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A case of acute generalized exanthematous pustulosis caused by butylphthalide sodium chloride injection and review of the literature

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Abstract: A 73-year-old female patient with small artery occlusive cerebral infarction was given atorvastatin calcium tablets 20 mg orally once/d, aspirin enteric-coated tablets 100 mg orally once/d, Clopidogrel bisulfate tablets 75 mg orally once/d, Citicoline sodium tablets 200 mg orally three times/d, and butylphthalide and sodium chloride injection 100 ml intravenously twice/d.nine days later, the body appeared scattered erythema with sharply demarcated and different sizes, which was considered to be caused by butyl phthalein sodium chloride injection or Clopidogrel bisulfate tablets. This drug was discontinued and other drugs continued to be used. Three days later, the body temperature began to rise, reaching over 38 ℃. On the fourth day, the body temperature continued to rise, presenting classical skin lesions: Based on generalized diffuse, edematous erythema, there were dense, superficial, non-follicular yellow-white pustules, some of which formed pus lakes. After a consultation with a dermatologist, the patient was diagnosed with acute generalized exanthematous pustulosis, and treated with intravenous drips of methylprednisolone, human immunoglobin and human albumin, etc. After 3 weeks of symptomatic treatment, the skin lesions were cured. Clopidogrel bisulfate tablets were re-applied after specialist evaluation and no similar lesions occurred.

1. Introduction

The patient was admitted to the Department of Neurology of our hospital on 2022-07-03 due to immobility of the right upper limb for 1 day. The patient noticed hand inflexibility when writing 1 day ago for no apparent reason, denied limb numbness, no dizziness, headache, no nausea, and vomiting. He went to the local hospital and underwent cranial CT, which showed multiple lacunar cerebral infarcts in the lateral paraventricular and frontal lobes and left insula bilaterally. Atorvastatin calcium tablets were given 20 mg orally once/d and aspirin enteric-coated tablets 100 mg orally once/d. After a night's rest, I found that my symptoms had worsened and I had difficulty

tying buttons in the morning, so I came to our hospital. No special history, deny the history of drug and food allergies.

