4 Palder SB, Frey CB. Jejunal diverticulosis. *Arch Surg* 1988; **123**:889–94.
5 Altemeier WA, Bryant LR, Wulsin JH. The surgical significance of jejunal diverticulosis. *Arch Surg* 1963;**86**:732–45.
6 Clarke PJ, Kettlewell MGW. Small bowel obstruction due to an enterolith originating in a jejunal diverticulum. *Postgrad Med J* 1985;**61**:1019–20.
7 Soofi R, Abouchedid C. Intussusception of small bowel secondary to jejunal diverticulosis. *NJ Med* 1986;**83**:309–12.

Adverse drug reaction

Disseminated intravascular coagulation and vasculitis during propylthiouracil therapy

Imtiaz Khurshid, Jay Sher

The use of antithyroid drugs in the early 1940s revolutionised the management of hyperthyroidism. Since their introduction, a variety of adverse reactions, including haematological, dermatological, and rheumatological effects, have been associated with these drugs. The incidence of these side-effects is similar to many other commonly used drugs, ie, 1–5%.[1] The most common side-effects include skin rash, fever, arthralgias/arthritis and neutropenia while lupus-like reaction, vasculitis, hepatitis, agranulocytosis and thrombocytopenia are uncommon.[2] Disseminated intravascular coagulation (DIC) is a rare adverse effect of propylthiouracil therapy.[3] Herein we report a case of DIC and vasculitis following a short course of propylthiouracil therapy.

Case report

A 42-year-old African-American woman with Grave's disease, diagnosed 20 years earlier, had received propylthiouracil (100 mg tid) for the past 2 weeks because of recent exacerbation of symptoms. She was admitted to the hospital because of sudden onset of palpable purpuric rash, which started on the face and later spread to her trunk and extremities.

Laboratory test results on admission disclosed the following data: haemoglobin 12.2 g/dl, haematocrit 37.8, white blood cells 15.5×10^9/l, platelets 49×10^9/l, erythrocyte sedimentation rate 23 mm/h, free thyroxine 3.7 ng/dl (normal 0.71–1.85); and thyroid-stimulating hormone <0.03 mIU/ml. Tests for erythrocytes were normal. Tests for coagulation studies revealed prothrombin time 14.3 s (10.6–13.4); activated partial prothrombin time 28.0 s (18–38); D-dimer test positive; fibrinogen degradation products positive; fibrinogen level 344 mg/dl (152–392). Serum complement studies showed C_3 133 mg/dl (88–200), C_4 12 mg/dl (16–47) and CH_{50} 126 U/ml (100–300 CH_{50}). Serum haptoglobin level was normal.

Urinalysis showed trace protein and moderate blood in the urine. Antinuclear, anti-DNA single stranded, anti-DNA double stranded, antihistone, antithyroglobulin and antineutrophil cytoplasmic antibody (ANCA) titres were normal. Blood cultures were negative and chest X-ray was normal. Bone marrow aspiration showed myelosuppression with no evidence of leukaemia. Skin biopsy showed acute vasculitis involving small and medium-sized vessels with fibrin thrombi. No immunohistochemical testing was done. The skin of the left cheek revealed focal superficial epidermal and dermal haemorrhagic necrosis with marked acute inflammation and pustule formation.

The patient was admitted to the hospital and treated with intravenous methylprednisolone 125 mg every 8 hours. Propylthiouracil was discontinued. She responded to intravenous methylprednisolone and the purpuric rash gradually disappeared. Subsequently steroids were tapered over next 2 weeks. The haematological abnormalities returned to normal.

Discussion

The most frequent adverse effects related to propylthiouracil and methimazole, the two most commonly used thionamides, are haematological. Transient leucopenia, perhaps the most common side-effect, has been reported in 12% of adults and up to 25% of children,[4] while cutaneous adverse reactions occur in 3–5% of adults and up to 18% of children.[4 5] Generalised maculopapular and papular purpuric eruptions are perhaps the most common thionamide-induced cutaneous reactions, but rarely bullous haemorrhagic, generalised vesicular and necrotic ulcerative forms have been described.[5] Propylthiouracil induces a clinically distinctive cutaneous eruption consisting of symmetrical, tender, palpable purpuric lesions, often in a livedoid pattern and curiously involves the ear lobes and malar areas.[5–9] Cutaneous vasculitis is usually seen early in the course of propylthiouracil therapy, but has also been observed after long-term treatment. Its exact incidence is not known. Vasculitic involvement of skin is far more common than other organs. Cases of nephritis, myositis, and cavitary pulmonary infiltrates have been reported.[6 7]

