



# Carbimazole Induced ANCA Positive Vasculitis

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## Abstract

Anti-thyroid drugs, like carbimazole and propylthiouracil (PTU) are commonly prescribed for the treatment of hyperthyroidism. One should be aware of the side effects of antithyroid medications. Antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis is a potentially life-threatening adverse effect of antithyroid medications. We report a patient with Graves' disease who developed ANCA positive carbimazole induced vasculitis. The episode was characterized by a vasculitic skin rash associated with large joint arthritis, pyrexia and parotiditis but no renal or pulmonary involvement. He was referred to us for neurological evaluation because he had difficulty in getting up from squatting position and was suspected to have myositis. Carbimazole and methimazole have a lower incidence of reported ANCA positive side effects than PUT. To the best of our knowledge this is the first ANCA positive carbimazole induced vasculitis case reported from India. ©

## INTRODUCTION

Hyperthyroidism a common endocrine disorder, is often treated using oral anti-thyroid medications. The most important anti-thyroid drugs are thionamides which include propylthiouracil, carbimazole and its active metabolite methimazole. These medications have a number of well-known adverse effects. Some are common, such as allergic skin reactions, and some are rare, like agranulocytosis. Classical vasculitis is uncommon, but ANCA positivity is more common being reported to occur in 37.5% of patients receiving propylthiouracil and rarely with carbimazole and methimazole.<sup>1</sup> We report a patient with Graves' disease, who developed ANCA-associated vasculitis while on treatment with carbimazole.

## CASE REPORT

A 20-year-old unmarried man was referred to us for neurological evaluation with a two months history of difficulty in getting up from squatting position, stiffness and painful swelling of both knee joints, mild to moderate grade fever, malaise and myalgia. There was history of rashes over legs two months back. There was no history of abdominal pain, haematuria, cough, breathlessness, haemoptysis, headache, vomiting or genital or oral ulcers. He denied history of contact with commercial sexual worker. Past history included hyperthyroidism (Graves' disease) diagnosed two years back. For this he was prescribed

oral carbimazole 15 mg three times a day. After taking carbimazole for three weeks he stopped the treatment as he was not getting any relief. After consultation with another physician he restarted it five months back when he had worsening of symptoms. After eight weeks of treatment with carbimazole he developed macular rash over trunk and legs along with joint pains. He was started on oral prednisolone 50 mg per day and carbimazole was continued. His symptoms improved, rashes disappeared and pain also improved. Oral prednisolone was tapered off after four weeks but he again developed severe painful restriction of movements and swelling of both knee joints and became bed bound. He was suspected to have myositis and referred for neurological opinion.

On examination his blood pressure was 130/84 mm Hg, pulse 100/min, temperature 100.2°F. He appeared to be clinically euthyroid and had a mild-sized diffuse goiter, bilateral painful parotid gland swelling, and arthritis of both knee joints. Systemic examination was normal.

Investigations showed (Table 1) leucocytosis, raised erythrocyte sedimentation Rate (ESR) and C- reactive protein (CRP). Electrocardiogram, ultrasonography of abdomen, X-rays chest and echocardiogram were normal. X-rays of knee joints were normal. Creatinine phosphokinase was within normal limit. HIV, HBsAg were nonreactive. Serum proteinase 3 antibody was negative while Antimyeloperoxidase Antibody was positive. Thyroid peroxidase and TSH receptor antibodies were >680 U/mL and 208 U/L respectively. Nerve conduction velocity and electromyography study were normal. Muscle biopsy was normal.

Provisional diagnosis of carbimazole induced MPO-ANCA vasculitis was made. Carbimazole was discontinued in with

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**Table 1 : Laboratory investigation of patient at the time of admission**

Investigation	Patient value	Normal range
Total Leukocyte count	13500/cc	4000-11000/cc
Differential count	Polymorphs-78% Lymphocytes-14% Eosinophils-8%	
Platelets	402000/cc	150000-450000/cc
Erythrocyte-sedimentation rate	110/1st Hr	<20 /1st Hr
Antistreptolysin (ASO)	<200 Todd unit	<200 Todd unit
C reactive protein	3.3 mg/dl	0-1 mg/dl
C- ANCA	1.5 u/ml	>5 u/ml
P- ANCA	8 u/ml	>5 u/ml
Thyroid Peroxidase	680 IU/ml	0-50 IU/ml
TSH receptor antibody	208 U/L	0-10 U/L

consultation with treating endocrinologist and started on oral prednisolone 60 mg once a day. He showed dramatic improvement over next 48 hours. Prednisolone was tapered of over the next two weeks. He became asymptomatic thereafter. For hyperthyroidism he was treated with radioactive iodine. At the end of three months he was totally symptom free and was back to his work. His MPO-ANCA after 3 months was negative (4.40 U/ mL).

