Acta Dermatovenerol Croat 2010;18(2):104-106 CASE REPORT

Propylthiouracil-Induced Anti-Neutrophil Cytoplasmic Antibodies (ANCA) Skin Vasculitis: The First Case Reported in Croatia

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Received: August 25, 2009
Accepted: April 1, 2010

SUMMARY Drug-induced vasculitis is a known side effect of prolonged treatment with several drugs. It is characterized by inflammation and cellular infiltration of small vessels and presence of anti-neutrophil cytoplasmic antibodies (ANCA). Propylthiouracil and hydralazine (anti-thyroid and antihypertensive drugs) are the drugs most commonly associated with drug-induced vasculitis. Small vessels of the skin are most frequently affected, while affection of the vessels of the kidneys, central nervous system and lungs make the diagnosis life-threatening. When drug-induced vasculitis is suspected, quick and punctual diagnostic procedure should be carried out to exclude systemic manifestations. Treatment comprises of elimination of the causative drug, which is sufficient in most cases, but sometimes oral or parenteral glucocorticoids and even immunosuppressants are indicated. A case is presented of an 18-year-old male with a history of Graves disease treated with standard dose of propylthiouracil. Approximately 2.5 years after starting therapy he noticed formation of shallow skin ulcerations on both of his ear lobes and elbows. Detailed hospital work-up found high titers of perinuclear-staining anti-neutrophil cytoplasmic antibodies/myeloperoxidase (pANCA/MPO, 1:1024). Biopsy of the affected skin revealed leukocytoclastic vasculitis. Additional tests excluded systemic vasculitis. The patient was diagnosed with propylthiouracil-induced vasculitis, a form of drug-induced vasculitis. Propylthiouracil was discontinued and the skin lesions disappeared over time without the need of any specific therapy (such as glucocorticoids).

KEY WORDS: drug-induced vasculitis, skin lesions, propylthiouracil, anti-neutrophil cytoplasmic antibodies

INTRODUCTION

Vasculitides are a heterogeneous group of systemic diseases characterized by inflammatory process in the anatomical structures of the vessels. Any type, size and location of the blood vessel can be involved resulting in ischemia of the tissue supplied. If vasculitis is the sole manifestation of the disease it is called primary, and if it is part of another disease it is called secondary. The most

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common primary vasculitides include Takayasu's and temporal arteritis, Wegener's granulomatosis, Kawasaki's and Behçet's diseases, Henoch-Schönlein purpura, Churg-Strauss syndrome, and polyarteritis nodosa. Secondary vasculitides are most frequently associated with drugs (drug-induced vasculitis), serum sickness, malignancies, infections and other rheumatic diseases. Antineutrophil cytoplasmic antibodies (ANCA) are antibodies against protein structures in the cytoplasmic granules of monocytes and neutrophils. These antibodies are seen in a high percentage of patients with vasculitis. According to the pattern of perinuclear or cytoplasmic staining, there are two categories of ANCA: cytoplasmic (c-ANCA; major antigen is enzyme proteinase-3) and perinuclear (p-ANCA; major antigen is enzyme myeloperoxidase). These antibodies play a key role in the development of inflammation, mostly through a classic immune complex-mediated mechanism. The presence of ANCA is not always essential for the development of clinically manifest vasculitis, as then some other mechanism of disease may be involved (1).

Drug-induced vasculitis is an inflammation of the small vessels caused by a prolonged treatment with several different categories of drugs. The majority of reported cases include propylthiouracil (anti-thyroid drug) and hydralazine (antihypertensive, direct vasodilator). Most patients present with skin manifestations (palpable purpura, urticarial lesions, hemorrhagic blisters and ulcers). Life-threatening renal and central nervous system (CNS) involvement can be the first sign of drug-induced vasculitis and requires prompt diagnosis and aggressive treatment, together with complete withdrawal of the causative drug. Patients with a medical history of chronic disease with prolonged medication intake should be monitored regularly and advised not to neglect new symptoms and signs they note (skin lesions, respiratory, renal and CNS symptoms).

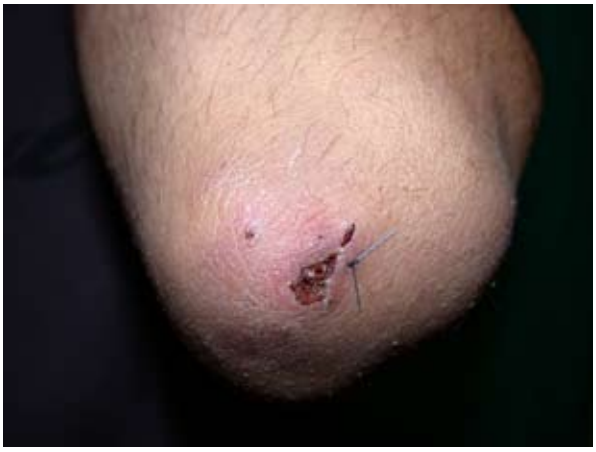

Figure 1. Shallow skin ulcerations on the elbow covered with hemorrhagic scabs; surrounding skin is erythematous and edematous.

