Clinical Case Report

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Possibly propylthiouracil-induced antineutrophilic cytoplasmic antibody-associated vasculitis manifested as blood coagulation disorders

A case report

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Abstract

Background: Propylthiouracil is the most common drug used to treat hyperthyroidism. However, this drug could cause a severe disease, antineutrophilic cytoplasmic antibody-associated vasculitis (AAV), which was usually misdiagnosed.

Methods: We reported a 60-year-old woman of propylthiouracil-induced AAV manifested as blood coagulation disorders. The patient was admitted because of hyperthyroidism and leukopenia. At the time of hospitalization, she suffered from dry cough, erythema and knee joints ache, and gradually became febrile. And then BP decreased and PLT was reduced with coagulation disorders. ANCA: c-ANCA positive (1:100), p-ANCA positive (1:320), MPO-IgG positive, PR3-IgG positive, GBM-IgG negative. Erythrocyte sedimentation rate and C-reactive protein increased markedly. Chest high-resolution computed tomography (HRCT) showed that scattered spots, patch and ground-glass opacity.

Results: Finally, we made a terminal diagnosis of PTU-induced AAV possibly. After drug withdrawal and use of steroid, the patient recovered well and then accepted RAI therapy. As the patient was given imipenem-cilastatin before the reduction of PLT and coagulation disorders, we considered that the hematologic disorders might be caused by antibiotics or a clinical presentation of the vasculitis itself.

Conclusion: Drug-induced vasculitis is relatively good prognosis, but early diagnosis and timely withdrawal of associated drugs are the key to the treatment.

Abbreviations: AAV = ANCA-associated vasculitis, ANCA = antineutrophilic cytoplasmic antibody, APTT = activated partial thromboplastin time, c-ANCA = cytoplasmic antineutrophilic cytoplasmic antibody, CRP = C-reactive protein, D-D = D-dimer, DIC = disseminated intravascular coagulation, ELISA = enzyme-linked immunosorbent assay, ESR = erythrocyte sedimentation rate, FDPs = fibrin(ogen) degradation products, Fg = fibrinogen, FT3 = free triiodothyronine, FT4 = free thyroxine, Hb = hemoglobin, HRCT = high-resolution computed tomography, IIF = indirect immunofluorescence, MPO = myeloperoxidase, N = neutrophil granulocyte percent, NEUT = absolute neutrophil count, p-ANCA = perinuclear ANCA, PCT = procalcitonin, PLT = platelet, PR3 = proteinase 3, PT = prothrombin time, PTU = propylthiouracil, RAI = radioactive iodine, TGAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody, TRAb = TSH receptor antibody, TSH = thyroid stimulating hormone, WBC = white blood cell.

Keywords: antineutrophilic cytoplasmic antibody, case report, coagulation disorders, propylthiouracil, vasculitis

1. Introduction

Antineutrophilic cytoplasmic antibodies (ANCA), first reported by Davies et al[1] in 1982, are a group of autoantibodies against antigens in the cytoplasm of neutrophil granulocytes and monocytes. Currently, there are 2 methods to detect ANCA. One is indirect immunofluorescence (IIF), and the other is enzyme-linked immunosorbent assay (ELISA). Based on IIF, ANCA are mainly divided into 2 patterns, respectively, cytoplasmic ANCA (c-ANCA) which is specific for proteinase 3 (PR3) and perinuclear ANCA (p-ANCA) which is specific for myeloperoxidase (MPO).

Systemic small vessel vasculitis refers to a set of diseases characterized by the inflammation and fibrinoid necrosis of the small vessel walls, which can affect most organs and systems of the body. ANCA are found positive in some of the systemic small vessel vasculitis, so these vasculitis are also called ANCA-associated vasculitis (AAV). AAV can be classified into 2 groups[2]: primary small vessel vasculitis (including microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome) and secondary small vessel vasculitis (including drug-induced vasculitis).

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Hyperthyroidism is a condition caused by excessive production of thyroid hormone by the thyroid gland itself. Diffuse toxic goiter (Graves disease) contributed to ~80% of hyperthyroidism. Medical treatments for Graves' disease are primarily propylthiouracil (PTU) and methimazole. Both PTU and methimazole could induce a rare adverse drug reaction that is AAV. AAV has a variety of clinical manifestations including fever, weakness, skin rash, musculoskeletal pain, muscle and joints pain, cough and expectoration, and hematuria, which are always nonspecific, making it difficult in diagnosis and easy to be misdiagnosed. Here we presented a case of PTU-induced AAV manifested as blood coagulation disorder and a review of literature.

