Cryoglobulin and antineutrophil cytoplasmic antibody positive cutaneous vasculitis due to propylthiouracil

Sir,

A 34-year-old female presented with purpuric plaques with central necrosis on the gluteal areas for one week [Figure 1]. Treatment with propylthiouracil (PTU) for autoimmune hyperthyroidism had been started six weeks ago. She had no other symptoms and her physical examination revealed no abnormalities. Complete blood count and serum biochemical parameters were within normal limits. Cryoglobulin, cryofibrinogen, cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) and anti-SSA were positive. Histopathological examination demonstrated a neutrophil-rich inflammatory cell infiltrate, nuclear fragments, erythrocyte extravasation and fibrin within vessel walls in the dermis [Figure 2]. The patient was diagnosed as leukocytoclastic vasculitis limited to the skin and methylprednisolone was initiated at a dose of 32 mg/day. Propylthiouracil was stopped and methimazole was initiated until thyroid surgery. The skin lesions improved in one week. Five months later, the patient was still in remission but cryoglobulins, cryofibrinogens, c-ANCA and anti-SSA remained positive.

Patients with thyroid diseases may be prone to develop drug-induced autoimmune diseases.[1] ANCA positivity is more frequent among patients using antithyroid drugs. It may occur weeks, months and even years

after initiation of antithyroid drug treatment.[2] We diagnosed our patient as propylthiouracil-induced ANCA-positive leukocytoclastic vasculitis. The additional presence of cryoglobulins and anti-SSA were thought to be due to the drug.

Propylthiouracil most often induces ANCA-associated microscopic polyangitis or lupus-like disease.[3] Graves' disease is the most frequent underlying thyroid disease in this senario.[2] Other ANCA-positive dermatologic conditions associated with propylthiouracil include pyoderma gangrenosum, Sweet's syndrome and erythema nodosum. How propylthiouracil induces ANCA is still not known. Accumulation of the drug and its metabolites within neutrophils and the binding and modification of myeloperoxidase might turn it and other neutrophil proteins immunogenic. The different clinical features (vasculitis or lupus) may be a reflection of different spectrums of autoantibodies.[1]

Vasculitis due to propylthiouracil comprises a wide clinical spectrum ranging from mild forms with rash and/or arthralgia to severe forms with renal or pulmonary involvement. Severe forms can be life threatening if left unrecognized and untreated. Due to its rarity and variable clinical presentations, diagnosis may be challenging and a high index of suspicion is necessary.[4] Vasculitis limited to the skin is an unusual manifestation of propylthiouracil-induced ANCA-associated vasculitis, and only individual cases have been reported. The presence of multiple autoantibodies may be observed in this scenario.[5] Since we did not re-challenge our patient, we cannot exclude the possibility of a coincidental association of vasculitis and propylthiouracil intake.

In contrast to patients with idiopathic systemic vasculitis, antithyroid drug-induced ANCA-positive patients had milder disease with more frequent skin manifestations, especially urticaria-like vasculitis.[3] Cryoglobulin positivity in addition to multispecific ANCA positivity has been reported in five patients with leukocytoclastic vasculitis. After an average follow-up of 18 months, all patients were in clinical remission. Cryoglobulins disappeared and p-ANCA persisted for a long time.[5] The serological profile of our patient had not changed after five months. Although cessation of the drug causing ANCA positivity typically leads to decrease in ANCA titers, ANCA positivity may persist for months to years.[2]

Drug-induced vasculitides may be clinically and histologically similar to ANCA-associated idiopathic systemic vasculitides. Even though it has been stated that drug-induced autoimmune diseases have a milder course and often do not require cytotoxic drug therapy, criteria for discrimination have not been standardized. Histopathology can be inconclusive since both entities are characterized by leucocytoclasia and fibrinoid necrosis of the blood vessels.[3]

Another propylthiouracil-induced autoimmune syndrome which should be differentiated from vasculitis is lupus-like syndrome. Patients with drug induced lupus have been found to be of younger age and have better outcomes. p-ANCA may be positive in both conditions; however, c-ANCA is detected only in propylthiouracil-induced vasculitis.[1]

Patients with ANCA positivity without any evidence of vasculitis should be followed with caution. The onset of urticaria-like vasculitis, erythrocyturia or pulmonary complaints demands immediate discontinuation of antithyroid drugs.[3] The first steps in the treatment

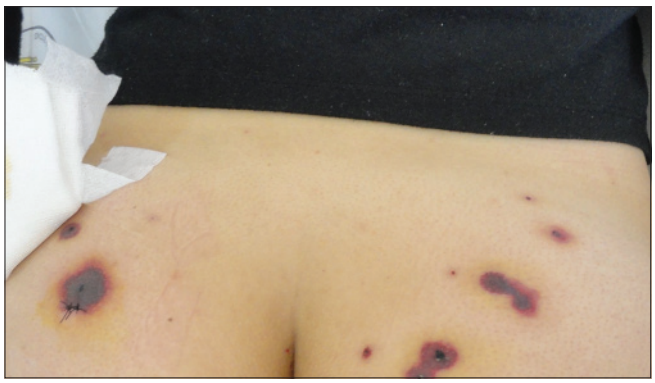

Figure 1: Centrally necrotic purpuric plaques on the gluteal areas

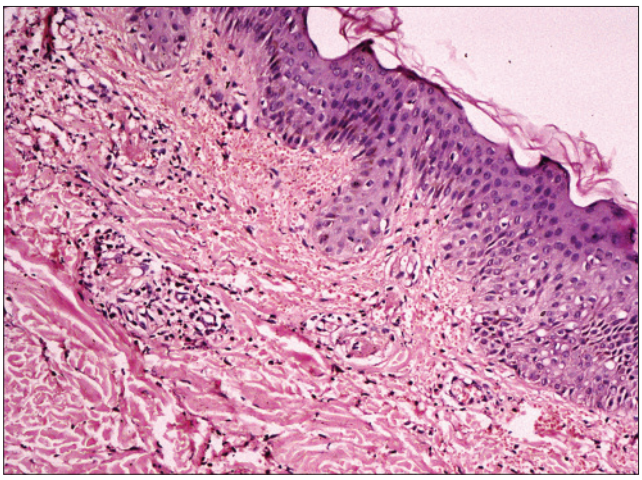

Figure 2: Extravasated erythrocytes and perivascular neutrophils and nuclear fragments are seen (H and E, ×100)

of vasculitis are withdrawal of the drug and detailed investigation for systemic involvement. Steroids and immunosuppressive agents may be necessary if severe disease is present.[4] Since propylthiouracil is more commonly associated with ANCA-positive drug-induced disease, methimazole may be preferred but it should be noted that at the molecular level, these two drugs are based on thionamide, and the substitution of one with the other should be undertaken with caution.[3]

We present this case to emphasize that propylthiouracil, a commonly used antithyroid drug may have potentially serious cutaneous side effects related to the production of autoantibodies of various types.

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