A case of herbal medicine induced toxic epidermal necrosis in a hypergammaglobulinemic purpura of Waldenström patient

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Abstract

We are reporting a case of toxic epidermal necrosis induced by herbal medicine in a 54-year-old woman who had been diagnosed with primary Sjogren’s syndrome for nine years and had discontinued all conventional therapies for at least one year. Approximately two weeks prior to her current admission, she developed crops of petechiae and purpuric macules on her lower extremities, which are typical symptoms of hypergammaglobulinemic purpura of Waldenström, and began taking herbal medicine. The following day, she presented to us with a high fever and new, generalized erythematous rashes over her face and trunk. She was ultimately diagnosed with toxic epidermal necrosis induced by the herbal medicine.

Introduction

Toxic epidermal necrolysis (TEN) is a severe and acute mucocutaneous reaction, typically caused by drugs, which results in the loss of epidermis and multi-site mucositis, accompanied by systemic disturbance. Lamotrigine, carbamazepine, allopurinol, sulfonamide antibiotics, and nevirapine are some of the most common drugs associated with TEN\cite{1, 2}. Although there are numerous reports of drug-induced TEN, most of them focus on synthetic agents rather than herbal medications. In this report, we present a rare case of herbal medicine-induced toxic epidermal necrosis in a patient with hypergammaglobulinemic purpura of Waldenström (HGP).

Case Report

A 54-year-old woman with a history of primary Sjogren’s syndrome for nine years, who had been treated with prednisone and total glucosides of paeony capsule but had discontinued the medications for at least one year, was admitted to the hospital with fever and rashes. Approximately two weeks prior to her current admission, she developed crops of petechiae and purpuric macules on her lower extremities (Figure 1) and was ultimately diagnosed with hypergammaglobulinemic purpura of Waldenström (HGP), a rare complication of Sjogren’s syndrome. She began taking herbal medicine two days prior to admission, with a daily dose of approximately 200ml. The prescription included 5 g Safflower, 5 g Peach kernel, 5 g Ligusticum Chuanxiong Hort, 5 g Ephedra, 10 g Paris Rhizome, 15 g Gegen, 15 g Perilla, 5 g Cassia Twig, 10 g Atractylodes, 10 g Bergamot, 15 g Achyranthes Bidentata Blume, and 10 g Caulis Cissi. The day after starting the herbal treatment, she developed a high fever and new generalized erythematous rashes over her face and trunk. Additionally, she had painful blisters with crusting over her lips and oral mucosa, accompanied by mucopurulent secretion flowing out from her lacrimal punctum (Figure 2). Over the course of two days, the rash spread peripherally to involve more than 80% of her body surface area and progressed rapidly from discrete and confluent macules to blisters. Dermatological examination revealed that all of the rash, except that on her lower extremities, was markedly erythematous, edematous, tender, and peeling off from her body. Nikolsky’s sign was positive.
Her clinical presentation and history of taking herbal medicine strongly suggested a diagnosis of herbal medicine induced TEN (Table 1). However, due to the patient’s reluctance to undergo further testing, the exact causative medicine could not be identified. Nonetheless, the clinical picture and timing of symptoms in relation to the herbal medicine intake supported this diagnosis.

Based on the patient’s medical history, laboratory data and physical examination, a diagnosis of hypergammaglobulinemic purpura of Waldenström complicated with primary Sjögren’s syndrome was made. The presence of lower extremities purpura, mild anemia (hemoglobin 104 g/L), hypergammaglobulinemia (IgG 25.56 g/L), elevated ESR (ESR 65 mm/h), and positive anti-extractable nuclear antigen antibodies, including anti-SSA, anti-SSB, and anti-Ro-52, were indicative of this diagnosis. The fact that the purpura rashes on her lower extremities were the only residual sequelae of the disease process with lesions over other parts of the body disappeared was also considered significant.

The treatment plan of stopping the herbal medicine and administering methylprednisolone (500 mg/day) and immunoglobulin (20 g/day) intravenously was appropriate for managing the patient’s TEN. Pain control, skin, mouth, and eye care, as well as infection prevention, are also crucial components of the management of TEN. In addition, liver and renal protection are important as certain medications used in the treatment of TEN can cause liver or kidney damage. Overall, the management plan appears to be comprehensive and appropriate for the patient’s condition.

