CASE REPORT
OLGU SUNUMU

Propylthiouracil induced p-ANCA+ pyoderma gangrenosum: Case report and review of literature

Propiltiourasil kaynaklı p-ANCA + piyoderma gangrenozum: Olgu sunumu ve literatürün gözden geçirilmesi

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SUMMARY

Propylthiouracil is a drug commonly used in patients with hyperthyroidism. Some patients with Graves using this drug may have a positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA) associated with different forms of vasculitis and neutrophilic dermatoses. However, skin lesions such as maculopapular purpura, erythema, sensitive nodules, ulceration, vesiculobullous lesions, and livedo can be induced by antineutrophil cytoplasmic antibody (ANCA) -positive vasculitis. In these cases, the development of pyoderma gangrenosum (PG) is very rare. We aimed to present a concurrent development of pyoderma gangrenosum, p-ANCA positivity and inraalveolar hemorrhage in a patient who had been using PTU for a long time and to discuss the current literature with this presentation. We think that the baseline ANCA levels should be measured in all graves patients because of severe ANCA-related vasculitis in some patients during PTU therapy

Keywords: ANCA, PTU, pyoderma gangrenosum, vasculitis

INTRODUCTION

Propylthiouracil (PTU) is a medication commonly used in the treatment of hyperthyroidism and is associated with the development of antineutrophil cytoplasmic antibodies (ANCA) in 20% of patients treated for Graves' disease (1,2). ANCA-positive PTU-induced pyoderma gangrenosum (PG) was first identified in 1999 by Darben et al. (1). ANCAs are found in the blood of many patients with necrotizing systemic vasculitis and in some patients with neutrophilic dermatoses such as drug-induced vasculitis, Sweet's syndrome, Behçet's disease and PG. Some reports have described the ANCA phenomenon in patients with PG or in neutrophilic dermatosis with the characteristics of PG (3). We aimed to present development of PG with p-ANCA positivity in a patient who had been- using PTU for a long time and to discuss the current literature with this case-based review.

CASE REPORT

A 40-year-old female patient presented with a maldorous and traumatic deep ulcerous scar on both legs. No history of trauma was noted. This lesion had started as a small papule 1 year ago, developed into a pustule, and then an ulcer with blood, pus and granulation tissue, which was rapidly spreading into the adjacent normal skin. Her health was otherwise good and she had no past history of malignancy or symptoms of autoimmune disease. When the patient's drugs were questioned in detail, it was learned that the patient received PTU 150 mg/day for nearly five years because of Graves' disease.

In laboratory tests evaluation, C-reactive protein (CRP) level was 44.5 mg/dl, erythrocyte sedimentation rate (ESR) was 50 mm/h. There were no abnormal findings on the complete

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blood count (CBC), serum electrolytes, liver function tests (LFTs), rheumatoid factor (RF), antinuclear antibody (ANA), renal function tests (RFTs), thyroid function tests (TSH and free T4), pulmonary function tests (PFTs) and chest X-ray. Normal or negative test results were obtained for HLA-B27, C3 and C4 complement levels, urine and serum electrophoresis, HIV, hepatitis B and C serology. Immunofluorescence was positive at p-ANCA 1/100-1/320 dilution, and myeloperoxidase-ANCA (MPO-ANCA) was 107.79 RU/ml (negative<20) with ELISA method.

A skin punch biopsy was performed, and tissue culture was obtained. The bacterial, fungal, and mycobacterial culture results from the ulcer were negative. The histopathological examination of the biopsy materials taken from the ulcers revealed; edema, fibrosis, irregular acanthosis, local suppurative inflammation and dermal inflammation marked with neutrophils and lymphocytes (Fig. 1). The patient was diagnosed with PG.

She was investigated for conditions known to be associated with PG with no evidence of malignancy, infection, or other autoimmune-related disease being found. Despite apparent pathergy, Behçets' syndrome was thought unlikely in view of the lack of eye involvement or genital ulceration and minimal oral mucosal disease. The endoscopy and colonoscopy results were normal in terms of inflammatory bowel diseases (IBD).

The PTU therapy was discontinued than corticosteroid (1 mg/kg/day) and cyclosporine (200mg/day) therapy was started with diagnosis for PG. The reepithelization was observed in the lesions in both legs during the 4-week follow-up period (Fig. 2).

