week history of generalized erythema, scaling and swollen face

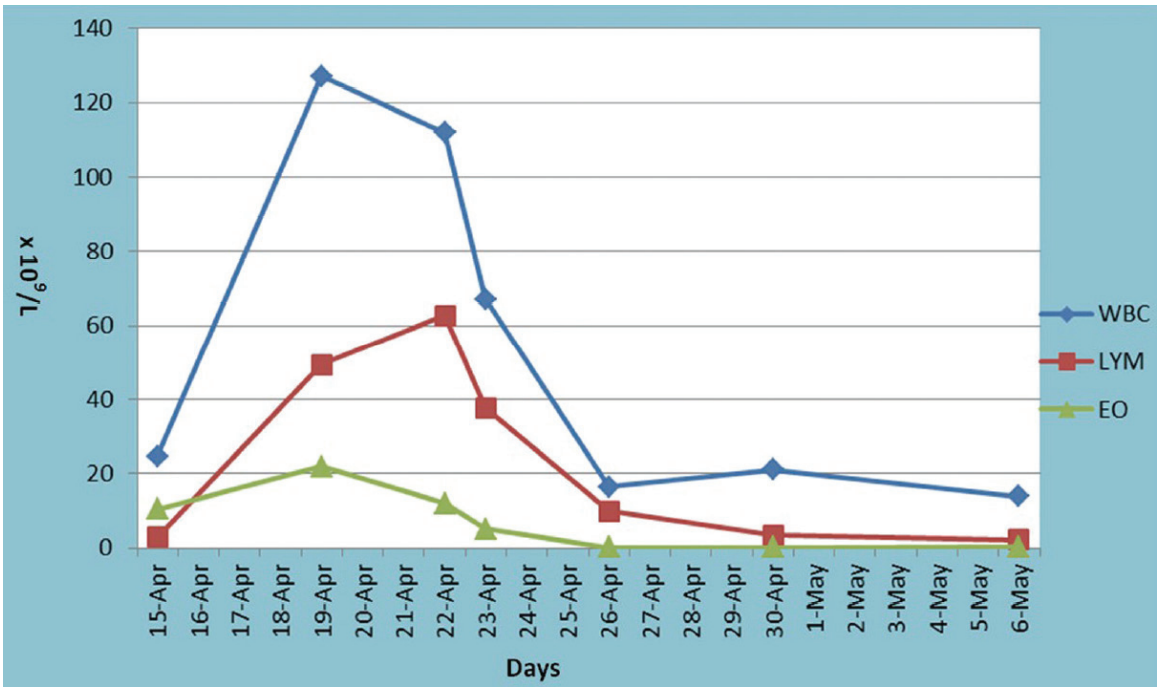

Figure 1. The number of white blood cells (WBC), lymphocytes (LYM) and eosinophils (EO) during the hospitalizing.

and 5-day history of fever following three weeks of PHB 100mg at bedtime for epilepsy. The patient was diagnosed with epilepsy in 2005 and had received valproic acid for 5 years. Recently, the effect of valproic acid treatment was weak. So she was started on PHB instead of valproic acid 100mg daily one month ago. One week prior, she had been seen by a private practitioner for pruritic erythema on face and hands. With unknowing treatment, the patient's condition got worse, and the erythema spread to a total body rash. Five days prior, she stated to have a fever (39.4°C) and had myalgia. Suspecting of drug allergy to PHB, PHB was stopped by an outside hospital. During five-day hospitalization in the outside hospital with treatment of oral methylprednisolone 80 mg daily (other drugs were unclear), there was no sign of clinical manifestation recovering. She came to our dermatology department with fever, persistent rash, myalgia, malaise, and swollen face. No history of measles or pertussis etc. and no contact history with tuberculosis or other infective diseases. Her past medical history had been unremarkable. No history of operation, trauma and blood transfusion. And she denied having any known drug allergies and using tobacco, alcohol, or i.v. drugs.

On physical examination, temperature was 39°C, pulse 98 beats per minute, respirations 22 breaths per minute, and blood pressure 110/80 mmHg. The patient appeared acute facies and bad state of mind. The skin revealed a diffuse maculopapular erythematous eruption with scales. Pitting edema of face was obvious. Superficial lymph nodes were found enlarged in her neck, but no flare tenderness and no pain. And there was no hepatosplenomegaly. Systemic examination did not reveal any abnormalities.

