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Drug-Induced Hypersensitivity Syndrome Followed by Subacute Thyroiditis

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Key Words

Drug-induced hypersensitivity syndrome · Drug rash with eosinophilia and systemic symptoms · Subacute thyroiditis · Human herpesvirus 6 · Cytomegalovirus

Abstract

Drug-induced hypersensitivity syndrome (DIHS) is a severe multiorgan system adverse drug reaction with reactivation of human herpesviruses (HHVs) such as HHV-6, HHV-7, cytomegalovirus (CMV) and Epstein-Barr virus. Various complications, including autoimmune diseases, sometimes appear during the course of DIHS. We report a case of salazosulfapyridine-induced DIHS associated with HHV-6 reactivation. Two and a half months after the onset of DIHS, subacute thyroiditis occurred, possibly associated with CMV reactivation. Prednisolone (20 mg/day) was effective for subacute thyroiditis. Long-term follow-up is needed in patients with DIHS because of the possible onset of autoimmune diseases. © 2015 S. Karger AG, Basel

Introduction

Drug-induced hypersensitivity syndrome (DIHS), also called drug rash with eosinophilia and systemic symptoms (DRESS), is a severe multiorgan system adverse drug reaction characterized by skin eruption, fever, lymph node swelling, liver dysfunction and eosinophilia. This disease is associated with reactivation of human herpesvirus 6 (HHV-6) and/or other herpesviruses such as HHV-7, cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Multiple organ failure and autoimmune diseases sometimes appear during the course of DIHS [1]. We report here a case of DIHS induced by salazosulfapyridine, which was associated with

HHV-6 reactivation. Subacute thyroiditis, possibly associated with CMV reactivation, occurred two and a half months after the onset of DIHS.

Case Report

A 60-year-old Japanese woman with rheumatoid arthritis experienced fever (38.5°C), flu-like symptoms and maculopapular eruptions with erythema on her entire body after taking oral salazosulfapyridine (1,000 mg/day) for 1 month. Although salazosulfapyridine was discontinued, nonpruritic eruptions on the patient's face, four extremities (fig. 1a) and trunk (fig. 1b) continued, as did her fever (>38.5°C) and lymph node swelling of the bilateral neck. Laboratory data showed the following results: aspartate aminotransferase 63 IU/l, alanine aminotransferase 204 IU/l, lactate dehydrogenase 338 IU/l, C-reactive protein (CRP) 1.58 mg/dl, erythrocyte sedimentation rate (ESR) 22 mm/h, leukocyte count 10,310/ μ l (lymphocytes 17.1%, atypical lymphocytes 6.5%, eosinophils 4.5%) and IgG 688 IU/l (normal 890–1,850). The levels of thyroid-stimulating hormone (TSH) (1.03 μ IU/ml, normal 0.35–4.94), free triiodothyronine (fT3) (1.80 pg/ml, normal 1.71–3.71) and free thyroxine (fT4) (0.97 ng/dl, normal 0.70–1.48) were within normal ranges. A skin biopsy specimen obtained from a maculopapular eruption on the thigh showed slight lymphocytic infiltration in the epidermis and massive infiltration of lymphocytes and eosinophils around the capillaries in the upper dermis (fig. 1c). Therefore, a diagnosis of DIHS/DRESS induced by salazosulfapyridine was made. The patient was treated with 30 mg/day of prednisolone. The skin eruptions, fever and lymph node swelling rapidly disappeared, and liver function returned to normal. The dose of prednisolone was gradually reduced. IgM antibodies to HHV-6, HHV-7, CMV and EBV as well as antinuclear antibodies were negative at the initial consultation. The HHV-6 IgG antibody titers (fluorescent antibody test) increased from 1:20 to 1:160 on day 37 from onset.

On day 78, the patient developed painful swelling on the right side of her neck, temperature of >39°C, palpitations and hidropoiesis. Laboratory tests revealed the following: TSH <0.01 μ IU/ml, fT3 10.75 pg/ml, fT4 4.67 ng/dl, CRP 7.60 mg/dl and ESR 98 mm/h. Anti-thyroid peroxidase antibodies (titer 9 IU/ml, normal <16) and anti-thyroglobulin antibodies (titer 144 IU/ml, normal <28) were positive, but anti-TSH receptor antibodies were negative. Ultrasonography of the thyroid gland revealed an area of low absorption in the thyroid gland consistent with subacute thyroiditis. The prednisolone dose was increased from 10 to 20 mg/day and the patient's symptoms, including fever and right-sided neck pain, disappeared, with fT3 and fT4 levels returning to normal ranges. The dose of prednisolone was gradually reduced to 3 mg/day. During the tapering of the dose, a transient increase in the TSH level occurred. Titers of the antibodies to thyroperoxidase and thyroglobulin decreased during tapering. On day 78, the anti-HHV-6 antibody IgG titer remained at 1:160, but the anti-CMV antibody IgG titer (enzyme immunoassay) had increased from 40 to 107 (fig. 2). IgG antibodies to HHV-7 and EBV were unchanged from initial values.