## DISCUSSION

ANCA-associated vasculitis is a rare adverse effect of antithyroid medications, with over 32 cases reported in the English literature.<sup>2</sup>

Recent studies have shown a high frequency of ANCA positivity in patients with Graves' disease treated with antithyroid medications, especially with PTU. Most cases of ANCA positivity are seen in patients on long term (>18 months) therapy or in those with a recent commencement of therapy. However only a small percentage of these go on to develop features of vasculitis.<sup>2</sup>

The underlying thyroid disease is usually Graves' disease (GD), although cases have also been reported in association with toxic multinodular goiter and Hashimoto's thyroiditis (HT). The spectrum of vasculitis may range from a mild arthralgia and rash to severe form with renal or pulmonary

involvement. The presenting symptoms are variable and include renal (67%), arthralgia (48%), fever (37%), skin (30%), respiratory (27%), myalgia (22%), scleritis (15%) and other manifestations (18%).<sup>2</sup>

In comparison with idiopathic ANCA associated vasculitis, antithyroid drug (ATD) induced vasculitis has very high female preponderance, early age of onset and high ANA positivity. Antithyroid drug-induced ANCA-positive vasculitis is divided in two groups. The first group consists of PR3- or MPO-ANCA-positive drug-induced resembling idiopathic systemic vasculitis (ISV). The second group consists of MPO-ANCA-positive patients with LLD (lupus like disease). The first group has more severe course.<sup>3</sup>

The majority of cases of vasculitis (88%) have been reported in association with PTU. Vasculitis associated with carbimazole, is exceedingly rare. Till date only nine such cases have been reported (Table 2).<sup>4,6</sup> The most common manifestations of carbimazole induced vasculitis are skin rash and leucocytoclastic vasculitis like picture. In reported cases so far one patient had predominantly gastrointestinal manifestation,<sup>5</sup> one had polyneuropathy<sup>4</sup> and one had myositis.<sup>4</sup> Interestingly our patient had presentation like that of myositis but investigations revealed normal CPK, EMG and muscle biopsy. Majority of the reports are from Japan, indicating high prevalence in Asian community.<sup>4</sup> The antibody specificity is additionally against other neutrophil antigens as against only PR3 or MPO in idiopathic systemic vasculitides. This is an important distinguishing feature. Additionally in drug induced vasculitis ANA is often positive, but no so in idiopathic systemic vasculitides. This is an important distinguishing feature. Additionally in drug induced vasculitis ANA is often positive, but no so in idiopathic systemic vasculitides. Only a small number of studies have looked at ANCA positivity in hyperthyroid patients before and after the initiation of antithyroid medications.

Wada et al, have reported that 25% patients were positive for MPO-ANCA in PTU group, whereas in the methimazole group, 3.4% patients were positive.<sup>3</sup> Most of their MPO-ANCA positive patients were asymptomatic, except for two patients in whom rheumatic arthritis or membranous glomerulonephritis developed. One each of the MPO-ANCA

**Table 2 : Carbimazole induced vasculitis : summary of review of literature**

Reference	Case no	Disease	Clinical presentation
Seve et al 2005 <sup>5</sup>	1	Hyperthyroidism (Grave's Disease)	Gastrointestinal symptom
Calañas-Continento et al 2005 <sup>6</sup>	2	Hyperthyroidism	Glomerulonephritis and pulmonary hemorrhage
Day et al 2003 <sup>4</sup>	3	Hyperthyroidism	Leucocytoclastic vasculitis, Interstitial nephritis
Yazbeck et al 1999 <sup>4</sup>	4	Hyperthyroidism	Macular skin rash, Leucocytoclastic vasculitis
Miler et al 1998 <sup>4</sup>	5	Hyperthyroidism (Grave's Disease)	Skin rash, leucocytoclastic vasculitis, atypical P-ANCA
D'cruz et al 1995 <sup>4</sup>	6	Hyperthyroidism	Skin rash, shifted to Propylthiouracil then systemic vasculitis
D'cruz et al 1995 <sup>4</sup>	7	Hyperthyroidism	Fever, arthralgia, epistaxis
Pasquier et al 1991 <sup>4</sup>	8	Hyperthyroidism	Myositis with microvasculitis
Leger et al 1984 <sup>4</sup>	9	Hyperthyroidism	Polyneuropathy

positive patients were diagnosed as having classical ANCA-associated vasculitis.<sup>3</sup>

Sera et al found anti-MPO titers 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 titers, nine of whom developed myalgia, arthralgia and flu-like symptoms.<sup>1</sup> 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 make it less likely that ANCA positivity is induced by the underlying thyroid disease or is due to cross-reactivity with thyroid autoantibodies.

In 1999, Gunton et al reviewed 27 cases of ANCA-associated vasculitis secondary to antithyroid medication.<sup>2</sup> 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 were seen in 67% of the patients, and potentially life-threatening respiratory tract involvement that manifested as pulmonary haemorrhage or respiratory failure occurred in 27% of patients. 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 the form of severe arthritis and pyrexia. Neither severe large joint inflammatory arthritis nor transient bilateral parotitis has been reported in any study as a manifestation of drug induced vasculitis syndrome nor the role of steroids in acute management of symptoms. Our case belongs to LLD group as he had arthritis and skin rash without pulmonary–renal syndrome which is more severe and present as ISV.

In conclusion, this case highlights the importance of being aware of this relatively rare and not so well-known adverse affect of antithyroid medications with so varied clinical manifestations especially with carbimazole, which may lead to fatal renal and pulmonary complications. Early diagnosis and prompt withdrawal of the offending

medication is important to allow the resolution of vasculitis, thereby preventing potentially life-threatening complications. The significance of ANCA positivity in asymptomatic patients remains unclear, but this should lead to earlier consideration of definitive treatment with radioiodine or surgery

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## Announcement

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