

Concurrent Takayasu's Arteritis and Antineutrophil Cytoplasmic Antibody-related Glomerulonephritis Related to Use of Propylthiouracil

To the Editor:

Propylthiouracil (PTU) is a thioamide used to treat the hyperthyroid state of Graves' disease¹. Among the side effects of this medication, the induction of antineutrophil cytoplasmic antibodies (ANCA) has gained recent attention¹. It has been shown that the antigenic target of cytoplasmic ANCA (c-ANCA) is proteinase 3, whereas that of perinuclear ANCA (p-ANCA) is usually myeloperoxidase, although other intracellular molecules are sometimes targets². Children are at relatively high risk for developing PTU-related autoimmune disorders because of the long duration of this therapy while awaiting radioablation or surgery¹. We describe a rare case of concurrent Takayasu's arteritis and p-ANCA-associated crescentic glomerulonephritis associated with a 20-year history of PTU use.

A 29-year-old African American woman was admitted to the nephrology service at the University of North Carolina, Chapel Hill, with progressive renal failure. She had fever, fatigue, hoarseness, and an unintentional 15-lb (6.8 kg) weight loss beginning after the birth of a healthy male infant 8 months previously, followed by 2–3 days of nausea and vomiting. Serum creatinine was 4.0 mg/dl on presentation. Urinalysis showed 2+ protein, > 150 red blood cells per high power field, and 18 white blood cells per high power field. A 24-h urine specimen showed protein of 4.7 g, with urine protein-to-creatinine ratio of 5.740. Serum protein electrophoresis was negative for monoclonal gammopathy. The patient underwent renal biopsy, and histopathology showed pauciimmune crescentic glomerulonephritis. Noncontrast computed tomography of the neck, done to evaluate hoarseness, showed a vascular mass in the right anterior neck. Magnetic resonance angiogram of the neck and chest showed severe dilatation of the ascending through mid-descending thoracic aorta to a maximum diameter of 6.8 cm (Figure 1a). There was also dilatation of the brachiocephalic (2.9 cm), right and left carotid (1.6 cm and 1.5 cm, respectively), and main pul-

monary (4.2 cm) arteries (Figure 1a). The ascending and descending thoracic aortic walls were thickened to 5 mm. Laryngoscopy revealed paralysis of the left vocal fold consistent with pressure on the left branch of the recurrent laryngeal nerve (also known as Ortner's effect³).

The patient's medical history was notable for childhood Graves' disease at age 7 years, for which she received PTU for 20 years. One and a half years prior to her presentation, she underwent radioiodine thyroid ablation and received post-ablation thyroid replacement. Since her teenage years, she had had a rash consisting of papular, necrotic skin lesions on her upper and lower extremities (Figure 1b). A clinical diagnosis of pyoderma gangrenosum was supported by skin biopsy.

On examination, she had a blood pressure of 136/88 mm Hg in the left arm and 151/89 in the right arm. She had a 2 cm right-sided pulsatile mass in the anterior neck, and bruits were present over the right carotid and right subclavian arteries. The skin showed lesions of pyoderma gangrenosum at various stages of healing (Figure 1b). Abdominal examination was normal.

Laboratory data showed serum p-ANCA at a 1:160 titer, although antigen-specific tests for myeloperoxidase were negative. Erythrocyte sedimentation rate was 50 mm/h (after steroids had been administered). Antinuclear antibody was weakly positive at a titer of 1:80, and anti-double-stranded DNA antibody was negative. Antiphospholipid antibody panel, human immunodeficiency virus ELISA, and polymerase chain reaction (PCR), hepatitis B and C serologies, serum RPR, anti-glomerular basement membrane antibodies, extractable nuclear antigens, and tuberculin skin test were all negative.

She received a 3-day course of intravenous methylprednisolone (1000 mg daily) and intravenous cyclophosphamide (1000 mg). This was followed by prednisone at 1 mg/kg daily, along with metoprolol to treat hypertension and to minimize shear forces on the aortic wall. She also received aspirin for prevention of thrombosis. The vascular surgery service recommended aortic arch reconstruction after a positron emission tomography scan that revealed no evidence of active inflammation. The resected aortic arch showed panarteritis, with an inflammatory infiltrate consist-