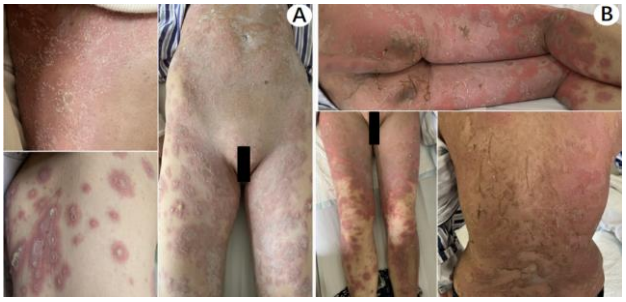
Admission physical examination: body temperature 36.3 ℃, pulse 72 times/min, respiration 19 times/min, blood pressure 123/70 mmHg. The chest and abdomen examination showed no abnormality, the whole body's skin color was normal, and no rash was seen. Neurological examination: clear consciousness, good spirit, bilateral nasolabial fold symmetry, tongue extension centered, soft neck without resistance, right upper limb muscle strength grade IV, bilateral facial and limb nociception identical, bilateral Bartholomew's sign (-), normal ataxia, NIHSS score 0, MRS score 2, ADL score 100, Kubota test grade 1, VTE score 2.After admission, cranial MRA was completed: 1. fresh cavernous infarcts in the left centrum semiovale and radial crown; 2. multiple cavernous infarcts and focal demyelination in the bilateral frontal, parietal, centrum semiovale, radial crown, parietal ventricle, and right basal ganglia regions. Laboratory tests: routine blood and coagulation series were normal, blood potassium 3.24 mmol/L, total calcium 2.08 mmol/L. Admission diagnosis: small artery occlusive cerebral infarction; hypokalemia. Symptomatic treatment such as antiplatelet aggregation, lipid-lowering, and improvement of collateral circulation was given, The specific medication regimen: butylphthalein sodium chloride injection (Shiyapharm Group Enbep Pharmaceutical Co., Ltd., Lot No. 6182204154; Specification: 100 ml: butylphthalein 25 mg and sodium chloride 0.9 g) 100 ml intravenous drip, 2 times/d, atorvastatin calcium tablets (Lipitor) 20 mg orally, 1 time /d, Clopidogrel Hydrogen Sulfate Tablets [Sanofi Winthrop Industrie, Lot No. DA582; Specification: 75 mg (based on $C_{16}H_{16}ClNO_2S$)] orally, 1 time/d, Bactrim Enteric Dissolve Tablets (Bactrim) 100 mg orally, 1 time/d, Cytarabine Tablets 200 mg orally, 3 times/d. After 9 d of medication (July 12), erythema appeared on the face and inter-rub areas, partially fused, and swollen in both ears, and vesicles were visible on the oral mucosa, followed by a generalization of the erythema to the whole body with mild pruritus; Laboratory tests: WBC 9.65 x 10^9/L, NEUT% 90.2, N 8.7 x 10^9/L; Drug dermatitis was initially considered, and the allergenic drugs were suspected to be clopidogrel hydrogen sulfate tablets or butyl phthalein sodium chloride injection after pharmacist evaluation. Suspected allergenic drugs were immediately stopped, and methylprednisolone sodium succinate 40 mg was given intravenously twice/d, levocetirizine tablets 5 mg was given orally once/d, and topical application of glycopyrrolate lotion was made. The erythema partially subsides after medication, but more new rashes are still visible.3 d later (July 15), the lesions were significantly worse than before, accompanied by fever and a body temperature of 38.2 ℃. The erythematous patches all over the body were enlarged than before and partially fused into a large area, and a few pinpoint-sized pustules appeared on the buttocks and lower limbs. Laboratory tests: WBC: 13.87×10^9/L, NEUT% 88.5, N 12.26×10^9/L, CRP 43.2 mg/L, drug dermatitis was considered (acute generalized eruptive pustulosis?). The dermatitis was considered to be drug dermatitis (acute pustular eruption?) and was increased to 80 mg/d with intravenous methylprednisolone sodium succinate. On the 5th day (July 16), the patient continued to have a high fever, with temperature fluctuating from 38.5 ℃ to 40.0 ℃, and typical skin lesions appeared (Figure 1 A): dense pinpoint-sized, non-follicular yellow-white pustules based on diffuse, edematous erythema were seen all over the body, partly forming a pus lake, with heavier back and buttocks, localized ruptured erosions were visible, Nisei's sign was negative, the face and abdomen were covered with a small number of scales, and the mucous membrane of the vulva was visible A small number of pinpoint-sized pustules on erythema, oral mucosal erosion improved. Combined with the patient's auxiliary examinations: WBC: 19.1×10^9/L, NEUT% 86.2, N 16.47×10^9/L, CRP 64.25 mg/L, blood potassium 3.14 mmol/L, total calcium 1.94 mmol/L; liver function: total protein 61.3 g/L, albumin 36.2 g/L; renal function did not show significant abnormalities; blood culture: no bacterial, anaerobic bacteria growth, Blood culture: no bacterial or anaerobic bacteria growth. Diagnosis: drug dermatitis (acute generalized eruptive pustulosis); The patient refused skin biopsy

and was given intravenous methylprednisolone sodium succinate 80 mg/d and human immunoglobulin (0.4 mg per kg body weight, 18.8 mg of human immunoglobulin 17.5 g per 7 bottles), cefazoxime sodium 2 g intravenous drip 2 times/d to prevent wound infection, correction of electrolyte disturbance, and nutritional support, The patient was treated with topical fusidic acid cream and moist burn cream to enhance wound care. On the 11th day (July 22), the temperature dropped to 37.4 ℃, and most of the pustules dried up and began to desquamate extensively (Figure 1B). The rash did not reappear. The hormone was changed to methylprednisolone tablets 40 mg orally once/d. After the condition stabilized, the patient was discharged on 2022.08.15. At the time of discharge, the hormone was gradually reduced to 8 mg/d and discontinued after 10 days of oral administration.

