CASE REPORT

A case of propylthiouracil ANCA associated vasculitis with extensive skin necrosis and bizarre gastro-intestinal ulcers

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ABSTRACT
ANCA-associated vasculitis is a rare complication of anti-thyroid treatment. It can involve several organs and can be life-threatening. Skin is commonly involved. In this study, we present a case who was under treatment with propylthiouracil (PTU) for two years and developed ANCA-associated vasculitis with skin and gastrointestinal lesions. She had necrotic cutaneous ulcers and mucosal superficial ulcers in jejunum, without indurations of ulcer edge, and surrounding mucosa that led to severe gastrointestinal bleeding. She had complete recovery after cessation of PTU and institution of immunosuppressive therapy.

Key words: ANCA-associated vasculitis, propylthiouracil, gastro-intestinal ulcer, rectorrhagia, anti-thyroid agents, drug-induced gastrointestinal bleeding, Salman’s sign

INTRODUCTION
Propylthiouracil (PTU) is a thiourea anti-thyroid agent which inhibits the synthesis of thyroid hormones, it is frequently used in the managing of hyperthyroidism, and is usually prescribed for a long periods of time.
Several adverse effects related to PTU have been described including agranulocytosis, aplastic anaemia, hepatitis, and interstitial pneumonitis. Autoimmune disorders including vasculitis and lupus erythematosus-like syndromes are unusual but serious complications of anti-thyroid drugs. Serological and histologic findings on skin biopsy, and the variable patterns of clinical manifestations, support that the vasculitis and lupus-like syndromes are a hypersensitivity reaction because of circulating immune complexes; and can damage several organs. Skin is commonly damaged. Almost 3% to 5% of adults and up to 18% of children have skin eruptions which is sometimes associated with systemic disorders. Positive ANCA and absence of immunofluorescence findings in several cases hypothesize that it can be a pauci-immune vasculitis. Gastro-intestinal involvement is very rare, specially involvement of small intestine.

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The patient is a 30-year-old woman with Grave’s disease that was diagnosed during her first pregnancy two years before admission. Treatment with PTU (300 mg/day) had been started. After her second delivery she had started feeling abdominal pain that was constant with some exacerbations. She had several admissions to emergency department and was treated symptomatically because all primary evaluations such as laboratory tests, X-rays and ultra-sonography studies were normal. She had developed necrotic ulcers in her buttock and then her right leg, which were initially considered to be due to intra-muscular injections during last 10 months (Fig. 1, 2). Finally she was admitted to ICU because of severe abdominal pain and gastrointestinal bleeding (melena that progressed to frank rectorrhagia) with hemodynamic signs (haemoglobin about 4 g/dl). Her first endoscopy and colonoscopy were negative but because of continued blood loss, repeat colonoscopy was done.
with pediatric colonoscope up to the small intestine and there were multiple ulcers along the mucosa of jejunum that was suggestive for vasculitis (Fig. 3).

Her cutaneous ulcers were necrotic and did not respond to supportive therapies. Blood tests including ESR, CRP, RF, FANA, c-ANCA, p-ANCA, anti-dsDNA, and serologic tests for hepatitis B and C were requested.

Her initial ESR was 63 mm for the first hour and, CRP, c-ANCA, p-ANCA showed positive results. All other tests were negative. Skin biopsy showed acute inflammation with necrosis.

The most appropriate diagnosis was PTU-induced ANCA-associated vasculitis. So PTU was stopped and treatment with lithium, (900 mg/day) and cholestyramine powder and intravenous pulsed methylprednisolone was started and continued with maintenance oral prednisolone and azathioprine (50 mg/day). Prednisolone was tapered then after. After pulse corticosteroid therapy, gastrointestinal (GI) bleeding was stopped and repeat enteroscopy with pediatric colonoscope revealed completely healed ulcers. She was candidate for radioactive iodine to achieve complete recovery. Now she is in a good health with completely healed skin lesions without further GI bleeding and rather good thyroid control without PTU.

DISCUSSION
PTU can cause some auto-immune disorders, such as; lupus-like syndrome and systemic vasculitis. Despite a benign course of PTU induced lupus-like syndrome, PTU-induced vasculitis could be a serious and life-threatening condition. The occurrence of overt vasculitis may vary from one month to 13 years after initiation of PTU.4

In one report from Japan, annual incidence of myeloperoxidase-ANCA associated vasculitis (MPO-AAV) were reported in 92 patients from 88 hospitals. The incidence was between 0.53 to 0.79 per 10,000 patients for PTU with Graves’ disease, and 0.057 to 0.085 patients per 10,000 patients for methimazole with Graves’ disease.6

MPO-AAV can disturb multiple organs. The most involved organs are skin, kidneys and lungs, which are described in many case reports.7,8

Skin manifestations may include purpuric lesions like cryoglobulinemia, necrotic ulcers, purpura fulminans,9 and erythema nodosum.10 In kidneys it can cause glomerulonephritis11 and in lungs nonspecific inflammation have been reported.3

The first small intestine ulcers in ileum, cecum and right colon have been reported by Gaburri.14 Our case could be the second one with involvement of small intestine secondary to PTU. The ulcers were superficial, without induration (thickening of mucosa that indicates severe inflammatory response and this indurated mucosa is usually surrounding the ulcer) of ulcer edge, and surrounding mucosa seemed completely normal. It sounds that the mucosa was shedding from its base and more attention should be paid to discover the normal appearing borders of mucosal ulcer in these settings. In our experience this ulcer was completely different from the other ones that is occasionally seen in the setting of other types of vasculitis and so we would suggest a new name for this endoscopic finding that could be specific or characteristic for PTU-induced GI ulcers as “Salman’s sign”. In another case with GI presentation of PTU, there was colon ulcer as GI presentation with rectorrhagia. That ulcer was deep with indurated edge and was completely different from our case with small intestinal involvement.15

It seems that the genetic background determine the pathogenesis of ANCA-associated vasculitis, the initiation of immunological reaction, severity of vasculitis process and, the site of involved organs.16 Our patient had GI and skin lesions without involvement of kidney and lungs. Involvement of kidney is associated with an ominous prognosis.17 In our case despite involvement of both small intestine and skin the prognosis was good.

CONCLUSION
Despite rarity of PTU-induced ANCA-associated vasculitis, it can be life-threatening. As a result we recommend physicians to contemplate this complication in their daily practice. In the setting of lower GI bleeding, involvement of small intestine should be considered and extensive endoscopic evaluation should be done.

REFERENCES
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