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CASE REPORT

A case of severe erythema nodosum induced by methimazole

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KEYWORDS

Anti-thyroid drugs;
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Abstract Erythema nodosum (EN), is the most common variant of septal panniculitis and is possibly a delayed hypersensitivity reaction triggered by a wide range of antigenic stimuli. Hypersensitivity reactions due to medications have been recognized as a cause of 3–10% of EN cases. Case reports of EN associated with the anti-thyroid drugs are quite rarely reported in the literature even if there is a common use of anti-thyroid drugs. We report an EN case due to methimazole. The complaints of patients arose immediately fifteen days after the beginning of methimazole treatment. To the best of our knowledge, this case report is the first of an erythema nodosum induced by methimazole.

1. Introduction

Erythema nodosum (EN), is the most common variant of septal panniculitis. Cutaneous lesions are usually acute, painful, erythematous, round or oval subcutaneous nodules on the extensor areas of the lower extremities. EN is possibly a delayed hypersensitivity reaction triggered by a wide range of antigenic stimuli. The most common causes include drugs, bacterial, viral and fungal infections, pregnancy, systemic diseases such as sarcoidosis, malignant diseases, and inflammatory bowel diseases. However, in more than 55% cases etiologic factors cannot be cleared and are considered to be idiopathic. Hypersensitivity reactions due to medications have been recognized as a cause of 3–10% of EN cases (Blake et al., 2014; Schwartz and Nervi, 2007). We report an EN case due to methimazole, as an unusual cause. To the best of our knowledge, this case report is the first of an erythema nodosum induced by methimazole.

2. Case

A 64-year-old female patient was admitted to our outpatient clinic with the complaints of multiple erythematous, painful, nodules on both of the legs for fifteen days (Fig. 1). Laboratory examination revealed normal hepatic and renal functions. Complete blood count showed mild neutrophilia. Skin biopsy

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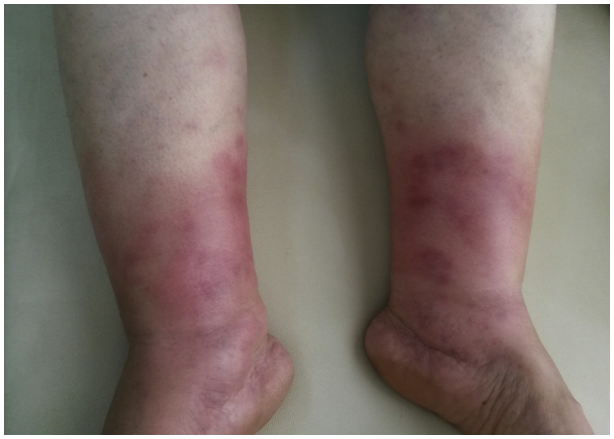

Figure 1 Multiple erythematous, nodules on both of the lower legs.

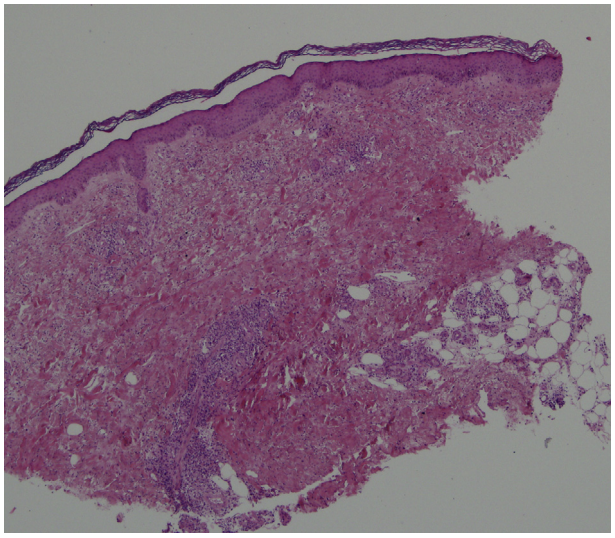

Figure 2 Mixed type inflammatory cell infiltration and lymphocytic vasculitis in dermis. HE, 40×.

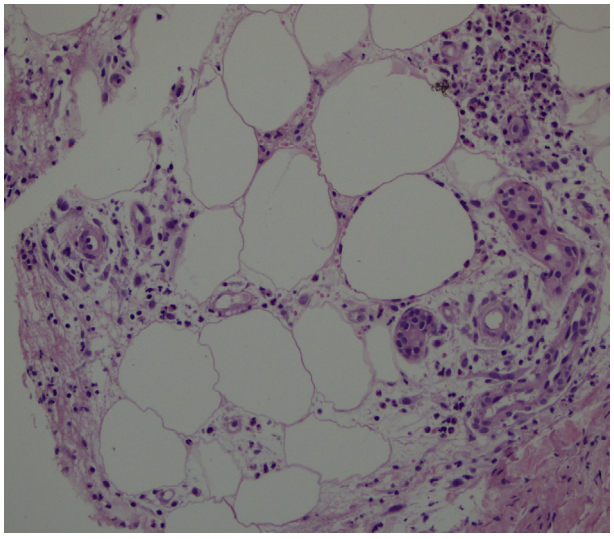

Figure 3 There is an inflammation compatible with septal panniculitis in subcutaneous fat tissue. HE, 200×.

