Singapore Med J 2006; 47(2) : 163

Recurrent episodes of arthritis in a hyperthyroid patient

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis is a potentially life-threatening adverse effect of antithyroid medications. We present a 22-year-old woman with Graves' disease who developed recurrent episodes of arthritis while on treatment with propylthiouracil. A diagnosis of propylthiouracil-induced ANCA-associated vasculitis was established only after exhaustive rheumatological investigations failed to establish a cause for her arthritis. Anti-myeloperoxidase antibody (anti-MPO) titres were grossly elevated at 172.7 RU/mL (0-20). Her arthritis resolved promptly following the withdrawal of propylthiouracil and the anti-MPO titres declined over 16 months to 66.8 RU/mL. While she did not develop the life-threatening renal or respiratory tract complications, there was a delay in establishing the correct diagnosis with its attendant morbidity. This case highlights the need for greater awareness of this relatively rare adverse effect of antithyroid medications so as to allow its early detection, leading to the prompt cessation of the offending medication.

Keywords: antineutrophil cytoplasmic antibody, arthritis, hyperthyroidism, propylthiouracil, vasculitis

Singapore Med J 2006; 47(2):163-165

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INTRODUCTION

Hyperthyroidism is a common endocrine disorder, often treated using the oral anti-thyroid medications carbimazole and propylthiouracil, either as primary therapy or in preparation for radioiodine administration or surgery. However, these medications have a number of well-known adverse effects. Some are common, such as allergic skin reactions, and some are rare, such as agranulocytosis. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a relatively rare side effect of anti-thyroid drugs. It was first reported in 1992 and since then, over 40 cases have been reported in the English literature[1]. We describe a patient with Graves' disease, who developed ANCA-associated vasculitis while on treatment with propylthiouracil, and presented initially to a rheumatologist with recurrent episodes of generalised arthritis.

CASE REPORT

A 22-year-old woman was admitted with a five-day history of low-grade fever, lower abdominal pain, malaise, myalgia and polyarthralgia affecting the small joints of her hands, wrists, ankles, elbows, shoulders and knees. Two weeks prior to the onset of this illness, she had had a self-limiting episode of diarrhoea that had lasted for three days. Past history included hyperthyroidism due to Graves' disease diagnosed eight months ago, for which she was currently taking propylthiouracil 100 mg twice daily, having earlier developed an allergic urticarial skin rash while on treatment with Carbimazole. On examination, she had a temperature of 37.8ºC. There was a moderate-sized diffuse goiter. She was clinically euthyroid. There was bilateral episcleritis, a small tongue ulcer, and features of arthritis affecting her ankle, knee and wrist joints. Physical examination was otherwise normal apart from mild lower abdominal tenderness.

The development of fever, flu-like symptoms, oral ulceration, episcleritis and polyarthritis, two weeks following an acute diarrhoeal episode, was interpreted as suggestive of acute reactive arthritis secondary to infective enterocolitis due to *Yersenia, Salmonella*, *Shigella* or *Campylobacter*. The other differential diagnosis considered was that of reactive arthritis secondary to *Neisseria gonorrhoea* or Chlamydia infection, in view of the history of lower abdominal tenderness in a sexually-active lady. Possibility of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis were

also considered in this young lady with Graves' disease.

She was initially treated with oral cefuroxime and doxycycline. However, the blood, urine and stool cultures, available subsequently, were all negative for pathogens. Urinalysis was negative for cells, protein or casts. Polymerase chain reaction of high vaginal swab failed to identify Gonococcus or Chlamydia. Her chest radiograph was normal. Laboratory results showed a total white blood cell count of 5.16 x 10^9/L (normal 3.2 - 8.9 x 10^9/L), erythrocyte sedimentation rate (ESR) 28 mm/hr (normal 10-12 mm/hr), C-reactive protein 2.3 mg/dL (normal 0-1 mg/dL) and normal serum electrolytes, creatinine and liver function test. Rheumatoid factor was <20 IU/mL (normal 0-20 IU/L), anti-double stranded DNA antibody titre was 4 IU/L (normal <15 IU/L) and serum complement levels were normal. Free thyroxine (FT4) was 13.2 pmol/L (normal 10.0-20.0 pmol/L) and thyroid stimulating hormone (TSH) was <0.005 mIU/L (normal 0.45-4.5 mIU/L). Anti-thyroid peroxidase and TSH receptor antibodies were elevated at >1000 IU/mL (normal 0-50 IU/mL) and 143.5 U/L (normal 0-10 U/L), respectively.