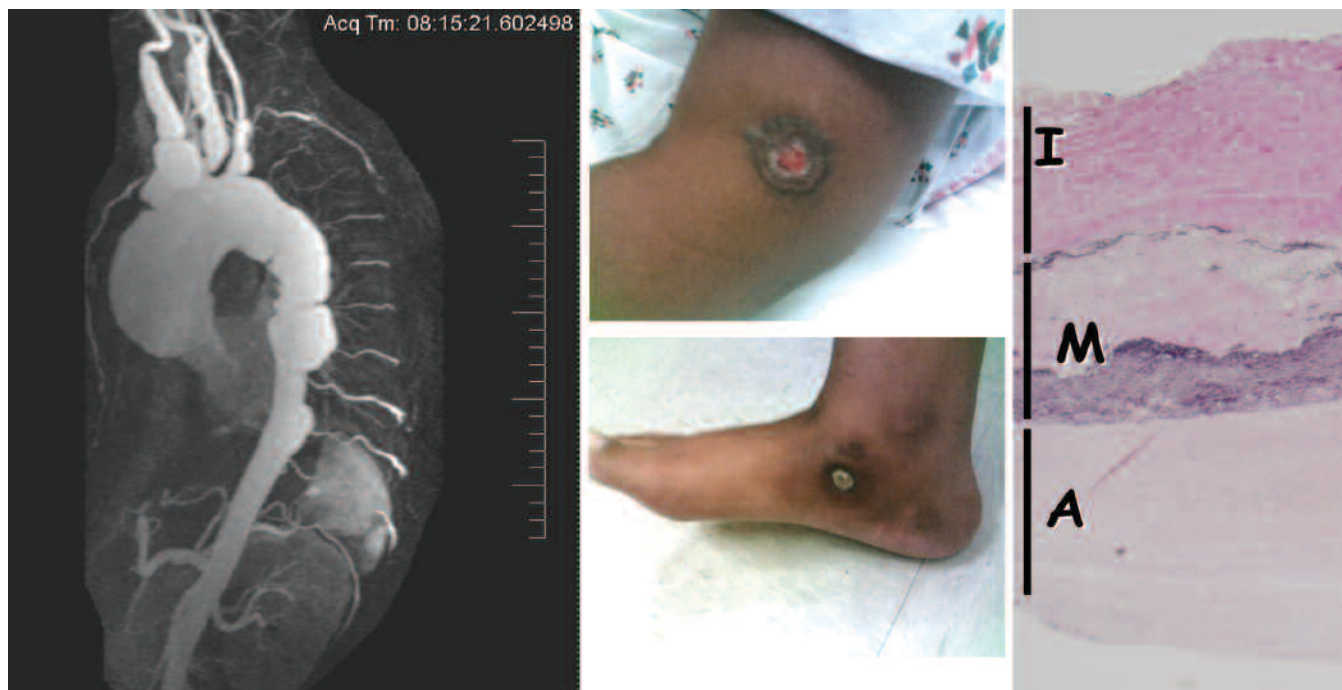


Figure 1. Concurrent large and small-vessel vasculitides related to propylthiouracil. (a) Magnetic resonance angiogram of the neck and chest shows aneurysmal dilatation of the ascending through mid-descending aorta, brachiocephalic, right and left carotid, and main pulmonary arteries with thickening of the aortic walls. (b) Upper and lower extremities had necrotic skin lesions at various stages of healing consistent with pyoderma gangrenosum. (c) Resected aortic arch demonstrates thickening and fibrosis of the intimal layer (I), with disruption of the elastic lamina of the medial layer (M), which contained giant cells (not shown). Adventitia (A) is normal.

ing of neutrophils, lymphocytes, and occasional giant cells. Intimal thickening and fibrosis and severe disruption of the medial elastic lamina were observed (Figure 1c). The resected aortic segment was negative for parvovirus, cytomegalovirus, and Epstein-Barr virus by PCR. She continued to receive monthly infusions of cyclophosphamide for a total of 4 doses, and her creatinine normalized to 0.8 mg/dl. She has been followed for 2 years, with no recurrence of vasculitis.

Our patient had multiple disorders with a presumed autoimmune etiology — childhood Graves' disease, pyoderma gangrenosum, Takayasu's arteritis, and crescentic glomerulonephritis. An explanation for the concurrence of these entities in a single patient must address an autoimmune diathesis. We propose that her long history of PTU treatment may be related to the development of combined small and large-vessel vasculitides.

The mechanism by which PTU induces autoimmunity is currently unclear. PTU has been linked to a number of rheumatologic disorders including lupus, serum sickness, and vasculitis⁴. It has also been linked to seropositivity for ANCA, although only about 20% of patients developing such antibodies will subsequently develop clinical disease⁵. Both the age at which a patient is exposed to PTU and the duration of its use affect the likelihood of developing seropositivity for ANCA. In one series, ANCA were found in 64% of children with Graves' disease receiving PTU for 4.0 ± 3.6 years¹.

The molecular similarity between myeloperoxidase and thyroid peroxidase has been suggested as one mechanism of autoantibody formation⁴. It has been shown that the presence of antiendothelial cell antibodies in patients with PTU-related ANCA vasculitis correlates to disease activity, implicating these antibodies as pathologic⁶.

A number of other aspects of our case are noteworthy. Although the association of pyoderma gangrenosum and Takayasu's arteritis is well known in the Japanese population, this association has only recently been characterized in North American patients, in whom it is rarer⁷. Interestingly, when pyoderma gangrenosum has been reported in conjunction with ANCA-associated vasculitis, PTU has frequently been implicated^{8,9}. Further, there have appeared cases of concurrent large-vessel and ANCA-associated small-vessel vasculitis, although these have not been previously linked to PTU use¹⁰⁻¹³. It has been noted in these cases that when ANCA-associated small-vessel vasculitis and aortitis coexist, the aortitis is characterized more by features of aneurysm formation and dissection than by stenotic lesions¹⁴, as occurred in this case.

In patients with both vasculitis and current or previous PTU use, there is often difficulty in distinguishing whether the vasculitis is related to PTU use or represents the emergence of an independent primary disease, as no clinical or diagnostic test currently available can make this distinction. All of these difficulties were present in our case, especially given that the patient stopped taking PTU prior to her diagnosis of vasculitis. We do not know with certainty the timepoint at which vasculitis began in this case, although her preceding 8 months of constitutional symptoms and the degree of vascular dilatation at presentation suggest that the onset of her disease likely predated her hospital admission. Although in some cases of PTU-induced vasculitis there is a rapid resolution of ANCA and clinical vasculitis after withdrawal of the drug, this is not always the case, as PTU-induced vasculitis has been shown to worsen months after PTU discontinuation¹⁵. In our case, the prior use of PTU for 20 years suggests a relationship to the emergence of her 2 forms of vasculitis, but this remains an associative rather than a causative relationship.

Ours is the first case report linking concurrent Takayasu's arteritis and ANCA-associated crescentic glomerulonephritis to prior use of PTU. As the mechanism of autoimmune antibody induction by this compound is further deduced, increased awareness of its broad effects on immune function will likely produce more reports.

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