Case 19
A 26-year-old Thai woman from Kalasin

Chief complaint: Multiple discrete, non-blanchable, tender, erythematous to violaceous papules on both lower extremities for 5 days

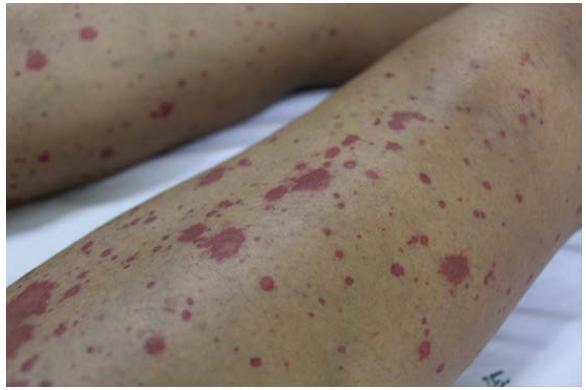

Fig. 19.1

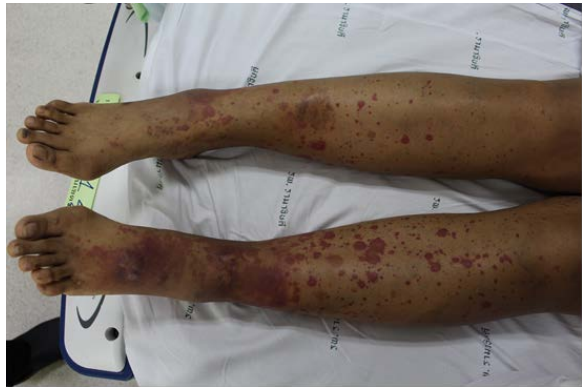

Fig. 19.2

Present illness:
Seven years before this presentation, at another hospital, the patient received a diagnosis of hyperthyroidism caused by Graves' disease (GD) which was confirmed by the radioactive iodine uptake test (Thyroid I131 scan) showing homogeneously increased uptake in both lobes of the diffusely enlarged thyroid gland. At the time, treatment with propylthiouracil (PTU) (200 mg/day) and propranolol (10 mg/day) were initiated.

The patient had been in his usual state of health until 5 days before this presentation when multiple tender erythematous papules on both lower extremities developed.

Two days earlier, an increase in the number of erythematous papules was noted and was accompanied by a low-grade fever, a sore throat, and a runny nose with clear mucus. She also complained of mild pain in both knees. There was no history of hemoptysis, bloody urine, motor weakness, loss of sensation, myalgia, or abdominal pain.

Underlying disease: Unremarkable

Family history: Her mother was diagnosed with a nontoxic goiter.

Dermatologic examination: (Fig. 19.1, Fig. 19.2)
Multiple discrete non-blanchable, tender, erythematous to violaceous papules, coalescing to plaques on both lower extremities with predominance on the distal part

Physical examination:

- Vital sign: BT 37°C, BP 110/60 mmHg, P 100 bpm, RR

16/min
- GA: a Thai female, good consciousness
- HEENT: exophthalmos, eyelid retraction, and lid lag were noted, and diffuse palpable goiter (80 grams) without thyroid bruit was detected
- The remainder of her physical examination was unremarkable.

Investigations:

- **CBC**:
  - WBC 8,100/mm^3 (N 69.1, L 18, M 9.2, E 3.1, B 0.6)
  - Hb 11.3 g/dL, Hct 34.0 %, MCV 83.1 fL
  - Plt 296,000/mm^3
- **Renal function:** BUN/Cr 15/0.7 mg/dL
- **Liver function test:** AST/ALT 22/10 U/L, ALP/GGT 88/18 U/L, TP/Alb 78.9/28.7 g/L, TB/DB 0.8/0.3 mg/dL
- **Urinalysis:** pH 5.0, Sp.gr 1.006, protein negative, glucose negative, RBC 2-3/HPF, no dysmorphic RBC, WBC 0-1/HPF, Squamous epithelial cell negative
- **ESR:** 103 mm/hr
- **ANA profiles:** ANA 1:80 (staining pattern: nucleolar and homogeneous), anti-dsDNA positive 1+, Jo-1 positive 1+, MPO-ANCA positive (123.81 RU/ml), and PR3-ANCA negative (5.1 RU/ml)
- **Complement:** C3c 1.34 (0.9–1.8 g/L), C4 0.27 (0.1–0.4 g/L)
- **Viral profiles:** Anti-HBs, HBs-Ag: Negative, Anti-HCV: Negative, Anti-HIV: Negative
- **Thyroid function test:** TSH <0.0038 (0.35 – 4.94 uIU/mL), free T3 4.45 (1.88–3.18 pg/mL), free T4 1.24 (0.70–1.48 ng/dL)