Laboratory investigations revealed a white blood cell (WBC) count of 24.7 x 10^9/L (neutrophils, 35.6%; lymphocytes, 11.4%; monocytes, 3.6%; eosinophils, 42%; basophils, 1.6%). The patient's liver enzymes were elevated (AST, 85.0U/L; ALT, 244.5U/L). The serum total bilirubin (TBILI) was 28.2umol/L and the direct bilirubin (DBILI) was 15.6umol/L. The serum total protein (TP) was 51.8g/L and the albumin (ALB) was 21.8g/L. Outcomes of tests on liver virus and human immunodeficiency virus were negative. Otherwise, the red blood cells and platelets stool, routine and urinalysis, renal function test etc. were normal. Chest X-ray was normal but abdominal ultrasound examination revealed splenomegaly.

During her hospital stay, along with the pathological progress of the disease, the patient had indirect fever and the patient noticed a gradual exacerbation of her rash with diffuse rubeosis and large desquamation of the whole body skin. The edema of face was more significant. And her epilepsy frequently attacked. At this time, the WBC count was up to 127.2 x 10^9/L (neutrophils, 28.9%; lymphocytes, 38.8%; monocytes, 1.4%; eosinophils, 17.2%; basophils, 5.4%) (**Figure 1**). Owing to her massive WBC, our patient underwent bone marrow biopsy to exclude leukemia and finally demonstrated a lack of myeloid clonality. Bone marrow aspiration revealed a moderate increase in the granulocyte series with high percentage of eosinophiles series showing normal morphology, and there were no increased blast cells. There were 24% atypical lymphocytes in the peripheral blood. For this kind of emergency, we closely monitored the evolution of the disease and obtained specialist consults frequently. A laboratory work-up for infectious diseases produced negative finding on bacterial and parasitic studies, but positive finding on EB-IGM.

PHB was discontinued sequentially after admission, and the patient was first started on intravenous methylprednisolone 80mg daily, along with antianaphylactic treatment, liver protection and supporting therapy. Three days later, for the gradual exacerbation of the patient's symptoms (persistent high fever, worsened rash with diffuse rubeosis and aggravated edema), intravenous immunoglobulin shock therapy was stated 20g daily for three days combining with methylprednisolone. Six days later, the patient's condition gradually improved with normal temperature, stopping of skin pruritus and zero of new erythema. In the subsequent hospitalization, the skin rash, face swelling, lymphadenopathy and myalgia had generally resolved, and the liver enzymes, TP and ALB had progressively improved. Subsequent total count and classification of leukocyte had been normal. During the whole treatment process, methylprednisolone tapered as the erythema and desquamation subsided.

Discussion

PHB is a very potent aromatic anticonvulsant. In 1910, PHB, which was used to induce sleep at that time, was accidentally found to have antiseizure activity and became the drug of choice for many years. As a gamma-aminobutyric acid(GABA-A) receptor agonist, PHB has a direct action on GABA-A receptors by binding the barbiturate-binding sit that prolongs the duration of chloride channel opening. And it also can reduce sodium and potassium conductance and calcium influx and depress glutamate excitability. PHB is effective in a wide variety of seizures and it is still a first-line drug for treatment of status epilepticus. Although in developed countries, the use of PHB has reduced for its adverse effects, it is widely prescribed around the world, especially in developing countries because of its efficacy and cheapness. Its most common adverse effects are sedation, cognitive alteration, paradoxical hyperkinesis in children and other behavioral disturbances [1, 7]. HS to PHB associated with leukemoid reaction is a rare side effect.

Antiepileptic drug induced hypersensitivity syndrome has been reported to have an incidence of 1 in 1,000 to 1 in 10,000 exposures to PHB, phenytoin and carbamazepine [3]. There is no association with dose, sex or age. HS is characterized by triad of fever, rash (a maculopapular erythematous eruption is the most common, diffuse pustulation or erythroderma is not uncommon, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are rare) and internal organs involvement (50% liver and 11% kidney). And the triad usually occurs in the first few weeks after the initiation of anticonvulsant treatment. Lymphadenopathy (70%) and eosinophilia (30%) are also frequent. Other clinical manifestations such as atypical lymphocytes, facial edema, myalgia and leukocytosis also may be included [3, 4]. Our patient presented with classic symptoms of HS including fever, rash, face swell, lymphadenopathy, myalgia, hepatitis, eosinophilia, atypical circulating lymphocytes and leukocytosis.

