Turkish Journal of Endocrinology and Metabolism, (2005) 4 : 125-127 **CASE REPORT**

A Case of Methimazole Induced Leukocytoclastic Vasculitis

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Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis has been described frequently in patients treated with propylthiouracil (PTU). However, other antithyroid drugs, carbimazole and methimazole (MMI), rarely cause vasculitis. We report a case of MMI induced ANCA negative leukocytoclastic vasculitis.

Keywords: Antithyroid drugs, methimazole, adverse effects, vasculitis, ANCA

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Antithyroid drugs, methimazole (MMI), carbimazole, and propylthiouracil (PTU) are a mainstay of therapy of thyrotoxicosis. Although antithyroid agents are generally safe, a variety of minor side effects, as well as potentially life-threatening complications may limit their usefulness. Side effects of antithyroid drugs are classified as minor or major, based on their degree of morbidity or possible mortality. Vasculitis is one of the major side effects of antithyroid drugs, associated with antineutrophil cytoplasmic antibodies (ANCA) has been reported on following treatment with PTU. However, vasculitis rarely appears with methimazole and carbimazole (1). We report on a patient with toxic multinodulary goiter who after being treated with methimazole for one week, developed eruptions on the legs.

Case Report

A 56-year-old man referred to dermatology for evaluation of extensive purpuric lesions on the legs. He had a 3-years history of hyperthyroidism, which was treated with a 2-years course of PTU without any problems, had discontinued the PTU for one year until the recurrence of hyperthyroidism. He was treated with one week course of MMI 20 mg/day for preparative therapy before surgery due to the diagnosis of toxic multinodulary goiter. At 7th day of methimazole treatment, erythematous rashes were started on the ankles. The skin lesions spread out and got worsen over the next week and turn into palpable purpura and ecchymosis on the legs (Figure 1). A skin punch biopsy specimen of the rash revealed leukocytoclastic vasculitis. The patient did not have a history of systemic rheumatic disease. The patient had no fever, arthralgias, or diarrhea. The laboratory studies revealed free T4 was 3.47 ng/dl (normal: 0.8-1.9), TSH was 0.007 μU/ml (normal: 0.4-4) and C reactive protein concentration was 23.7 mg/ml (normal <5 mg/ml). Chest radiographs and other laboratory investigations were normal, including anti-thyroglobulin antibody, anti-microsomal antibody, complete blood cell count, erythrocyte sedimentation rate (ESR), urinalysis, prothrombin time, activated partial thromboplastin time and the rheumatoid factor. The results of blood cultures and serological tests for hepatitis B, hepatitis C, syphilis and HIV were negative. Antinuclear antibody was found negative at a serum dilution of 1:40 by means of indirect immunofluorescence microscopy, using HEP-2 cells. Anti-ds DNA was noted as 2.0 IU/ml (normal < 5). Also pANCA and cANCA tests were found negative by means of indirect fluorescence antibody method. Methimazole was discontinued and, treatment with methylprednisolone 40 mg/day was started. The systemic steroid dose was gradually tapered after ten days with a marked clinical improvement. For preparation to surgery, we started PTU because of

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previous uncomplicated long-term use of this agent. Although there was a cross reaction risk, patient was tolerated the drug well.

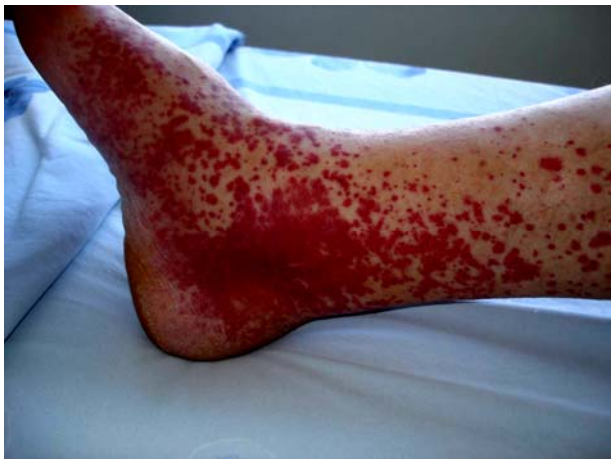

Figure 1. Extensive purpura and ecchymosis on the leg.

Discussion

Vasculitis can affect small, medium, and large blood vessel walls of cutaneous, renal, pulmonary, musculoskeletal, neurologic, and mucosal tissues (2). The etiologies of vasculitis include autoimmune disorders, infections, and medications. In general, drug induced vasculitis are associated with PTU, hydralazine, granulocyte-colony stimulating factor (G-CSF), cefaclor, minocycline, allopurinol, D-penicillamine, phenytoin, isotretinoin, and methotrexate. The pathogenesis of drug-induced vasculitis is not well understood. Recently, there has been a spate of reports of patients with antithyroid drug-induced vasculitic syndromes associated with pozitive ANCA. This antibody is classically seen in systemic vasculitic disorders that include Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and necrotizing crescentic glomerulonephritis, as well as drug-induced vasculitis (3). ANCA is classified into two types, cytoplasmic pattern (c-ANCA) and perinuclear pattern (p-ANCA), by indirect immunofluorescence. P-ANCA is directed primarily against myeloperoxidase (MPO), whereas that of c-ANCA is proteinase 3 (PR3) as shown by enzyme-linked immunosorbent assay (ELISA) (4).

PTU has been the most commonly implicated drug related to vasculitic reactions inducing anti-neutrophil cytoplasmic antibody (ANCA) (5). Methimazole and carbimazole, two other antithyroid drugs, can also cause ANCA-positive vasculitis, but much less frequently than propylthiouracil (6). Although the pathogenesis of methimazole-induced vasculitis is unknown, some mechanisms for PTU induced ANCA-positive vasculitis have been proposed (7,8). Although ANCA positivity is seen most of the patient, it is not a rule as in our patient. This reaction can involve the skin, lungs, kidneys, muscles, and ears. Symptoms include purpura, ecchymosis, abdominal pain, hearing loss, epistaxis, weakness, pulmonary or respiratory tract symptoms (hemoptysis, dyspnea, sinusitis), artralgias, myalgias, and lupus-like syndrome. The laboratory abnormalities included anemia, leukocytosis, positive antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-ds DNA, and elevated ESR. The diagnosis of vasculitis in patients receiving antithyroid agents has been established, based on the results of tissue biopsy specimens showing infiltrates of neutrophils and leukocytes. The syndrome generally resolves after drug cessation, but immunosuppressive therapy, including high doses of glucocorticoids and cyclophosphamide, has been used in some cases. Although MMI and PTU have similar structures containing a thionamide group, vasculitis cross-reactivity has not been described (9). Our patient developed methimazole induced, ANCA negative cutaneous vasculitis presenting with purpura and ecchymosis. A skin punch biopsy specimen of the rash revealed leukocytoclastic vasculitis. After withdrawal of the drug and treatment with steroid therapy his condition improved rapidly. PTU is reused without any problem for preparations of surgery. The following clinical course was excellent.

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