Propylthiouracil Induced ANCA Positive Vasculitis: a Case Report

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Anti-thyroid drugs, methimazole, carbimazole and propylthiouracil are commonly prescribed for the treatment of hyperthyroidism due to Graves' disease. We present here the report of a Caucasian patient with Graves' disease who developed ANCA positive propylthiouracil induced vasculitis. The episode was characterised by a vasculitic skin rash associated with polyarthralgia but no renal involvement. While carbimazole/methimazole has a lower incidence of reported ANCA positive side effects than PTU, the use of the latter in pregnancy may still be considered as reasonable because the immunosuppression of pregnancy may prevent the appearance of immune problems.

Key Words: Propylthiouracil, Carbimazole, Vasculitis, ANCA, Hyperthyroidism, Graves' disease

Introduction

Antithyroid drug treatment with thionamides such as carbimazole and propylthiouracil (PTU) is commonly used in the treatment of Graves' disease.[1] Anti neutrophil cytoplasmic antibody (ANCA) was first detected around 20 years ago in patients with segmental necrotizing glomerulonephritis.[2] Shortly afterwards, ANCA was found to be closely associated with vasculitic conditions and since then has been increasingly used as a diagnostic marker of vasculitis.[3] PTU has been known to promote formation of ANCA,[4] although only a very few of these patients with ANCA positivity go on to develop clinical vasculitis.[5] To our knowledge, 59 cases of ANCA positive vasculitis related to antithyroid medication have been reported in English literature with the first case being reported in 1992;[6] almost half of these are from Japan. We report a case of PTU induced vasculitis in a Caucasian lady with Graves' disease which has occurred following a prior similar clinical event while on a course of carbimazole.

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Case Report

A 26-year-old Caucasian lady was admitted to the hospital with a two-week history of migrating polyarthralgia and a rash around both her ankles. The patient was diagnosed with Graves' hyperthyroidism 6 years before, when she was commenced on carbimazole 10 mg thrice daily. Carbimazole was stopped five weeks after its commencement as she developed polyarthralgia and rash on this medication. No immunological studies were performed at that time. Polyarthralgia and rash disappeared within a week on discontinuing carbimazole. PTU was started instead at a dose of 50 mg twice daily which she took

for a year without any adverse effects. Subsequently her Graves' disease was in remission for 3 years. PTU was recommenced 2 years ago at 50 mg twice daily when her Graves' disease relapsed and she had been on this dose until her present admission with polyarthralgia and rash. There was no other significant past medical history or exposure to any other drugs.

On examination, she appeared to be clinically euthyroid and had a diffuse goiter. There was a non-tender, non-blanching, non-pruritic, maculopapular rash around both her ankles. There was no clinical evidence of arthritis although she complained of a migratory polyarthralgia affecting her ankle, knee and shoulder joints.

Investigations revealed Hb 10.8 g/dL (normal range: 12-16 g/dl), WBC 5.5×10^9/L (normal range: 4-11×10^9/L), neutrophils 3.8 $\times10^9$/L (normal range: 1.2-7.6×10^9/L), eosinophils 0.1×10^9/L (normal rangd: 0.1-1.25×10^9/L), platelets 273×10^9/L (normal range: 140-350×10^9/L), urea 3.4 mmol/L, creatinine 61 μmol/L, normal liver function tests, chest/Ankle Xrays and urinalysis. Thyroid function tests showed a normal free T_4 level of 22.3 pmol/L (normal range: 9.8-23.1), normal free T_3 level of 5.4 pmol/L (normal range: 3.5-6.5) and a TSH of 0.33 mU/L (normal range: 0.35-5.50). Inflammatory markers revealed a C-reactive protein of 56 mg/L (normal<11) and an ESR of 61 mm/hr. TSH receptor antibodies were positive consistent with a diagnosis of Graves' disease. Antinuclear antibodies were weakly positive at a titer of 1:100; however anti-dsDNA antibodies, ENA screen and rheumatoid factor were all negative. ANCA titres were strongly positive (> 1:320; a titer of 1:80 is considered positive) and of a perinuclear type. ELISA assays were positive for MPO (myeloperoxidase) antibodies.

Based on the above findings, the patient was diagnosed to have PTU induced ANCA positive vasculitis. PTU was discontinued immediately which was followed by a prompt relief from symptoms of polyarthralgia and fading of the rash within a week.

The patient attended for follow-up after two months when she was well and her symptoms of polyarthralgia and rash had disappeared completely. Clinically she continued to remain euthyroid off antithyroid medications. This was confirmed biochemically (free T_4=20.9 pmol/L, free T_3=5.9 pmol/L and TSH=0.30 mU/L). Her inflammatory markers had normalized, however the ANCA titers continued to remain positive (>1:320). TSH receptor antibodies were now undetectable. Further treatment options with radioactive iodine therapy were discussed in the event of her becoming hyperthyroid again in the future.

