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APPARENT VASCULITIS ASSOCIATED WITH PROPYLTHIOURACIL USE

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Propylthiouracil is among the drugs which have been implicated as causing vasculitis (1); however, the incidence and clinical findings have not been well described. We describe a young woman with Graves' disease who developed a reaction to propylthiouracil resembling a vasculitis.

Case report. A 26-year-old white female was admitted to West Virginia University Hospital in May 1977 with multiple necrotic ulcerations on the lower extremities. The lesions had developed one month prior to admission and were accompanied by nasal congestion, malaise, and a temperature of 101°F. The patient had taken propylthiouracil sporadically for the previous 13 years; her general indication for therapy was the sensation that her neck was more swollen than usual. Two months before the onset of the rash, she began taking 50 mg of propylthiouracil per day. She denied any previous skin rash, sinus drainage, arthralgias, or renal disease.

The patient had a pulse of 150 per minute, blood pressure of 120/80, and a temperature of 37.5°C. She had a smooth symmetrically enlarged thyroid gland approximately five times normal size. Exophthalmos was present. Examination of the nasal septum showed normal results. She had numerous necrotic ulcerations and purpuric lesions over her lower extremities. There were two 4 × 5 cm ulcerations over the left foot and ankle (Figure 1), extending into the subcutaneous tissue and down to the extensor tendons.

Laboratory findings included a WBC of 6,900 with 64 polymorphonuclear leukocytes and 1 eosinophil. Hemoglobin was 11.4 gm%. The serum creatinine

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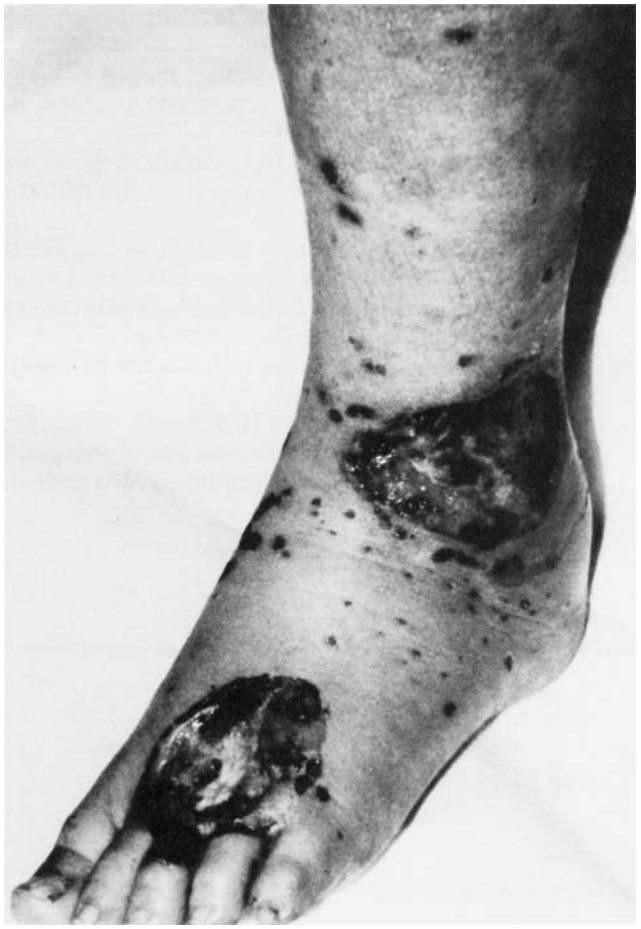

Figure 1. Admission vasculitic rash.

was 0.4 mg%. Serum thyroxine was 20.2 μg% (normal ≤ 11.4 μg%), T3 resin uptake 65.9% (normal 25–35%), and ^{131}I uptake of 77.8% (normal 10–35%). ESR was 62 mm/hr, by the Westergren method. Results of urinalysis were normal. The initial chest x-ray showed no infiltrates (Figure 2).

Rheumatoid factor was present in a titer of 1:320; ANA was positive at a titer of 1:10 in a peripheral pattern; cryoglobulins were absent; C'3 was 198 mg% and 223 mg% (normal 94–210 mg%); and anti-DNA binding was 9 units/ml (normal < 25). Blood cultures and cultures of the ulcerations for bacteria, acid fast organisms, and fungi were negative for pathogens.

The patient's propylthiouracil was discontinued and she was treated with propranolol and ^{131}I. The ulcerations were cleaned and debrided. Biopsy of the ulcerations revealed changes compatible with acute and chronic inflammation. Prednisone 60 mg/day was administered, but no obvious improvement in the ulcers could be seen.