Hematological and hepatic involvements are the two most common systemic involvements [8]. The hematologic abnormalities of HS generally consist of eosinophilia, atypical lymphocytosis, lymphocytosis, lymphopenia, and thrombocytopenia [8]. Our patient presented with eosinophilia and leukocytosis during the hospitalizing, and atypical lymphocytes were also

been found. With the progression of hypersensitivity, the WBC count was up to 127.2 x 10^9/L once. Our patient underwent bone marrow biopsy to exclude leukemia, which finally demonstrated a lack of myeloid clonality. Then leukemoid reaction associated with HS was diagnosed.

Leukemoid reaction was first reported by Krumbbarr in 1926 [9]. A leukemoid reaction is a clinical syndrome in which changes are found in the peripheral blood similar to what occurs in people with leukemia, but not the result of leukemic disease [10, 11]. The reaction can occur in many disorders such as severe infection, intoxications, malignancies, severe hemorrhage. It has also been reported to occur in allergic reaction of aromatic anticonvulsant drug [12]. As one of the aromatic anticonvulsant drugs, PHB associated with leukemoid reaction is rare. A case of PHB hypersensitivity probably associated with a leukemoid reaction had been reported [6]. And in this case, the highest WBC count was 50.1 x 10^9/L. In our case, the WBC count was up to 127.2 x 10^9/L (neutrophils, 28.9%; lymphocytes, 38.8%; monocytes, 1.4%; eosinophils, 17.2%; basophils, 5.4%). Two days later, the WBC count was 111.9 x 10^9/L (neutrophils, 17.4%; lymphocytes, 55.9%; monocytes, 2.8%; eosinophils, 10.7%; basophils, 6.1%). Then Bone marrow aspiration revealed a moderate increase in the granulocyte series with high percentage of eosinophiles series showing normal morphology, and there were no increased blast cells. There were 24% atypical lymphocytes in the peripheral blood. The patient was considered to have a lymphoid leukemoid reaction. In leukemoid reaction, blood count will usually return to normal when the underlying condition is treated. After withdrawing of PHB and administration of methylprednisolone combined with the intravenous immunoglobulin shock therapy, the blood count normalized with the control of drug allergy.

It's worth noting that hepatitis and subsequent liver failure are the most important factors affecting prognosis. So continuing of the liver function tests is important [13]. In our case, the patient's liver enzymes were elevated obviously (AST, 85.0U/L; ALT, 244.5U/L). We worried about the liver function very much and requested consultation frequently. Reduced Glutathione Tablets (GSH), Compound Glycyrrhizin for Injection and other drugs were applied to protect the liver. Fortunately, the liver enzyme persistently declined during our treatment.

The mechanisms of antiepileptic drug induced hypersensitivity syndrome are incompletely understood, but pharmacogenetic and immunologic mechanism is involved. The aromatic anticonvulsants undergo oxidative metabolism by the cytochrome p-450 system to arene oxides, which can contribute to an immunological response or even lead to cell death. Arene oxides are usually detoxified by enzyme systems such as epoxide hydroxylase. However, these enzyme systems may be lacking or mutated in some individuals and they may develop HS because of their inability to detoxify toxic metabolites [14]. Recent studies suggest that viral infections (EB virus, HHV-6, HHV-7 and CMV), especially HHV-6, contribute to the pathogenesis of HS to anticonvulsant. And some researchers indicated that syndromes of HS should be regarded as a reaction induced by a complex interplay among herpesviruses, antiviral immune responses and drug-specific immune responses [15, 16].

Treatment for HS includes discontinuing the offending drug, supportive treatment and the consideration of steroids. Withdrawing of the offending drug usually leads to recovering, although rash and hepatitis may persist for weeks [17]. Symptomatic support with hydrations and skin care are also very important. Steroids have been widely advocated in the management of HS for their anti-inflammatory properties, despite the lack of controlled studies to evaluate their efficacy [18, 19]. Mostly, patients need being treated with systemic steroids for a mean duration of 49 days [8]. And a slow taper is necessary. There are reports of treatment with high-dose intravenous immunoglobulin hastens recovery from HS for some patients [20, 21]. In our case, there was an exacerbation of patient's condition after admission. All initial symptoms exacerbated and the WBC count elevated up to 127.2 x 10^9/L. PHB was discontinued and we started on intravenous methylprednisolone 80mg daily and intravenous immunoglobulin shock therapy 20g daily for three days. Other treatments included antianaphylactic treatment, liver protection

and supportive treatment. Treatment of epilepsy should be cautious in selection between anticonvulsants because of high potential for cross-reactivity, especially between the aromatic anticonvulsants for their similar structure of having in common an aromatic benzene ring [22]. We used Depakene (compound sodium valproute and valproic acid sastaime reloase tablets) for the patient's epilepsy and it worked well.