Discussion

This case report is an attempt to highlight the importance of testing for ANCA in patients with suspicious symptoms whilst on antithyroid medication. The case is unusual in that the patient probably developed the disease in response to carbimazole as well as PTU and it is said that there is normally a low chance of side effect cross reactivity between the two drugs, although this is not unknown. The patient had symptoms of polyarthralgia and rash developing much earlier (within 5 weeks) when commenced on carbimazole, which prompted to switch her to PTU. Having been on PTU (50 mg twice daily) for around 2 years, the patient had a recurrence of her symptoms of polyarthralgia and rash. On both occasions, her symptoms settled promptly on discontinuation of the medication. Diagnosis of ANCA positive vasculitis was strongly suspected on clinical grounds supported by ANCA titers and by clinical resolution on stopping the medication. Previous studies have shown ANCA positivity to be significantly associated with the duration of therapy with PTU, but there has been no such association with duration of carbimazole therapy.[7]

Recent studies have shown high frequency of ANCA positivity in patients with Graves'

disease treated with antithyroid medications, especially with PTU where the prevalence is estimated to be as high as 25% as against carbimazole/methimazole, which have a much lower prevalence of 3.4%.[8] Most cases of ANCA positivity have occurred in patients on long term (>18 months) therapy with antithyroid medications or in those with a recent commencement.[7] However only a small percentage of these patients go on to develop features of vasculitis.[7,9] A Chinese study by Guo et al.[11] has reported ANCA positivity of 5.9% in untreated Graves'disease as against 22.6% in those treated with PTU and 6.5% in those treated with methimazole. However none of the untreated patients had clinical signs and symptoms of vasculitis. ANCA vasculitis associated with antithyroid medication occurs more frequently in women, which may simply be accounted for by the female predilection for Graves' disease. The underlying thyroid disease is usually Graves' disease, although cases have also been reported in association with toxic multinodular goiters.[10] The pathogenesis behind PTU inducing ANCA is not clearly understood, however PTU has been shown to accumulate within neutrophils, binding to myeloperoxidase to alter its config.uration, which subsequently promotes antibody formation by polyclonal activation of B lymphocytes in susceptible individuals.[4, 11] The commonest skin lesion is leukocytoclastic vasculitis, which typically causes purpuric lesions in lower limbs.[12] In this case there was no skin biopsy taken and no overt renal involvement. The spectrum of vasculitis may range from a milder form with arthralgia and rash to a more severe form with renal or pulmonary involvement. We recommend biopsy confirmation of vasculitis (skin biopsy wherever possible or renal biopsy if indicated).

Mild forms of vasculitis respond well to discontinuation of the responsible medication but severe forms, especially with renal or pulmonary involvement may need more aggressive treatment with steroids, cyclophosphamide and in rare cases, plasmapheresis.[12] Once the vasculitic process is controlled, it is also important to treat the underlying hyperthyroidism which may be achieved by considering destructive treatment with radioactive iodine or using other antithyroid medications like lithium or ipodate. Some patients may also be offered treatment with thyroidectomy if appropriate. Fortunately, this patient remained euthyroid off antithyroid medication at follow up.

It appears reasonable to select carbimazole rather than PTU as initial antithyroid therapy as the prevalence of ANCA positivity is much lower. The issue of monitoring ANCA in patients on antithyroid medication needs to be addressed although it has been suggested that ANCA should be tested in patients on long term treatment (>18 months) or in those developing suspicious vasculitic features on these medications.[7] The significance of ANCA positivity in asymptomatic patients on these medications remains unclear, but this should lead to earlier consideration of definitive treatment with radioiodine or surgery. In our case, ANCA titers continued to remain positive at follow-up after stopping PTU despite normalization of inflammatory markers. Although ANCA titers are expected to fall with time, some patients do continue to remain ANCA positive for many years as noted by Gunton et al in his review of 32 cases of thionamide associated ANCA positive vasculitis.[7] The significance of this persistent ANCA positivity remains unclear. It should be remembered that vasculitis may also be triggered by exposure to other drugs (eg. Hydralazine and sulfonamides.[13] and some viral infections (eg. hepatitis C[14]).

Patients developing ANCA vasculitis on PTU may be offered treatment with carbimazole for treating underlying hyperthyroidism; however prescribing PTU to patients with carbimazole induced ANCA vasculitis seems inappropriate given the fact that PTU is associated with a very high prevalence of ANCA positivity (25%). PTU is the preferred antithyroid medication during pregnancy but no significant vasculitic cases have been re-

ported in this group of patients which may simply be explained by the shorter duration of PTU course and the immunosuppression associated with pregnancy.

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