2. Discussion

Any drug has the potential to cause adverse reactions, and about 45% of adverse drug reactions occur on the skin[1]. Acute generalized exanthematous pustulosis (AGEP) is a rare delayed hypersensitivity reaction caused by drug allergy, described in 1980 by Beylot[2] et al was first reported. The rash usually occurs within 1-2 days after drug administration and quickly spreads throughout the body. The lesions resolve within 15 days after drug discontinuation and are characterized by edematous erythema based on dense sterile small pustules, pustules, and fever that usually persist for about 1 week before rapidly resolving, followed by extensive desquamation. This patient had a score of 7 based on the European study of severe cutaneous adverse reactions (EuroSCAR) scale, which means that AGEP is likely, but since the patient refused to undergo a skin biopsy, the histology score was 0, so the score value Since the patient refused to undergo a skin biopsy, the histology score was 0, so the score did not reach the score required to confirm the diagnosis. The patient was in good health and had no history of psoriasis. The diagnosis of AGEP was made in the context of lesion characteristics, febrile features, routine peripheral blood tests, and blood cultures.

To objectively assess the causal relationship between drug use and adverse reactions in this patient, reports of AGEP caused by clopidogrel bisulfate tablets were identified by searching relevant literature included in PubMed, China Knowledge Network, Wanfang Medical Database, and Chinese Academic Journals Full Text Database up to September 2022, but no reports of AGEP caused by butalbital sodium chloride injection, cytarabine tablets, atorvastatin calcium tablets, and bayaspirin enteric soluble tablets were found. The suspect drugs were scored using Naranjo's assessment scale: butylphthalide sodium chloride injection (+5 points), clopidogrel hydrogen sulfate tablets (+5 points), and all other coadministered drugs had a score of ≤1 on Naranjo's scale, and could be largely excluded. Butylphthalide is an artificially synthesized racemic n-butylphthalide, which has the same structure as natural levulinic acid, and its high lipid solubility makes it easy to pass the blood-brain barrier and act directly on the infarct site, which can effectively regulate the energy metabolism level of the patient's brain in the ischemic state, thus improving the low blood flow caused by the brain blood disorder, reducing the degree of brain edema, and achieving the effect of promoting the recovery of the patient's central nervous function[3]. Clopidogrel is a new type of anti-platelet coagulation drug, which can effectively block ADP receptors, and then bind to platelet membrane receptors in the patient's body blood to enhance platelet activity and achieve the effect of inhibiting platelet aggregation. Combined with butylphthalide in the treatment of acute cerebral infarction, it is effective in reducing inflammation levels and plasma viscosity, promoting improvement in neurological function and improving the quality of life of patients[4-5], in recent years, it has been widely used in clinical practice for the treatment of acute cerebral infarction, and the incidence of adverse effects may increase.



A: Typical skin lesions: diffuse and edema erythema, with dense yellow and white pustules of tip size and visible part of lower limbs; B: Most of the pustules dried up after anti-allergy treatment and began large desquamation, and large erythema was still seen in both lower limbs

Figure 1: AGEP skin lesions caused by sodium butylphthalide injection

In the process of identifying allergenic drugs, re-initiation tests in adverse drug reaction studies provide the most direct and effective evidence of the causal relationship between adverse drug reactions[6], the instructions for clopidogrel bisulfate tablets state that adverse reactions to AGEP are very rare, and that after the patient's skin lesions have improved, to reduce the recurrence of stroke[7], anti-platelet aggregation therapy with clopidogrel sulfate tablets was restarted after evaluation by a specialist, and the patient was closely monitored for skin lesions; no skin lesions were found as before. Therefore, it is considered unlikely that the patient's AGEP was induced by hydro clopidogrel sulfate tablets alone. In addition, considering the irreversibility of the pathological damage and the principle of medical ethics of not harming, butylphthalide was not reapplied to the patient. The drug that triggered the patient's AGEP was preferentially considered to be butylphthalide in combination with Noah's Assessment Scale score. After the rash's onset, the clinician could not make a timely pathological histological examination due to the patient's poor compliance. Fortunately, we correctly diagnosed the disease based on clinical symptoms and other ancillary tests and provided symptomatic supportive treatment, which eventually allowed the patient to improve and be discharged. Since there are no contemporary reports of AGEP triggered by butylphthalide sodium chloride injection and the occurrence of adverse drug reactions cannot be predicted, clinicians and pharmacists should increase their clinical acumen and pay close attention to the occurrence of skin lesions when using this drug.

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