Histopathology: (S18-014889, left leg) (Fig. 19.3)

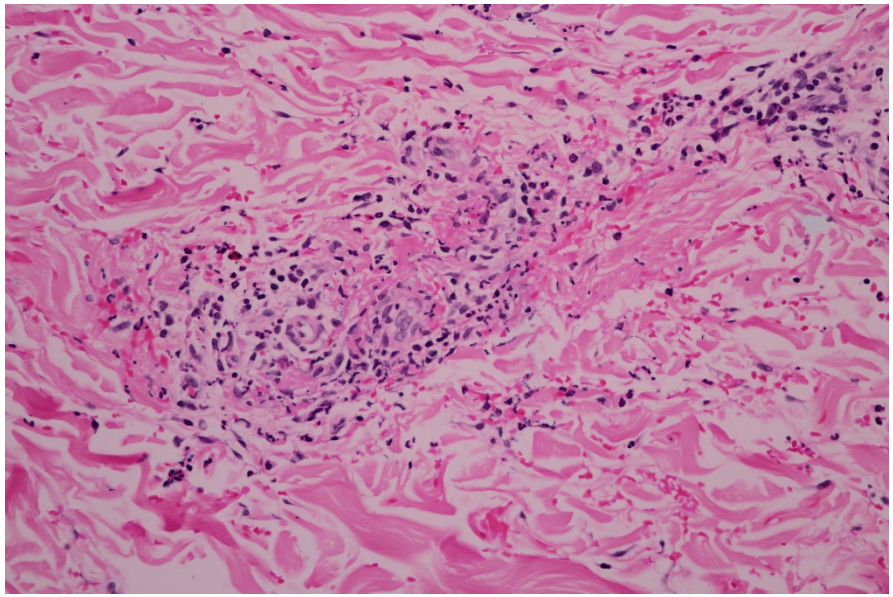

Fig. 19.3

- Dense perivascular inflammatory cells infiltrate composed of lymphocytes, neutrophils, extravasted erythrocytes and nuclear dust in the upper dermis
- Fibrin deposit around and within small blood vessels

Direct immunofluorescence: (Fig. 19.4)

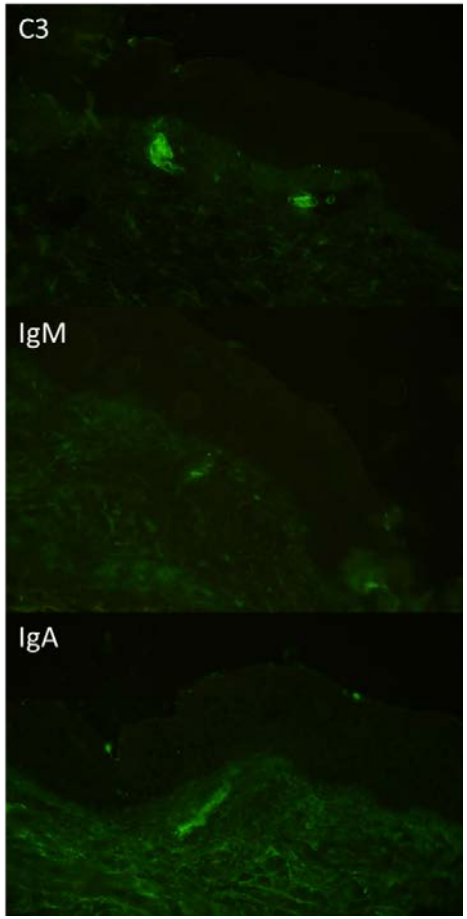

Fig. 19.4

- IgA, IgM deposition at subepidermal blood vessel
- Few cytoid bodies stained positive to IgM
- Compatible with small vessel vasculitis