LITERATURE REVIEW METHOD

We conducted our literature search for case reports of PTU-induced and p-ANCA positive PG using keywords on PubMed, and Medical Subject Heading (MeSH) terms on MEDLINE and EMBASE carefully.

DISCUSSION

PG is a rare inflammatory disease of unknown etiology characterized by neutrophilic infiltration of the dermis and tissue destruction. PG is idiopathic at 25-50% but systemic diseases coexist at a rate of 50%. The disease was reported to be associated particularly with IBD, rheumatoid arthritis, myeloproliferative and lymphoproliferative diseases. It was rarely reported to be associated with the hepatobiliary diseases, hematological disorders, joint diseases, solid neoplasms, drugs, and other neutrophilic dermatoses (4-6).

The relationship of PG-like ulceration with positive ANCAs after PTU therapy was first described by Darben et al. in 1999 (1). A total of five cases reported as PTU-associated PG in the literature are female patients treated for hyperthyroidism (Table 1) (1,3,7-9). The indirect immunofluorescence MPO-ANCA is positive in all reported cases. Lesions occurred between 1.5 and 6 years after the onset of PTU. In all cases, an ulcer healing was seen with the discontinuation of PTU and the initiation of systemic corticosteroid treatment.

The incidence of MPO-ANCA positivity as a result of antithyroid drugs varies between 4.1-64% (10). PTU (1-5%) causes adverse effects such as agranulocytosis, pancytopenia, liver failure, and drug rash. The formation of such side effects can be reduced by reducing the dose (11). Although ANCA is relatively common in these patients, the prevalence of vasculitis is much lower (0-1.4%) (12,13). Therefore, the positivity of ANCA does not have to show the onset of signs of inflammation and vasculitis. Similarly, the presence of ANCA which is not associated with vasculitis indicates that ANCA alone is not enough to induce vasculitis (14,15).

The onset time of MPO-ANCA associated vasculitis differs. The dose dependence of MPO-ANCA associated vasculitis is also unclear because it occurs even at low doses for PTU. However, it is asymptomatic in many patients and the incidence of MPO-ANCA associated vasculitis is lower (16,17). There was no correlation between the MPO-ANCA titer and the severity of vasculitis in patients with MPO-ANCA associated vasculitis. MPO-ANCA associated vasculitis has a good prognosis with the discontinuation of antithyroid drugs, although the MPO-ANCA titer is positive for a long time (18,19).

The role of PTU in the pathogenesis of PG is unknown. The similarities of the nucleotide and amino acid sequences between thyroid peroxidase and human MPO are 46% and 44%, respectively and these similarities are particularly most apparent in the coding sequence encoding the functional subunits of MPO (16). Lee et al. (20) found that PTU treatment could reduce the oxidation activity of MPO, and this was associated with a change in the MPO structure. However, it was reported that PTU was selectively accumulated in neutrophils and bound to myeloperoxidase (MPO) and the enzyme caused a change in the heme structure. Probably the modified enzymes combined with the drugs can act as haptens and initiate the production of anti-MPO autoantibodies and this stimulates other neutrophils. Activated neutrophils degranulate and produce oxygen free radicals. In this case, the adhesion molecule expression increases in both neutrophils and endothelial cells and the release of interleukin 8 (IL-8) is stimulated. MPO, the structure of which can be modified by connecting to the PTU, can serve as a neoantigen. The PTU may inhibit the oxidation activity of MPO in a dose-dependent manner. Jiang et al. (21) found that PTU could undergo a chemical transformation

in the presence of extracellular hydrogen peroxide. In other words, it can be converted into cytotoxic metabolites by the neutrophil derived MPO. More importantly, the reactive metabolites of PTU are immunogenic to produce ANCAs dependent on T cells for T cells and activated B cells (13).

Following the detection of PTU induced ANCA-positive PG, PTU should be discontinued before other therapeutic measures are initiated (22). Systemic immunosuppressive treatment is recommended in patients with large surface area ulcers, rapidly progressive, unresponsive to topical treatment and in whom improvement is not achieved despite the underlying PG-related disease (6). It has been reported that oral prednisone (1-2 mg/kg/day) treatment is very effective in PG lesions and it can be seen in early period with intravenous methylprednisizone administration at a dose of 1 g/day up to 5 days (5,6). In many studies, the recommended immunosuppressive agent is oral cyclosporine. In patients with cyclosporine (2-5 mg/kg/day) treatment, it was emphasized that there was a good response to the treatment and the recurrence was significantly reduced after the treatment (23). The reduction in the diameter of the ulcer, improvement in the margins, diminution in the lesion color and decrease in depth, as well as the absence of new ulcer formation, indicate that the good response to the treatment. In this case, dose reduction should be planned. In the case of recurrence of the lesions while decreasing the steroid dose, dose increase is recommended. In the presence of treatment-resistant ulceration, the patient should be reassessed and new skin biopsy should be taken to ensure PG diagnosis. Long term use of immunosuppressive agents should be avoided in the stable period of the disease (24).