Discussion

TEN is a severe skin condition that can be life-threatening, characterized by widespread skin rash, blistering, and detachment of the epidermis and mucous membranes, often accompanied by systemic symptoms such as dehydration, sepsis, and multiple organ failure. The majority of TEN cases are caused by drug reactions, with up to 95% of cases being attributed to drug use. Lamotrigine, carbamazepine, allopurinol, sulfonamide antibiotics, and nevirapine are some of the most commonly reported causative drugs [1, 2]. While synthetic medications are often implicated, herbal medications have also been reported as a rare cause of TEN. In this case, the patient had a history of primary Sjögren’s syndrome for nine years and had stopped all conventional therapy for at least one year before taking herbal medicine, which was suspected to be the cause of her TEN. An algorithm called ALDEN (ALgorithm of Drug causality in Epidermal Necrolysis) has been developed to help identify the causative drug in TEN [3]. Skin tests, such as patch, prick, or intracutaneous tests, may also be useful in identifying the offending drug [4]. However, in this case, the patient declined further testing to determine which herbal medication was the culprit. The patient was treated with a combination of methylprednisolone and immunoglobulin, as well as other supportive measures, including pain control, skin, mouth, and eye care, and infection prevention.

Autoimmune disease such as systemic lupus erythematosus [5, 6] and Sjögren’s syndrome [6] may be risk factors for TEN. In our case, the patient had a history of primary Sjögren’s syndrome. About half month before taking herbal drugs she presented with crops of petechiae and purpuric macules on her lower extremities, which did not disappear in the exfoliation process of TEN. The clinical picture, together with her laboratory data, were consistent with a diagnosis of HGP, which was first described by the Swedish physician Jan Gosta Waldenström in 1943 [7]. He reported three cases of women with chronic relapsing purpura, hypergammaglobulinemia, an elevated erythrocyte sedimentation rate, and mild anemia. This syndrome was usually concomitant with autoimmune disease, most frequently Sjögren’s syndrome and occasionally rheumatoid arthritis or lupus erythematosus [8]. The pathogenesis of HGP remains incompletely understood. An immune dysregulation hypothesis, supported by the fact that the small circulating immune complexes containing monoclonal IgG or IgA rheumatoid factor had been isolated in individuals with a clinical presentation that fits this syndrome, were put forward to unfold the pathological mechanism [9, 10]. In the case under discussion, the patient’s rheumatoid factor was 405 IU/L and IgG was 25.56 g/L.

A noteworthy aspect of this case is that the patient had a history of autoimmune disease, which is a known risk factor for TEN. Furthermore, she stopped her regular therapy for Sjögren’s syndrome for at least one year before taking the herbal medicine. It is possible that the immune dysregulation caused by the underlying
autoimmune disease and the absence of proper medical management created an environment in which herbal medicine triggered a severe immune response, resulting in TEN.

It is essential to note that while herbal medicine is perceived as "natural" and "safe" by some individuals, it can have adverse effects and interact with conventional medications. The lack of regulation and standardized manufacturing processes of herbal products make it difficult to ensure their safety and efficacy. Moreover, herbal medicine use is often not disclosed to healthcare professionals, making it challenging to identify possible drug interactions and adverse effects.

In conclusion, healthcare providers should be aware of the potential adverse effects of herbal medicine use, especially in patients with underlying autoimmune diseases. Patients should be educated on the potential risks of herbal medicine use and advised to disclose all medications they are taking to their healthcare provider. A comprehensive approach that includes a thorough history, physical examination, laboratory evaluation, and skin testing can help identify the causative agent in TEN and other adverse drug reactions.

Declarations

Ethical Approval
Not applicable.

Consent for publication
All authors agree to publication.

Availability of data and materials
All data generated during this study are included in this published article.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors’ contributions
Author 1 (Tan xiaoli): Typesetting of articles and grammar changes. Author 2 (Li yaling) and Author 3 (Wu zhixiong): Revision of article grammar, checking. Author 4 (Tang liang): Organizing pictures. Author 5 (Fu qiang): Writing Original Draft; Provide case reports. Author 6 (ouyang fan) (Corresponding Author): Proofread the editor’s language.

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References


Table I. Similar type IV reactions caused by herbal prescriptions

Figure 1 Widespread petechiae and purpuric macules on the lower extremities

Figure 2 (A) Widespread erythematous rashes with blisters over the posterior trunk. (B) Blisters with exfoliation over the lips and oral mucosa. (C) Scattered erythematous rashes on the face with purulent conjunctivitis.
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Table1.docx available at https://authorea.com/users/618763/articles/643712-a-case-of-herbal-medicine-induced-toxic-epidermal-necrosis-in-a-hypergammaglobulinemic-purpura-of-waldenström-patient