Cytoplasmic Pattern Anti-Neutrophil Cytoplasmic Antibody (cANCA)-Positive Cutaneous Leukocytoclastic Vasculitis Induced by Propylthiouracil: A Case Report

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Abstract

Propylthiouracil (PTU) is a medication commonly used to treat hyperthyroidism, but it has various rare side effects such as anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV). In the last decades, multiple cases of PTU-induced AAV have been reported, some being fatal. While AAV is primarily related to perinuclear-staining ANCA/anti-myeloperoxidase (pANCA/anti-MPO), it can occur to a lesser extent in association with cytoplasmic staining ANCA/ proteinase 3 (cANCA/PR3). A case is presented of a 62-year-old female with a history of hyperthyroidism due to toxic multinodular goiter treated with a standard dose of PTU. Approximately 3 years after starting therapy, she noticed formation of skin ulcerations on both of her ear lobes, nose and bilateral limbs. Detailed hospital work-up detected cANCA positivity. Biopsy of the affected skin revealed leukocytoclastic vasculitis and additional tests excluded systemic vasculitis. The patient was diagnosed as PTU-induced vasculitis, a form of drug-induced vasculitis. Although clinical manifestations improved slightly after total thyroidectomy, the patient could not be saved because of the fulminant course of infected and disseminated skin ulcers. PTU is one of the causes of AAV. However, the presence of cANCA positivity when pANCA is negative in PTU-induced AAV is extremely rare. Here, we present a rather unusual case of PTU-induced AAV associated with cANCA.

Keywords: cANCA, leukocytoclastic vasculitis, propylthiouracil

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Introduction

Anti-neutrophil cytoplasmic antibodies (ANCAs) are a group of autoantibodies which can be detectable in various autoimmune and/or vasculitic conditions. ANCAs can be detected using direct immunofluorescence method. The primary molecular target is proteinase 3 within the cytoplasm of neutrophils and monocytes for cytoplasmic ANCA (cANCA) and myeloperoxidase (MPO) for perinuclear ANCA (pANCA). Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a complex phenomenon because of an inflammation of small and larger vessels with polymorph infiltration within the vessel walls and leukocytoclasis due to production of autoantibodies to neutrophil cytoplasmic components. It has been demonstrated that ANCAs are able to stimulate neutrophils. *In vitro*, ANCAs can activate neutrophils primed with tumor necrosis factor-alpha (TNF-α) for the production of reactive oxygen intermediates (ROI), the release of lysosomal enzymes, and the secretion of interleukin-1 [1-3]. Apart from inducing the activation of neutrophils, ANCAs also activate monocytes and/or endothelial cells [3-5]. The central mechanism in autoimmunity is the breaking of self-tolerance. Risk factors for breaking self-tolerance to ANCA antigens are genetic factors, drugs, chemical substances and/or infectious agents. A combination of risk factors may be present in patients who develop ANCA. Vascular damage in AAV and/or glomerulonephritis results predominantly from activation of neutrophils when these cells adhere to endothelial cells [6-8].

Propylthiouracil (PTU) is an anti-thyroid drug used for the treatment of hyperthyroidism. Although there are some cases in the literature with p-ANCA positive vasculitis associated with PTU treatment, the pathogenesis of PTU-related vasculitis is still unknown. It has been hypothesized that PTU serves as a MPO substrate for free radical production [9]. It is not clear if ANCA has a direct pathogenic role in the development of PTU-associated vasculitis. On withdrawal of PTU, clinical improvement was associated with a fall in the ANCA titer [10]. The literature reports 20 to 40 percent of patients treated with PTU for hyperthyroidism become ANCA positive and of these patients, nearly one-fifth develop features consistent with vasculitis [11-14].

When drug-induced vasculitis is suspected, quick diagnostic procedures should be carried out to exclude systemic manifestations. Treatment consists of withdrawal of the causative drug,

which is sufficient in most cases, but in others oral or parenteral glucocorticoids and even immunosuppressant drugs are indicated.