Jersey Shore Medical Center, Department of Endocrinology,1945 State Route 33, Neptune, NJ 07754, USA
I Khurshid
J Sher

Correspondence to
I Khurshid, MD,
Department of Medicine,
2N-64, East Carolina
University School of
Medicine, Greenville, NC
27858–4354, USA

Submitted 20 August 1999
Accepted 20 August 1999

The exact pathogenesis of propylthiouracil-induced vasculitis is not known. It has been suggested that circulating immune complexes may play a role, as immunoglobulin and complements have been found in the glomeruli and in the walls of dermal vessels using immunofluorescence.[6] In our patient, low C_4 serum level suggests the possibility of involvement of immune complex mechanism. The detection of ANCA in association with vasculitis suggests other possible pathogenic mechanisms.[9] No dose-dependent or age preference factor has been noted.[4 9]

In addition to leucopenia and agranulocytosis, the other reported haematological abnormalities associated with propylthiouracil therapy include anaemia, thrombocytopenia and polyclonal hypergammaglobulinaemia.[2] There has been only one reported case of DIC, which occurred in a paediatric patient.[3] Our case report is the first case of DIC secondary to propylthiouracil in an adult patient to be reported to the US Food and Drug Administration (FDA). Since our report, FDA have received a second adverse event report of DIC following propylthiouracil in a female patient. In our patient a diagnosis of DIC was suggested by the histological examination of purpuric skin lesion which showed fibrin thrombi in small blood vessels, a finding more appropriate for DIC than for primary vasculitis, in addition to low platelet count and abnormal coagulation profiles.

Learning points

- propylthiouracil therapy is associated with a clinically distinctive vasculitic cutaneous rash
- propylthiouracil should be considered in the differential diagnosis of drug-induced DIC and vasculitis
- corticosteroid use, in addition to the discontinuation of propylthiouracil, helps to resolve the symptoms

The outcome of propylthiouracil-associated adverse effects is mostly favourable, as exemplified in our patient. However, fatal cases of peri-arteritis and vasculitis have been described in the literature.[10] Most adverse effects usually reverse with discontinuation of the drug.[8] Steroids, and in some cases, non-steroidal anti-inflammatory drugs have been used successfully to alleviate the symptoms.[5 6 8] Our patient responded to both discontinuation of propylthiouracil and intravenous steroid.

Keywords: propylthiouracil; vasculitis; disseminated intravascular coagulation; adverse drug reaction

1 Cooper DS. Antithyroid drugs. *N Engl J Med* 1984;**311**:1353–61.
2 Pacini F, Sridama V, Refetoff S. Multiple complications of propylthiouracil treatment: granulocytopenia, eosinophilia, skin reaction and hepatitis with lymphocyte sensitization. J *Endocrinal Invest* 1982;**5**:403–7.
3 Sammon TJ, Penden VH, Witzleben C, King PK. Disseminated intravascular coagulation complicating propylthiouracil therapy. *Clin Pediatr* 1971;**10**:739–42.
4 Werner MC, Romaldini JH, Bromberg N, Werner RS. Adverse effects related to thionamide drugs and their dose regimen. *Am J Med Sci* 1989;**297**:216–9.
5 Vasily DV, Tyler WP. Propylthiouracil-induced cutaneous vasculitis. Case presentation and review of literature. *JAMA* 1980;**243**:458–61
6 Griswold WR, Mendoza SA, Johnston W, Nichols S. Vasculitis associated with propylthiouracil. *West J Med* 1978;**128**: 543–6.
7 Cassorla FG, Finegold DN, Parks JS, *et al*. Vasculitis, pulmonary cavitation, and anemia during antithyroid drug therapy. *Am J Dis Child* 983;**37**:118–22.
8 Carrasco MD, Riera C, Clotet B, *et al*. Cutaneous vasculitis associated with propylthiouracil therapy. *Arch Intern Med* 1987;**147**:1677.
9 Dolman KM, Gans RO, Veraat TJ, *et al*. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. *Lancet* 1993;**342**:651–2.
10 Reidy TJ, Upshaw JD Jr, Chesney TM. Propylthiouracil-induced vasculitis: a fatal case. *South Med J* 1982;**75**:1297–8.