Her symptoms failed to improve with antibiotic therapy alone but responded promptly to oral naproxen. Over the next four months, symptoms of low-grade fever, myalgia and malaise recurred intermittently, and she was admitted twice with episodes of acute arthritis flare. During the second such admission, possibility of ANCA-associated vasculitis was raised, which was confirmed by an elevation of anti-myeloperoxidase antibody (Anti-MPO) titres at 172.7 RU/mL (normal 0-20 RU/mL). Anti-proteinase 3 antibody (PR3) titre was normal at 4.7 RU/mL (normal 0-20 RU/mL) while the antinuclear antibody (ANA) titre was grossly elevated at 318% (normal <90%).

Propylthiouracil was stopped, and her constitutional and arthritic symptoms resolved within two weeks. She underwent subtotal thyroidectomy and was subsequently started on thyroxine replacement for hypothyroidism. When last reviewed 16 months following thyroidectomy, she was euthyroid on 75 mcg of thyroxine once daily. The constitutional symptoms had completely resolved and there had been no further episodes of arthritis. ANA titres had declined from 318% to 173% within two months of stopping propylthiouracil and subsequently normalised to 61% ten months later. Anti-MPO titres had declined but continue to remain elevated at 66.8 RU/mL, 16 months after withdrawal of propylthiouracil.

DISCUSSION

ANCA-associated vasculitis is a rare adverse effect of antithyroid medications, with over 40 cases reported since its first description in 1992[1]. Most reported cases have been associated with antibodies directed against myeloperoxidase (p-ANCA), but antibodies against proteinase 3 (c-ANCA) have also been described[2,3]. The majority of these patients had underlying Graves' disease, and almost 90% of them were on propylthiouracil[4].

A small number of studies have looked at ANCA positivity in hyperthyroid patients before and after the initiation of antithyroid medications[4-7]. Sera et al found anti-MPO titres to be negative in all 42 untreated patients and in 21 patients treated with methimazole, whereas 37.5% of the 56 patients treated with propylthiouracil had positive titres, nine of whom developed myalgia, arthralgia and flu-like symptoms[5]. The temporal relationship between the appearance of anti-MPO titres and vasculitis while on treatment with propylthiouracil was studied in 73 untreated patients with Graves' disease who were ANCA-negative at baseline. After a median follow-up of 23.6 months, three patients (4.1%) had elevated anti-MPO titres, one of whom developed fever, oral ulcer and polyarthralgia[6]. These studies suggest a causative role of propylthiouracil in inducing ANCA, and in a small percentage of susceptible patients, causing ANCA-associated vasculitis. The negative ANCA at baseline in these studies[4-6] make it less likely that ANCA positivity is induced by the underlying thyroid disease or is due to cross-reactivity with thyroid autoantibodies.

Propylthiouracil has been shown to accumulate in neutrophils and bind myeloperoxidase. The resulting alteration in the configuration of MPO has been proposed to allow for the initiation of autoantibody formation in susceptible individuals[8]. We did not measure ANCA titres in our patient before starting her on the antithyroid medication. However, the development of vasculitic symptoms while on propylthiouracil, and the complete disappearance of these symptoms, with reduction in ANCA titres after the discontinuation of propylthiouracil, strongly suggests a causal relationship between propylthiouracil and the appearance of ANCA.

In 1999, Gunton et al reviewed 27 cases of ANCA-associated vasculitis secondary to anti-thyroid medication[9]. Arthralgia (48%), fever (37%), skin involvement (30%), myalgia (22%) and scleritis (15%) occurred commonly and resolved following cessation of the offending drug,

an outcome similar to that seen in our patient. However, more serious complications like crescentic glomerulonephritis with renal failure was seen in 67% of the patients, of whom 7.4% had progressive decline in renal function. In addition, potentially life-threatening respiratory tract involvement that manifested as pulmonary haemorrhage or respiratory failure occurred in 27% of patients. A number of other reports have since drawn attention to this potentially fatal adverse effect of antithyroid medications, in particular propylthiouracil[10,11]. Our patient did not develop the life-threatening renal or respiratory complications. However, there was delay in establishing the diagnosis that resulted in morbidity.

In conclusion, this case highlights the importance of being aware of this relatively rare and not so well-known adverse affect of anti-thyroid medications, which may lead to fatal renal and pulmonary complications. Moreover, the milder form of vasculitis may present with non-specific constitutional symptoms leading to delay in diagnosis and treatment. Early diagnosis and prompt withdrawal of the offending medication is important to allow the resolution of vasculitis, thereby preventing potentially life-threatening complications.

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