Shortly after admission, the patient developed spiking fevers to 102°F and complained of a bloody nasal discharge. Ulceration of the nasal mucosa with perforation of the anterior nasal septum was noted for the first time. The patient began experiencing a nonproductive cough. A second chest x-ray revealed a left upper lobe infiltrate and a right hilar density of 4 cm (Figure 3). Multiple sputum cultures for AFB, fungi, and bacteria were negative. Sinus films were normal. Biopsy of the nasal septum revealed acute and chronic inflammation. Serial chest x-rays revealed cavitation of the LUL infiltrate and subsequent clearing of both the cavitated mass and the right hilar mass within 2 weeks (Figure 4). Multiple urinalyses were normal.

Because of poor healing of the extensive lesions, skin grafts were performed, but these were unsuccessful. After a 3-month period, the patient was discharged at her own insistence despite incomplete healing of the ulcerations. She was followed as an outpatient.

Two months after discharge, the patient's skin lesions were almost healed and she felt well. Seven

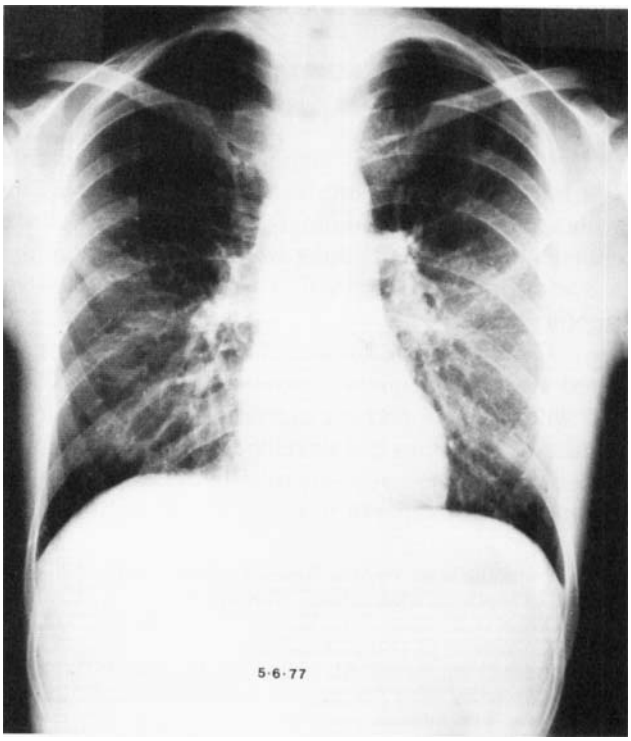

Figure 2. Admission chest film.

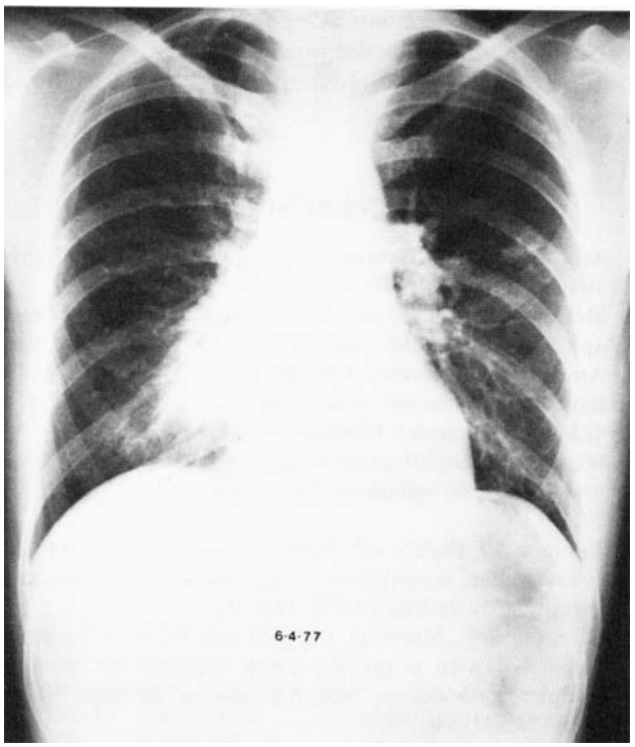

Figure 3. Right hilar density and left upper lobe cavity.

months after discharge, she felt that her neck was again becoming swollen and took the one propylthiouracil tablet remaining in her medicine cabinet. Five days later she was readmitted with multiple new small purpuric and ulcerating lesions on her upper and lower extremities which were identical to those present on her first admission. Physical examination revealed no other evidence of vasculitis. The nasal-septal perforation was still present and unchanged from the previous examination. Repeat laboratory studies showed normal results, including a chest x-ray, urinalysis, C3 level, ESR, ANA, rheumatoid factor, T4, and creatinine. She was observed without treatment for 2 weeks. During that time, the rash slowly resolved, leaving only the old scars from her original skin lesions. Since discharge she has refrained from taking propythiouracil.