The Case

Sixty-two years old woman admitted to Emergency Department of Samsun Research and Training Hospital with the complaints of multiple skin ulcerations in the whole body, predominantly in the ear lobes, nose and limbs. She was examined by a plastic surgery specialist, and diagnosed as "disseminated skin necrosis and Fournier's gangrene". After an initial examination, the patient underwent extensive debridement of necrotizing skin ulcers and infected soft tissues. She was followed at the Intensive Care Unit of Surgery Department after the operation. Wound cultures and surgical specimens' revealed acute inflammation and liquefactive necrosis associated with mixed bacterial flora, consistent with the diagnosis of Fournier's gangrene. A rheumatologist was consulted. As documented in her medical history, she had been using propylthiouracil (PTU) 150 mg t.d.s. for the treatment of hyperthyroidism for 3 years and the skin ulcerations had appeared 2 months ago. There were not any other chronic diseases such as renal failure or diabetes mellitus. It was learned that she was seen by a dermatologist a few months ago at another tertiary referral hospital in our city and diagnosed as "purpura fulminans" by histopathological examination of the skin lesions. She had been under follow-up by daily dressing changes of her skin ulcers. During her physical examination at our hospital, she was oriented and cooperative and also afebrile and normotensive. Her goiter was grade 3 nodular palpable. Cardiac auscultation showed arrhythmia which was confirmed by electrocardiographic monitoring. Her bilateral lung examination was normal. She had multiple necrotizing ulcers on the dorsum of the nose **(Figure 1)**, both ear lobes **(Figure 2)**, and disseminated ulcerations on the skin of limbs bilaterally (**Figures 3-6**). Based on her medical history including PTU administration, it was considered that the skin ulcers were caused by drug-induced vasculitis and the patient was referred to the Inpatient Clinic of Rheumatology Department.

Her laboratory tests revealed thyrotoxic status. Thyroid autoantibodies anti-thyroid peroxidase anti-TPO and anti-thyroglobulin (anti-TG) were negative. Although pANCA was negative, cANCA antibody was positive. Her laboratory tests are summarized in Table 1. Ultrasound

examination of thyroid gland was consistent with multinodular appearance and thyroid scintigraphy showed the presence of hyperactive nodules.