CASE REPORT

An 18-year-old male was diagnosed with Graves' disease 2.5 years before and was started on propylthiouracil (3x100 mg/day). Several members of his family had thyroid gland abnormalities: his mother and grandmother's sister had goiter and his father's sister had thyroid cancer. Approximately 8 months prior to hospitalization, he reported morning stiffness and migratory arthralgias of the large joints without swelling. He lost about 15 kg intentionally by a special diet. During the last two months, he noticed skin lesions on both of his earlobes and elbows (Figs. 1 and 2). His fingers turned livid upon exposure to cold and small ulcers appeared on distal ends near the nails. He was referred to our Department for additional tests and diagnostics.

Physical examination of the patient revealed shallow skin ulcerations on both elbows, covered by hemorrhagic scabs with erythematous and edematous surrounding skin. Shallow ulceration on the skin of the right earlobe was also noted, with an erythematous edge covered with adherent scab. Biopsy of the elbow skin was performed.

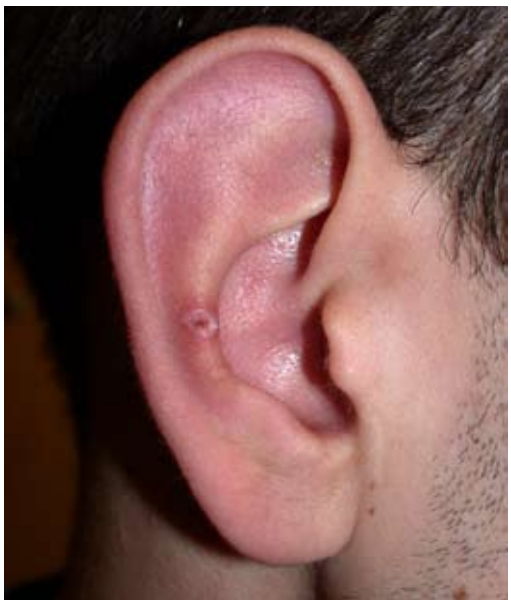

Figure 2. Shallow ulceration on the skin of the earlobe with an erythematous edge covered with adherent scab.

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Small vessels in the entire dermis and especially in the upper parts were surrounded and infiltrated predominantly with mononucleolar cells. Fragmented nuclei (leukocytoclasis) were apparent in many parts of the sample. Immunofluorescence revealed traces of immunoglobulins and complement component deposits in vessel walls. Pathologist's conclusion was that skin lesion biopsy revealed pauci-immune microscopic polyangiitis, i.e. leukocytoclastic vasculitis. Serologic findings indicated high titers of perinuclear-staining anti-neutrophil cytoplasmic antibodies/myeloperoxidase (p-ANCA/MPO, 1:1024) with polyclonal hypergammaglobulinemia and slightly elevated rheumatoid factor and anti-nucleolar antibodies. Radiological methods (chest x-ray, abdominal ultrasound) and laboratory findings (complete blood count, liver and kidney function test, urine) showed no signs of systemic vasculitis. The vasculitic lesions and positive p-ANCA in a patient taking propylthiouracil pointed to the diagnosis of drug-induced vasculitis. Propythiouracil was discontinued. His thyroid hormone status and thyroid-stimulating hormone (TSH) were normal. Over time, the skin lesions diminished. Unfortunately, the patient failed to present for regular check-ups and was lost to follow up.

Our case report may be found interesting and important because it is the first well documented case of ANCA positive propylthiouracil induced vasculitis reported in the Croatian medical literature.

DISCUSSION

Hydralazine (an antihypertensive) and propylthiouracil (an anti-thyroid drug) cause the majority of drug-induced vasculitides, but prolonged usage of many other drugs has also been associated with the same side effect. These drugs include antibiotics (cefotaxime, minocycline), other anti-thyroid medications, anti-TNF-alpha monoclonal antibodies, psychoactive agents, and other miscellaneous drugs (D-penicillamine, allopurinol, sulfasalazine, phenytoin, etc.) (2,3).

The pathogenesis of drug-induced vasculitis still remains unknown. Several mechanisms in genetically susceptible individuals have been suggested, e.g., formation of immune complexes, direct cytotoxic products of the causative drugs, and noxious effects of degranulation products from neutrophils (4,5).

In most cases, clinical manifestations of drug-induced vasculitis include predominantly skin manifestations such as palpable purpura, urticarial lesions, hemorrhagic blisters and ulcers. Other manifestations include more life-threatening conditions such as renal (glomerulonephritis), pulmonary (pulmonary hemorrhage) and CNS involvement.

As soon as drug-induced vasculitis is suspected, the possible causative drug should be withdrawn completely and the patient monitored regularly. In more advanced stages of drug-induced vasculitis or in case of major organ affection (CNS, kidneys), corticosteroids or immunosuppressants (cyclophosphamide) and plasmapheresis should be administered (6). Patients should be hospitalized and monitored until their condition improves. The prognosis of drug-induced vasculitis is favorable if there is no systemic involvement and the causative drug is discontinued (7).

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