Discussion. Vasculitis is an unusual manifestation of propylthiouracil toxicity. McCormick in 1950 described a fatal case of periarteritis nodosa after rechallenge with propylthiouracil in a patient who had previously developed toxic neurologic symptoms including a facial paralysis and a positive Babinski sign (2). McCombs found 2 cases of propylthiouracil vasculitis in 72 cases of vasculitis at the New England Medical Center Hospital from 1946 to 1963 (1).

Others have reported a lupus-like syndrome accompanied by arthralgias, fever, rash, and positive LE tests (3). Other findings described include leukopenia, pericarditis, urticaria, angioedema, migratory polyarthritis, hepatitis (4), and disseminated intravascular coagulation (5). Griswold et al described a patient with propylthiouracil vasculitis in whom cryoglobulins were isolated from the serum. Granular deposits of IgG, IgA, and IgM were noted in the walls of dermal vessels as well as in the renal glomeruli. These findings support the hypothesis of an immune complex disease (6).

After ingestion of propylthiouracil, our patient developed a picture suggestive of vasculitis with extensive skin lesions, fever, fleeting cavitating pulmonary infiltrates, and a bloody nasal discharge with perforation of the nasal septum. Although other conditions such as Wegener's granulomatosis were diagnostic considerations initially, the lack of renal disease and the dramatic recurrence of skin lesions after the patient's inadvertent rechallenge with propylthiouracil established the drug as the etiologic agent. Although vasculitis was not confirmed by biopsy, we believe that the clinical findings were strongly suggestive of such a state.

In reviewing our experience with propylthioura-

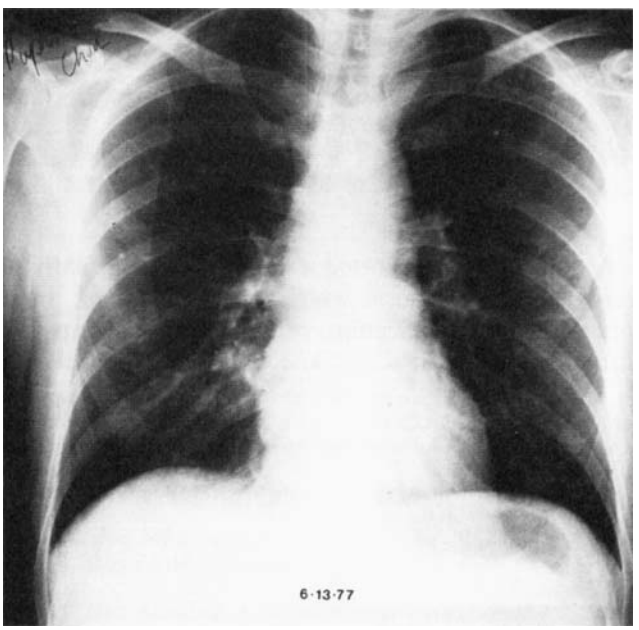

Figure 4. Subsequent clearing of right hilar density and disappearance of left upper lobe cavity.

cil, we found 2 additional cases of vasculitis associated with the use of this agent. A purpuric skin rash was the only manifestation of vasculitis in both cases. The first of these patients developed red, swollen, tender purpuric lesions on the buttocks, lower legs, breasts, abdomen, and soft palate after taking propylthiouracil. Laboratory findings included a C3 of 125 mg%, negative ANA, negative rheumatoid factor, negative cryoglobulins, and a sedimentation rate of 53 mm/hr. Biopsy of the skin lesions revealed leukocytoclastic vasculitis. The patient's propylthiouracil was discontinued and the skin lesions resolved without treatment over a 2-week period. The second patient also developed palpable purpura while taking propylthiouracil. There was no biopsy in this case and the rash resolved in 2 weeks after stopping the propylthiouracil.

Corticosteroids were used in our first patient without obvious benefit. The other 2 patients were not treated with steroids and their skin lesions cleared after propylthiouracil was discontinued.

On the basis of our experience it appears that propylthiouracil may be more commonly implicated as the cause of vasculitis than is commonly recognized.

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HLA ANTIGENS IN CHONDROCALCINOSIS AND ANKYLOSING CHONDROCALCINOSIS

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In 1970 we reported a woman with unusually severe chondrocalcinosis which included diffuse intervertebral disc calcification, osteitis pubis–like changes, and ankylosis of hips and knees (1). Of 200 Chiloe Islanders with chondrocalcinosis studied in the last 7 years, 9 more have progressed to a similar state with fibrous or bony ankylosis of the hip and knees along with marked lumbar spine involvement clinically mimicking ankylosing spondylitis. We have termed the latter patients *ankylosing chondrocalcinosis.*

This report describes the typing studies of the HLA–A and –B antigens in 47 Chiloe Islanders with familial chondrocalcinosis and the clinical and radiographic features of the 10 patients with ankylosing chondrocalcinosis.

Two stage microdroplet lymphocytotoxicity tests of Terasaki for 12 HLA–A and 15 HLA–B antigens, using reagents provided by the National Institutes of

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