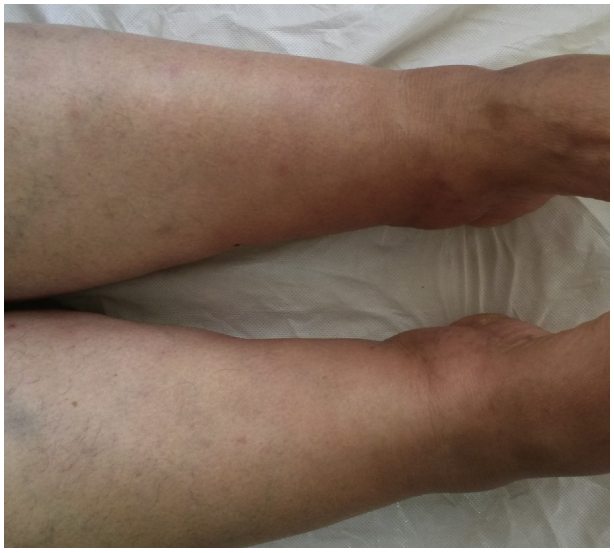

Figure 4 The appearance of the legs after healing.

was performed from erythematous nodules. Histopathological examination revealed spongiosis in epidermis, mixed type inflammatory cell infiltration and lymphocytic vasculitis in dermis and inflammation consistent with septal panniculitis at the subcutaneous tissue (Figs. 2 and 3). She was diagnosed as EN based on physical and histopathological examinations. Chest radiography, erythrocyte sedimentation rate, urinalysis, antinuclear antibody, and serum ACE levels were normal. Mantoux test, serology for hepatitis and laboratory tests for other infectious agents were negative. She had essential hypertension for 5 years and was using perindopril 5 mg/day and indapamide 1.25 mg/day. Methimazole 20 mg per day was also started for hyperthyroidism associated with Graves' disease, a month ago. Her serum free T4 and free T3 levels were in normal limits and TSH was 0.05 mIU/mL (0.27–4.2 mIU/mL) at that time. On the other hand, indomethacin 75 mg/day, and topical corticosteroid creams were prescribed for the treatment of erythema nodosum. Empirical amoxicillin/clavulanic acid (875 mg/125 mg twice daily peroral) was started against possible streptococcal infections before laboratory tests resulted. Elevation and wet dressing were also recommended at the same time. Since laboratory results did not show evidence of any infection, the antibiotic therapy was stopped after three days. We noticed that her complaints were increased at the second follow-up appointment. When we deepened the history of the patient we discovered that her complaints were started fifteen days after the beginning of methimazole treatment. Therefore methimazole was stopped and the lesions improved in one week (Fig. 4). Propylthiouracil was started instead of methimazole and after that time she has not reported any side effects or complaints about this drug during the medication for a year. The consent of the patient was received for this report.

3. Discussion

Anti-thyroid drugs (ATDs) that are the members of the thioamide group include methimazole, carbimazole and propylthiouracil have been used in the treatment of the hyperthyroidism for approximately 60 years. Methimazole is active metabolite of carbimazole (Taylor and Vaidya, 2012). The most common side effects of ATDs are skin rash, low grade liver dysfunction, granulocytopenia and arthralgia. Myeloperoxidase antineutrophil cytoplasmic antibody (ANCA) related vasculitis, agranulocytosis and severe hepatotoxicity are rare but serious complications of ATDs (Yang et al., 2015). EN is an immune associated non-specific cutaneous reaction that develops as a response to a specific stimuli. It has been presumed to be a hypersensitivity reaction. Hypersensitivity reactions due to medications have been recognized as a cause of 3–10% of erythema nodosum cases (Schwartz and Nervi, 2007). Case reports of EN associated with the anti-thyroid drugs are quite rarely reported in the literature even if there is a common use of anti-thyroid drugs.

Up to date there are only a few anecdotal cases about these anti-thyroid drugs and EN. Two case reports of EN induced by propylthiouracil have been reported (Keren et al., 1985; Wan et al., 2012). In the EN case induced by propylthiouracil that was reported by Wan et al., ANCA positivity was also accompanied (Wan et al., 2012). The third case of EN induced by ATDs was due to carbimazole. EN, acute pancreatitis and hepatic cholestasis were reported in a 33 year-old female patient using carbimazole. These side effects were observed one month later from the beginning of the carbimazole treatment in this patient (Marazuela et al., 2002). Different from the other cases, our patient was the first case of EN that was observed after the usage of methimazole. In our patient lesions continued to develop by increasing even if there is an adequate treatment for EN in a period of one month and lesions had disappeared by improving fast in one week after the cessation of the treatment. We could not find any other etiologic reasons for EN. Streptococcal infections are one of the most common causes of EN (Chowaniec et al., 2016; Starba et al., 2016). We had prescribed empirical antibiotic therapy against possible streptococcal infections, by the time the laboratory tests resulted. But streptococcal infection was not found on laboratory examinations and we stopped antibiotic therapy. Therefore we thought that these EN lesions were induced by methimazole. The EN lesions were localized on the lower legs typically. While the lesions are present, the methimazole treatment was stopped and propylthiouracil treatment was started. There was no recurrence in a period of 1 year follow-up during propylthiouracil treatment. Since these lesions appeared 2 weeks after the beginning of the methimazole, we think that these EN lesions are idiosyncratic hypersensitivity reaction. Sulfonamides are well-known causes of EN. Marazuela et al. (2002) suggested that the sulphydryl groups that are the components of thioamides can cause hypersensitivity reaction and EN. However, in our case propylthiouracil did not induce EN which was also a member of thioamide group. Probably, in our case methimazole caused immune–mediated reaction by another different way. Therefore we should keep methimazole induced EN in mind in the patients that have EN like lesions that the etiologic factors cannot be illuminated during methimazole treatment.

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