Diagnosis: PTU-induced ANCA-positive vasculitis

Treatment

- Specific treatment
  - Prednisolone 60 mg/day
  - Hydroxychloroquine 200 mg/day
  - Colchicine 1.2 mg/day
  - Betamethasone cream apply lower legs twice a day
- Supportive and Adjunctive treatment
  - Indomethacin 25 mg twice daily
  - Trimethoprim/sulfamethoxazole 480 mg/day
  - Acyclovir 800 mg/day
  - Calcium carbonate 1250 mg/day
  - Vitamin D2 20,000 IU/week

Presenter: Weeratian Tawanwongsri, MD

Consultant: Kunlawat Thadanipon, MD

Discussion:

Propylthiouracil (PTU), an antithyroid medication, is preferably indicated for the treatment of hyperthyroidism in particular circumstances: treatment of thyroid storm, treatment during the first trimester of pregnancy, and patients with minor reaction to.[1]

The mechanism of PTU includes inhibiting the thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin, blocking the conversion of thyroxine to triiodothyronine within the thyroid and in peripheral tissues, and playing a crucial role in immunosuppressive effects.[2] Unfortunately, adverse drug effects have been reported over six decades after its first introduction. Apart from hepatotoxicity and agranulocytosis, another serious adverse effect is PTU-induced antineutrophil cytoplasmic antibody-

associated vasculitis (PTU-induced AAV). Its pathogenesis has been not well established. Certain proposed hypotheses included PTU-induced alteration of granules in myeloperoxidase (MPO)-containing neutrophils, T-cell sensitization induced by reactive forms of PTU which are oxidized by MPO, and vascular cell wall damage due to the combination of PTU and MPO as cytotoxic products.[3]

In spite of that PTU contributed to the development of serum-positive antineutrophil cytoplasmic antibody (ANCA) with the percentage of 15-64%[4], only approximately one-third of the patients with PTU-induced ANCA developed clinical vasculitis.[5, 6] Serum-positive ANCA might not be, therefore, the only factor being attributed to PTU-induced AAV. Documented risk factors for developing PTU-induced AAV in adults included long-term exposure to PTU, high ANCA titer (particularly MPO), and genetic background.[4]

The largest clinical series in Japan estimated that the annual incidence of PTU-induced AAV was 0.47-0.74 patients per 10,000 patients with GD. Despite located in the same geographical region, nevertheless, only a few prospective studies or case series in Thai adults have been reported.[7-9] Hereby, we reported another GD patient—who was diagnosed with PTU-induced AAV—presenting with merely cutaneous manifestation. In agreement with previous studies, her risk factors were long-term exposure to PTU and high MPO-ANCA titer. With suspicious clinical manifestations and supportive positive MPO-ANCA, the diagnosis was confirmed by a histopathologic examination revealing fibrin in vessel walls, nuclear dust, and extravasated red blood cells.

Diagnosis of this adverse drug reaction can be, basically, made by exclusion using chronological factors and clinical manifestations. The kidney, lungs, and skin remain the most frequent organs affected by the disease. And the most common cutaneous lesion is leukocytoclastic vasculitis, which usually presents as purpuric papules, primarily on the lower extremities.[10] Other manifestations included urticaria-like lesion, ulcer, and pustules.[11] However, a more severe vasculitis involving small and larger vessels—presenting as a rapid onset of hemorrhagic skin lesions on upper arms and buttocks—was reported.[12]

Up till now, neither of ANCA screening strategy—before or during given PTU—or standard treatment protocol was developed owning the scant evidence-based information available. However, early cessation of PTU remains logically a cornerstone particularly in the patients with clinical suspicious signs of vasculitis. Addition of corticosteroids and cyclophosphamide for cases with severe major organ involvement is commonly considered, on a case-by-case basis, following the treatment recommendation of primary AAV.[13] Meanwhile the optimal duration of treatment had not yet been decided, one study found that patients with PTU-induced AAV had a better prognosis compared with those with primary AAV. After discontinuing the immunosuppressive therapy within one year, 80% of patients remained in complete remission over the mean follow-up of 55 months.[14]

In addition, there remains scarce data to conclude the necessity of MPO-ANCA monitoring after discontinuing PTU. Because it was found that MPO-ANCA levels, particularly in the patients with initial high MPO-ANCA levels, remained positive for longer than 5 years in spite of PTU cessation—but were rarely associated with clinical vasculitis.[15]

In this case, her erythematous to violaceous papules and plaques turned paler and less tender with good therapy compliance. Neither of additional skin lesion nor other systemic involvement was detected through a 3-month follow-up period.

Reference:

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