2. Case report

A 62-year-old woman was admitted to our hospital for leukopenia in June 2015. She lost appetite and felt weak for several months, and then she came to Endocrinology clinic for further treatment. She had been diagnosed of Graves disease in other clinics 1 year before and took PTU since then. Now her medications were PTU 50 mg 3 times daily. The patient had no any disease history or family history associated with autoimmune diseases. Physical examination: diffuse goiter II-III° with vascular murmur. Paroxysmal atrial fibrillation rhythm was heard in the cardiac auscultation areas. Both lower extremities showed mild pitting edema with sporadic erythema, ~2 mm in diameter. But the erythema disappeared on the second day from admission spontaneously. Thyroid function tests were as follows: free triiodothyronine (FT3) 11.39 pg/mL (2.19–3.9), free thyroxine (FT4) 1.01 ng/dL (0.61–1.12), thyroid stimulating hormone (TSH) 0.01 uIU/mL (0.35–3.5). TSH receptor antibody (TRAb) 35.2 IU/L (0.3–1.8), thyroglobulin antibody (TGAb) > 2261 Iu/mL (0.00–4.00), thyroid peroxidase antibody (TPOAb) 458.1 Iu/mL (0.00–9.00). Blood routine: white blood cell (WBC) 2.76×10^9/L (3.50–9.50), hemoglobin (Hb) 72.0 g/L (115.0–150.0), platelet (PLT) 142×10^9/L (101–320), absolute neutrophil count (NEUT) 1.72×10^9/L (1.80–6.30).

Based on her past history, physical examination and the laboratory findings, we made a presumptive diagnosis of hyperthyroidism with hyperthyroid heart disease and leukopenia. Considering that the most likely cause of leukopenia was PTU, we discontinued it immediately and gave diuretics and β-blocker. We had intended to complete the test of thyroidal radioiodine uptake rate 2 weeks after withdrawal of PTU to see if radioactive iodine (RAI) therapy was feasible. In addition, the patient was present with unexplained erythema and moderate anemia revealed by blood routine, coagulation studies and bone marrow aspiration were taken.

From the third day on, the patient had a dry cough, erythema and knee joints ache, and gradually became febrile. A few moist rales were audible over both lung bases. Paroxysmal atrial fibrillation rhythm was heard in the cardiac auscultation areas. Blood routine: WBC 2.04–3.13 $\times 10^9$/L, Hb 67–81 g/L, PLT 109–144 $\times 10^9$/L, neutrophil granulocyte percent (N) 53.3–86.3%. Procalcitonin (PCT): 0.08–0.4 ng/mL (0.00–0.05). Chest radiograph indicated inflammation in lower lobe of both lungs. Electrocardiogram showed sinus tachycardia. Other laboratory work-ups: urine blood (3+), urine protein (±), fecal occult blood (+). Baseline biochemistry tests, coagulation studies, and tumor markers were normal. Based on the above, we made a diagnosis of pulmonary infection. Since the patient was concomitant with leukopenia, pulmonary infection was hard to control. Therefore, the antibiotics was escalated into moxifloxacin. Meanwhile, we conducted a systematic review of the patients' symptoms. The patient had repeated ache of knee joints and calf muscles several months ago, with gradually worsened appetite and weakness, sometimes with abdominal pain. Autoimmune diseases were also taken into consideration. On the eighth day, the patient got the highest fever of 40.6 °C with shortness of breath obviously. Physical examination: P 110 bpm, BP 90/50 mm Hg (lowest 70/39 mm Hg). But there were no signs of shock. Pro-B-type natriuretic peptide was 8634 ng/L (0–198). Pulmonary infection was thought to be further exacerbated and induced heart failure. Then, we changed the antibiotics again to imipenem-cilastatin. On the ninth day, the patient suffered a sudden drop of PLT and coagulation disorders with erythema. Blood routine: WBC 4.30×10^9/L, Hb 70.0 g/L, PLT 50×10^9/L, N 81.7%. Coagulation studies: prothrombin time (PT) 15.1 s (10.5–13.7), activated partial thromboplastin time (APTT) 50.9 s (15.0–34.0), fibrinogen (Fg) 1.47 g/L (1.50–3.50), d-dimer (D-D) 9.16 mg/L (0.00–0.55), fibrin(ogen) degradation products (FDPs) 40.6 μg/mL (0.0–5.0). All of the above alert us to disseminated intravascular coagulation (DIC), and then we started treatment with hemostasis, anticoagulation, and supplying coagulation factors immediately. Coagulation function improved 2 day later except APTT, whereas Hb and PLT continued to decrease (Table 1). Repeated analyses of urine blood and fecal occult blood were positive. PCT and C-reactive protein (CRP) increased markedly. Blood gas analysis indicated type 1 respiratory failure. Blood and sputum cultures were sterile. ANCA: c-ANCA positive (1:100), p-ANCA positive (1:320), MPO-IgG positive, PR3-IgG positive, GBM-IgG negative. Erythrocyte sedimentation rate (ESR) 120 mm/h. Antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-streptolysin O test, and anticardiolipin antibody were all negative. Bone marrow aspiration was normal. Chest high-resolution computed tomography (HRCT) showed that scattered spots, patch and ground-glass opacity, and indicated possible lung involvement of AAV.