Discussion

The pathogenic mechanism underlying the reactivation of multiple herpesviruses and the associated organ failure that occurs in DIHS have not been fully elucidated. It may be explained by the expansion of fully functional regulatory T cells in the acute phase of DIHS, which allows viral reactivation but results in the loss of their suppressive function upon

clinical resolution [2]. A functional defect in regulatory T cells might be responsible for the subsequent development of autoimmune diseases [3]. Thyroid dysfunction, including Graves' disease [1], Hashimoto thyroiditis [4, 5], autoimmune thyroiditis and painless thyroiditis [6], has been reported to be the most frequent sequelae of DIHS [7]. The delayed development of these types of thyroiditis appears 1–17 months after DIHS [5, 6]. Patients with DIHS should be monitored for the possible onset of autoimmune diseases even after complete recovery [3].

To our knowledge, this is the first case of subacute thyroiditis occurring subsequent to DIHS. Subacute thyroiditis, often caused by an undefined viral infection, is characterized by fever and painful anterior cervical swelling with a reduced TSH level and increased levels of fT3, fT4, CRP and ESR [8]. Titers of autoantibodies to thyroid peroxidase and thyroglobulin are often transiently elevated. Although it is a self-limited inflammatory disorder, patients with subacute thyroiditis are treated with nonsteroidal anti-inflammatory drugs and/or corticosteroids to relieve symptoms. Based on the clinical and laboratory findings, our patient was diagnosed with subacute thyroiditis following DIHS. Prednisolone effectively resolved the patient's clinical symptoms and abnormal laboratory values. Since we were unable to perform a biopsy of the thyroid gland, a persistent presence of viral DNAs such as CMV and HHV-6 within the thyroid could not be shown. However, CMV reactivation can be assumed based on the increased titer of IgG antibody two and a half months after onset. Multiviral reactivation has been reported in DIHS [9], and HHV-6 reactivation has been shown to be followed by reactivation of CMV, HHV-7 or EBV [10]. Although CMV reactivation, which occurred following HHV-6 reactivation in the present case, may have been associated with subacute thyroiditis, viral infections other than HHV-6, HHV-7, CMV and EBV can also cause subacute thyroiditis.

Statement of Ethics

The authors state that the patient gave her informed consent. The research complies with all ethical guidelines for human studies.

Disclosure Statement

The authors declare no conflict of interest. There was no funding.

References

- 1 Brown RJ, Rother KI, Artman H, Mercurio MG, Wang R, Looney RJ, Cowen EW: Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol* 2009;145:63–66.
- 2 Shiohara T, Ushigome Y, Kano Y, Takahashi R: Crucial role of viral reactivation in the development of severe drug eruptions: a comprehensive review. *Clin Rev Allergy Immunol* 2014, Epub ahead of print.
- 3 Aota N, Shiohara T: Viral connection between drug rashes and autoimmune diseases: how autoimmune responses are generated after resolution of drug rashes. *Autoimmun Rev* 2009;8:488–494.
- 4 Caselli E, Zatelli MC, Rizzo R, Benedetti S, Martorelli D, Trasforini G, Cassai E, degli Uberti EC, Di Luca D, Dolcetti R: Virologic and immunologic evidence supporting an association between HHV-6 and Hashimoto's thyroiditis. *PLoS Pathog* 2012;8:e1002951.
- 5 Minegaki Y, Higashida Y, Ogawa M, Miyachi Y, Fujii H, Kabashima K: Drug-induced hypersensitivity syndrome complicated with concurrent fulminant type 1 diabetes mellitus and Hashimoto's thyroiditis. *Int J Dermatol* 2013;52:355–357.

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- 6 Ito K, Akita Y, Ishida N, Kasugai C, Tamada Y, Watanabe D: Painless thyroiditis in drug-induced hypersensitivity syndrome with prolonged reactivation of herpesviruses. *Int J Dermatol* 2013;52:475–477.
- 7 Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY: Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol* 2013;68:459–465.
- 8 Pearce EN, Farwell AP, Braverman LE: Thyroiditis. *N Engl J Med* 2003;348:2646–2655.
- 9 Seishima M, Yamanaka S, Fujisawa T, Tohyama M, Hashimoto K: Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. *Br J Dermatol* 2006;155:344–349.
- 10 Descamps V, Mahe E, Houhou N, Abramowitz L, Rozenberg F, Ranger-Rogez S, Crickx B: Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. *Br J Dermatol* 2003;148:1032–1034.