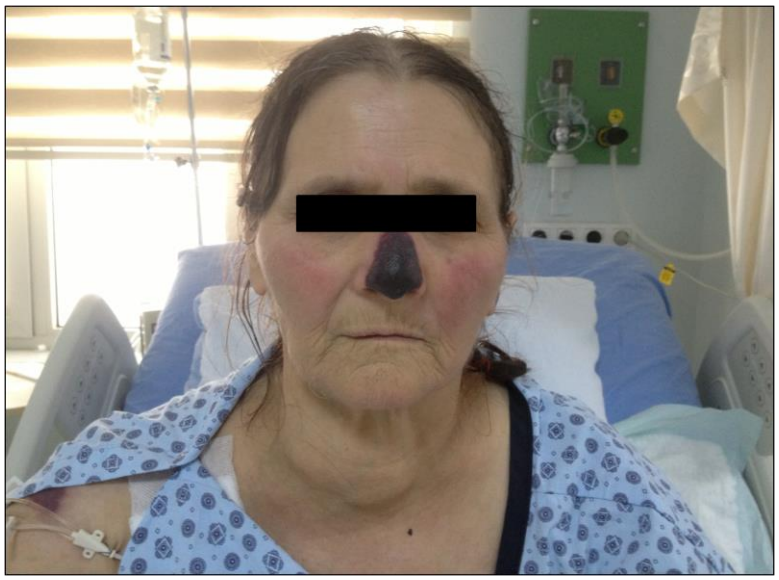

Figure 1. Multiple necrotizing ulcers on the dorsum of the nose

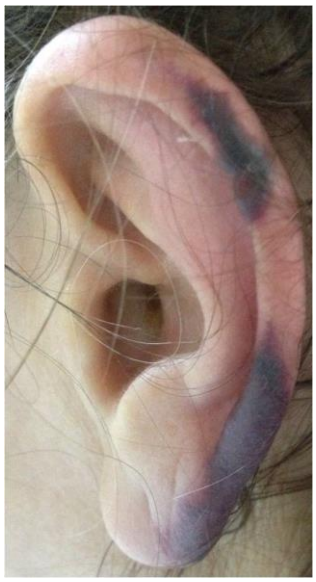

Figure 2. Multiple necrotizing ulcers on the both ear lobes

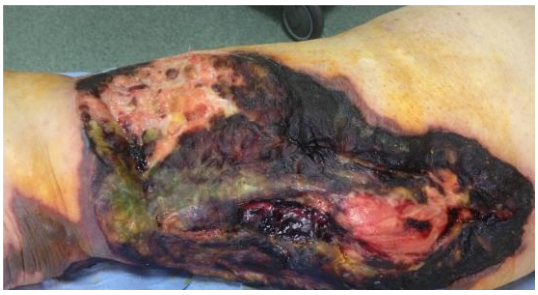

Figure 3

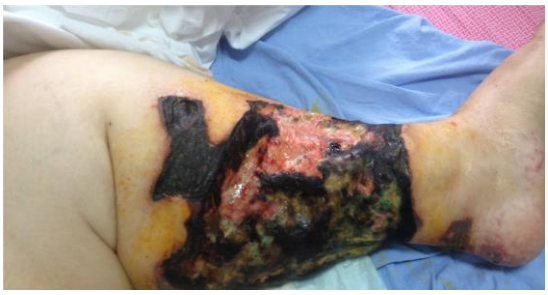

Figure 4

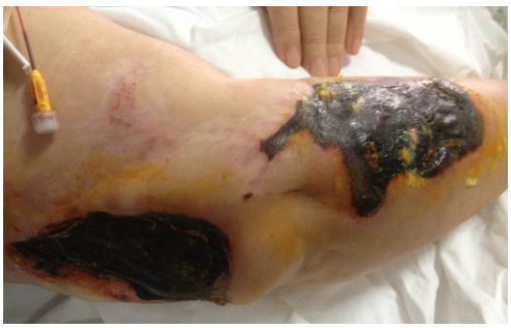

Figure 5

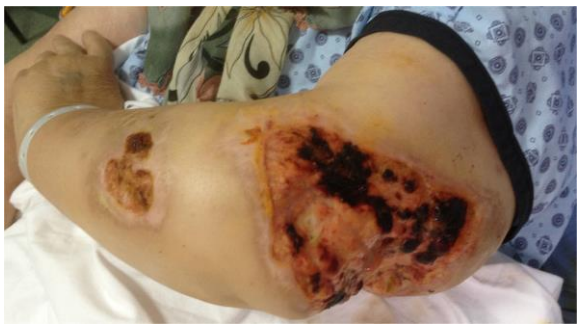

Figure 6

Figures 3-6. Disseminated ulcerations on the skin of limbs bilaterally

Table 1. Laboratory tests of the patient.

Parameters	Level	Reference ranges	Unit
Hemoglobin	9.9	12-16	gr/dl
Hematocryt	29.7	35-45	%
Leukocyte	12900	3500-10500	/mm^3
Neutrophil	9000	1700-7000	/mm^3
Platelet	32000	100-400x10^3	/mm^3
Glucose	94	70-110	mg/dl
Urea	25	10-40	mg/dl
Creatinine	1.0	0.5-1.2	mg/dl
Sodium	136	136-145	mmol/L
Potassium	4.4	3.5-5	mmol/L
Calcium	8.7	8.5-10.5	mg/dl
Phosphate	3.0	2.6-4.5	mg/dl
AST	15	10-40	U/L
ALT	22	7-56	U/L
f T3	4.2	1.7-3.7	pg/ml
f T4	2.6	0.7-1.5	pg/ml
TSH	0.001	0.35-4.9	µIU/ml
Sedimentation	89	<20	mm/h
CRP	67	>3	mg/dl
RF	Negative	-	-
Anti-TPO	<5	0-35	IU/ml
Anti-TG	11.4	0-40	IU/ml
c-ANCA (Pr3 ANCA)	Positive	1000	U/ml
p-ANCA (anti-MPO)	Negative	≤5	U/ml
ANA	Negative	<1	U
ASMA	Negative	<1:40	dilusion
AMA	Negative	<1:40	dilusion
Protein-C	70.1	70-140	%
Protein-S	72.5	50-130	%
HBs Ag	Negative	-	-
Anti HBs	Negative	-	-
Anti HCV	Negative	-	-
Anti HIV	Negative	-	-

Clinical Follow-Up: Pulse methylprednisolone therapy (1000 mg/daily, 4x250 mg in divided doses) was immediately started and dose was reduced by 250 mg after 3 days. After dose reduction, treatment was switched to oral prednisolone and tapered down to 20 mg/daily dose. Because of persistent thyrotoxicity, PTU treatment was switched to methimazole by dose tapering. Upon changes in the prior treatment regimen, skin ulcers improved significantly. Histopathological examination of the skin lesions revealed “chronic inflammatory reaction, compatible with leukocytoclastic vasculitis”. She had been using combined antimicrobial

therapy for polymicrobial infection from skin ulcers, and it was stopped after 7 days of antibiotic therapy. Simultaneously, it was found that cANCA was positive; thus, the diagnosis of necrotizing vasculitis was also confirmed. Pulse cyclophosphamide immunosuppressive therapy was planned but it could not be initiated because she developed thrombocytopenia. Her medical condition was deemed unfit for thyroidectomy and thyroid function tests did not confirm euthyroid status. As a result, total thyroidectomy was not performed and deferred until after resolution of thrombocytopenia. During the follow-up period, a plastic and reconstructive surgery specialist was consulted for the patient and remaining necrotic tissues were debrided again. However, despite all surgical measures, a green-colored suppurative layer developed on the surface of leg ulcers. Then, an infectious diseases specialist was reconsulted and her antibiotic therapy regimen was revised and resumed according to the wound culture antibiograms. During this period, her ulcers appeared again in a disseminated fashion. The patient was discussed at a multidisciplinary meeting which included specialists from Internal Medicine, Rheumatology, General Surgery and Endocrinology Departments and concluded with the decision to prepare the patient for a total thyroidectomy immediately in order to protect her from adverse events of the anti-thyroid drugs as soon as possible. Therapeutic plasmapheresis was not performed due to the lack of required equipment in our hospital. When her medical condition was suitable for having an operation the patient was operated promptly, and methimazole treatment was stopped. Following total thyroidectomy oral levothyroxin replacement therapy was started. In addition to her primary medical intervention, she was given supplemental therapy such as parenteral albumin, erythrocyte transfusion and isotonic fluids, and daily dressing changes. Despite all medical therapeutic interventions, the patient could not be saved and died due to nosocomial pneumonia and septic shock.