In the present case, the patient who received PTU treatment due to hyperthyroidism. The lesions appeared in the extremity 5 years after the initiation of medication. It was determined that MPO-ANCA was positive in both immunofluorescence and ELISA tests. An improvement was seen in the PG after cessation PTU therapy and treatment with the systemic corticosteroids and cyclosporine.

In conclusion, p-ANCA-positive PTU-induced PG is a rare side effect of this drug. However, physicians should be aware of this complication during PTU therapy; recognition of the skin lesion and identification of p-ANCAs permits early disease detection and related prognosis improvement. Further studies are needed to clarify the role of PTU in the development of ANCAs and the pathogenesis of PG.

Table 1 Cases of PTU induced PG reported in the literature

	Sex/age (years)	Drug	PTU Dose and route	Initiation to treat PG onset time (year)	PG	Anti-MPO	Management
Darben et al. 1999(1)	F / 44	PTU*	NR	4	All four limbs, vertex of scalp, roof of mouth	+	Methylprednisolone 1 g iv/day for 5 days and followed by 80 mg PO **
Hong and Lee 2004(8)	F / 27	PTU*	NR	2	Both lower legs anterior	+	Methylprednisolone (1 mg/kg/day PO) and cyclosporine **
Boulenger-Vazel et al. 2005(7)	F / 40	PTU*	NR	1,5	Right ankle	+	Methylprednisolone (1 mg/kg/day PO)**
Gungor et al. 2006(3)	F / 52	PTU*	NR	2	Both lower extremities	+	Methylprednisolone (1 mg/kg/day PO)**
Seo et al. 2010(9)	F / 60	PTU*	150 mg/day	6	Right lateral torso	+	Methylprednisolone (1 mg/kg/day PO)**, dapsone, colchicine and cyclosporine added consequently

PTU: propylthiouracil, PG: pyoderma gangrenosum, MPO: myeloperoxidase, PO: peroral
*Treatment for Grave's disease, ** Withdrawal of PTU

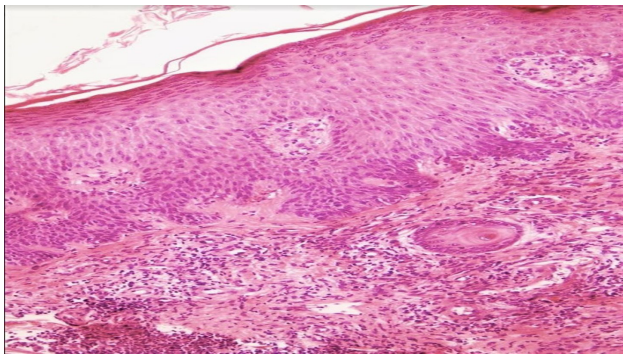

Fig. 1 Intracorneal neutrophils in the epidermis, irregular acanthosis, local suppurative inflammation in the dermis and active chronic inflammatory granulation tissue formation

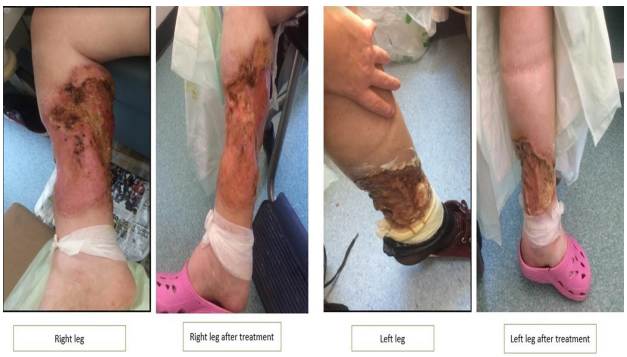

Fig. 2 Clinical photographs of the patient's right and left lower extremities before and after Cyclosporine and corticosteroid therapy

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