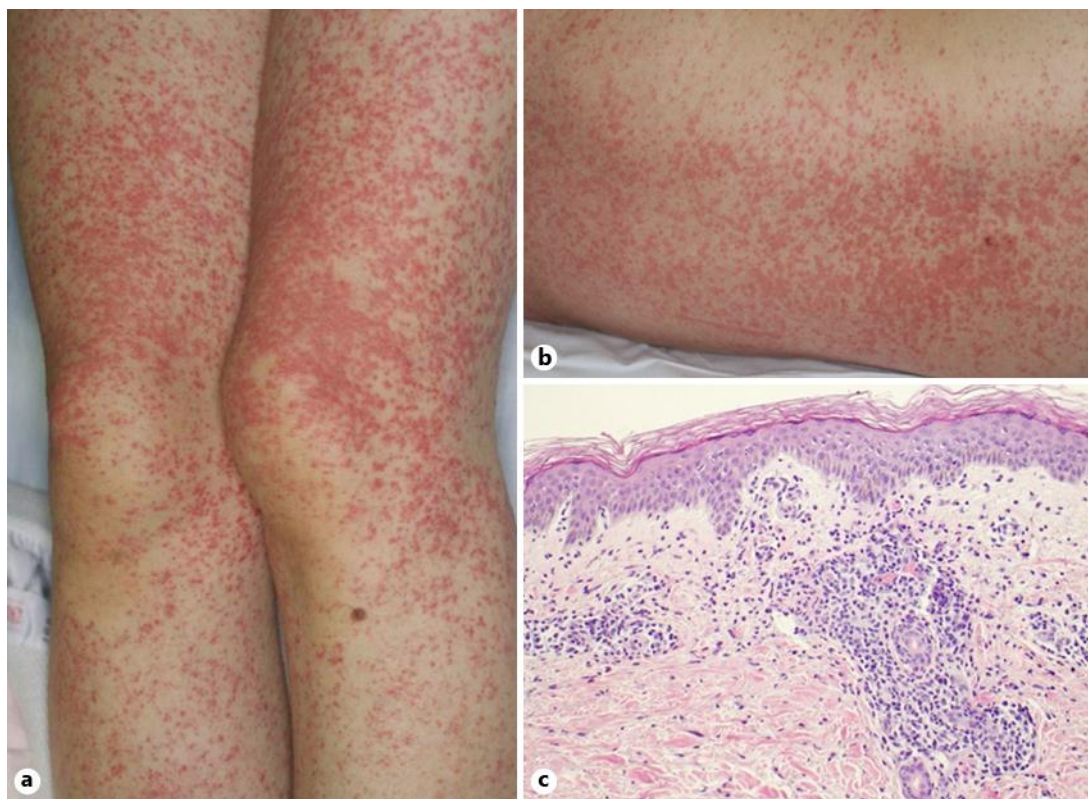


Fig. 1. Clinical findings of the lower extremities (a) and back (b), and histological findings of a maculopapular eruption on the thigh (c) (H&E stain, original magnification; $\times 100$) on initial consultation.

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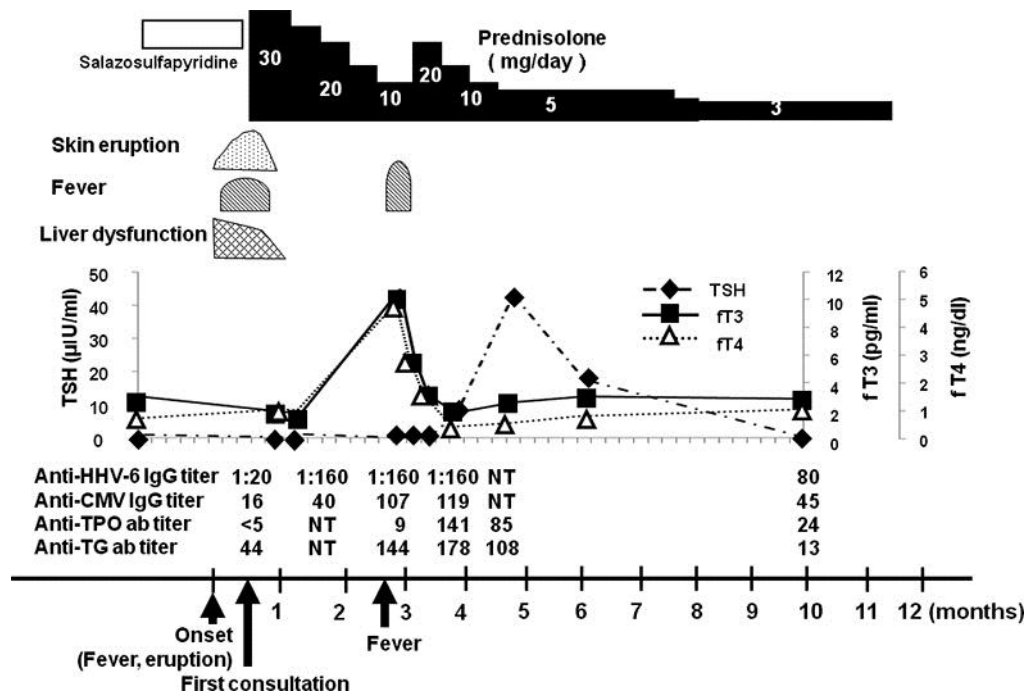


Fig. 2. Clinical course and treatment. Anti-TPO ab = anti-thyroid peroxidase antibody; Anti-TG ab = anti-thyroglobulin antibody; NT = not tested.