Conclusion

We report a case of leukemoid reaction secondary to hypersensitivity syndrome to phenobarbital.

Address correspondence to: Dr. Rong Xiao, Department of Dermatovenereology, Second Xiangya Hospital, Central South University, No. 139, Renmin Road, Changsha, Hunan 410011, PR china. Tel: +86 731 85295660; Fax: +86 731 85533525; E-mail address: xiaorong65@yahoo.com.cn

References

[1] Gélisse P, Crespel A, Genton P. Antiepileptic Drugs. Therapie 2008; 63: 425-451.

[2] Krauss G. Current understanding of delayed anticonvulsant hypersensitivity reactions. Epilepsy Curr 2006; 6: 33-37.

[3] Bota RG, Ligasan AP, Najdowski TG, Novac A. Acute hypersensitivity syndrome caused by valproic Acid: a review of the literature and a case report. Perm J 2011; 15: 80-84.

[4] Begon E, Roujeau JC. Drug hypersensitivity syndrome. DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms). Ann Dermatol Venereol 2004; 131: 293-297.

[5] Yang CY, Dao RL, Lee TJ, Lu CW, Yang CH, Hung SI, Chung WH. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. Neurology 2011; 77: 2025-2033.

[6] Sakai C, Takagi T, Oguro M, Tanabe N, Wakatsuki S. Erythroderma and marked atypical lymphocytosis mimicking cutaneous T-cell lymphoma probably caused by phenobarbital. Intern Med 1993; 32: 182-184.

[7] Lagae L. Cognitive side effects of anti-epileptic drugs. The relevance in childhood epilepsy. Seizure 2006; 15: 235-241.

[8] Wongkitisophon P, Chanprapaph K, Rattanakaemakorn P, Vachiramon V. Six-year retrospective review of drug reaction with eosinophilia and systemic symptoms. Acta Derm Venereol 2012; 92: 200-205.

[9] Krumbhaar EB. Leukemoid blood pictures in various clinical conditions. Am J Med Sci 1926; 172: 519-533.

[10] Laad G, Miranda MF. Eosinophilic leukemoid reaction associated with carbamazepine hypersensitivity. Indian J Dermatol Venereol Leprol 2005; 71: 35-37.

[11] Sun CY, Lin HC, Chen YC, Tsai CR, Wu MS. Leukemoid reaction after methotrexate-induced pancytopenia in a patient undergoing continuous ambulatory peritoneal dialysis. Chang Gung Med J 2006; 29: 513-517.

[12] Ray-Chaudhuri K, Pye IF, Boggild M. Hypersensitivity to carbamazepine presenting with a leukemoid reaction, eosinophilia, erythroderma, and renal failure. Neurology 1989; 39: 436-438.

[13] Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med 1995; 155: 2285-2290.

[14] Kim CW, Choi GS, Yun CH, Kim DI. Drug hypersensitivity to previously tolerated phenytoin by carbamazepine-induced DRESS syndrome. J Korean Med Sci 2006; 21: 768-772.

[15] Sato T, Kuniba H, Matsuo M, Matsuzaka T, Moriuchi H. Case of drug-induced hypersensitivity syndrome due to lamotrigine: demonstration of sequential reactivation of herpesviruses. No To Hattatsu 2012; 44: 69-72.

[16] Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol 2007; 156: 1083-1084.

[17] Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331: 1272-1285.

[18] Bavdekar SB, Muranjan MN, Gogtay NJ, Kantharia V, Kshirsagar NA. Anticonvulsant hypersensitivity syndrome: lymphocyte toxicity assay for the confirmation of diagnosis and risk assessment. Ann Pharmacother 2004; 38: 1648-1650.

[19] Lens S, Crespo G, Carrión JA, Miquel R, Navasa M. Severe acute hepatitis in the DRESS syndrome: Report of two cases. Ann Hepatol 2010; 9: 198-201.

[20] Dredge DC, Parsons EC, Carter LP, Staley KJ. Anticonvulsant hypersensitivity syndrome treated with intravenous immunoglobulin. Pediatr Neurol 2010; 43: 65-69.

[21] Criado PR, Criado RF, Avancini Jde M, Santi CG. Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) / Drug-induced Hypersensitivity Syndrome (DIHS): a review of current concepts. An Bras Dermatol 2012; 87: 435-449.

[22] Knowles SR, Dewhurst N, Shear NH. Anticonvulsant hypersensitivity syndrome: an update. Expert Opin Drug Saf 2012; 11: 767-778.