Discussion

Drug-induced vasculitis is a known side effect of prolonged treatment with several drugs. It is characterized by inflammation and cellular infiltration of small vessels and presence of ANCA. PTU is a drug most commonly associated with drug-induced vasculitis. Small vessels of the skin are most frequently affected, while affection of the vessels of the kidneys, central nervous system and lungs make the diagnosis life-threatening [8,10]. Duration of PTU therapy is positively correlated with ANCA development. In most cases, the use of PTU for

more than 18 months has been reported to be associated with the development of ANCA [12,15,16]. Some studies have even reported an increase in ANCA positivity with longer duration of PTU use [17]. One series revealed an average PTU treatment duration of 37 months prior to development of clinical symptoms such as vasculitis [15]. However, PTU-related AAV has been reported to occur from a few months to several years of treatment [13-18]. At the time of admission, our patient had a history of PTU use for approximately 36 months.

In the present case, the patient initially had only cutaneous symptoms without lung or kidney involvement which occurred after 3 years of PTU treatment and showed a rapid progression of clinical manifestations resulting in death. In literature, mostly pANCA/anti-MPO positivity is reported in vasculitis cases associated with PTU use and c-ANCA/PR3 positivity is seen to a lesser extent [12-14,19,20]. It is postulated that PTU acts as a hapten to bind MPO and results in ANCA positivity by stimulating neutrophils [19, 21]. ANCA development is thought to induce vasculitis by initiating vascular injury. Moreover, human MPO and TPO enzymes belong to the same genetic family and share similarity in nucleotide and amino acid sequences [22,23]. Thus, pANCA positivity can be expected in PTU-associated AAV seen in patients with Graves' disease. However, AAV induced by PTU use had developed in the setting of toxic nodular goiter without Graves' disease in our patient. Thyroid autoantibodies were checked in order to exclude Graves' disease and found negative and thyroid scintigraphy was consistent with toxic nodules with increased activity. This suggested that some other factors might be involved in the pathogenesis of AAV induced by PTU.

Since methimazole and carbimazole have not been shown to behave as haptens, ANCA-associated vasculitis occurs at a reduced incidence in patients treated with these agents compared to PTU [18,24]. Thus, we immediately switched from PTU to methimazole therapy with the minimum effective dose chosen for the patient. Plasmapheresis was not available in our hospital; so, total thyroidectomy was performed as soon as possible after achieving euthyroid state when general condition of the patient was considered fit for such procedure. With this approach, our aim was to discontinue antithyroid therapy altogether (also methimazole, even if it was relatively harmless) and keep her away from further antigenic stimulation. Despite switching from PTU to methimazole and achieving some clinical response with steroid therapy, the patient was lost. A contributory cause of her death was

Fournier's gangrene which is associated with high mortality per se and this clinical picture worsened the prognosis and adversely affected the clinical course [25]. Her treatment became more challenging due to a number of factors including disseminated, advanced ulcers in the whole body which exposed the patient to additional infections and requirement for debridement and long-term parenteral antibiotic therapy. Additional risks were also present such as susceptibility to potential nosocomial infections associated with long-term hospitalization. Eventually, the patient diagnosed at an advanced stage could not be saved despite all efforts.

Most importantly, cutaneous symptoms of the patient could have been linked with PTU use with appropriate history taking when they first appeared (several months in advance) and PTU treatment could have been withdrawn. Maybe then she could be saved before her clinical manifestations advanced to an irreversible point. Thus, clinicians and particularly dermatologists should be aware of AAV associated with PTU treatment.

Conclusion

While pANCA/MPO positivity is observed in cases of AAV related with PTU use, cANCA positivity may be rarely encountered as in our patient. A distinctive feature of our case was the presence of cutaneous symptoms solely without lung and kidney involvement despite cANCA positivity. During PTU use, physicians should be alert for potential dermal and systemic adverse effects of PTU and PTU treatment must be immediately discontinued at the slightest suspicion.

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