Combined with the patient's medical history, clinical symptoms, such as fever, weakness, loss of appetite, skin rash, joints and muscle ache, and laboratory work-ups, such as positive ANCA, markedly increased ESR and CRP, we made a terminal diagnosis of PTU-induced AAV possibly. As for the treatment of PTU-induced AAV, we continued the drug withdrawal. Prednisone 35 mg daily and cyclophosphamide 20 mg bid was commenced. For PCT level was still high, we could not totally rule out the existence of inflammation. Thus, we continued antibiotics, but changed to piperacillin-tazobactam. One week later, her appetite and symptoms, such as cough and shortness of breath, were better. Body temperature was normal. BP was fluctuated at about 100/60 mm Hg. Blood routine and coagulation studies were improved (Table 1). However, paroxysmal atrial fibrillation still existed. Then, we added lithium carbonate 250 mg 3 times a day to control hyperthyroidism. Steroid and cyclophosphamide tapered with improving of the patient's symptoms, laboratory work-ups, and imaging examination. On the fifth week of steroid therapy, the patient finished the test of thyroidal RAI uptake rate. The rate for 6 hours was 96%, and for 24 hours was 78.8%. Then, she was transferred to nuclear medicine department and had RAI therapy. The patients were followed-up regularly after discharge (Tables 1 and 2, Fig. 1). An informed consent was given by the patient. Because this article does not involve any human or animal trials, there is no need to conduct special ethic review and the ethical approval is not necessary.

Table 1

Changes in laboratory data before and after steroid therapy.

(1) Changes in ANCA before and after steroid therapy

	c-ANCA	p-ANCA	MPO-IgG	PR3-IgG	GBM-IgG
Before steroid	+	+	+	+	−
3 weeks after steroid	−	+	+	+	−
2 months after steroid	−	+	+	+	−
3 months after steroid	−	+	+	+	−
4 months after steroid	−	+	+	+	−

(2) Changes in blood routine before and after steroid therapy

	WBC ($\times 10^9$/L)	Hb (g/L)	PLT ($\times 10^9$/L)	NEUT ($\times 10^9$/L)
Before steroid	19.58*	63	32	17.92
1 weeks after steroid	11.13	94	47	10.04
2 weeks after steroid	6.76	105	70	5.78
3 weeks after steroid	4.87	79	65	4.14
2 months after steroid	5.11	112	132	4.04
3 months after steroid	5.49	125	108	4.22
4 months after steroid	3.85	123	75	2.83
10 months after steroid	5.32	119	99	3.71
12 months after steroid	6.73	125	75	5.53

(3) Changes in coagulation studies before and after steroid therapy

	PT (s)	APTT (s)	Fg (g/L)	D-D (mg/L)	FDPs (μg/mL)
Before "DIC" treatment	15.1	50.9	1.47	9.16	40.6
2 days after "DIC" treatment	12.8	50.7	1.72	1.64	5.4
1 weeks after steroid	13.1	28.3	1.72	0.79	2.7
2 weeks after steroid	12.6	27.1	1.7	0.82	2.6
3 weeks after steroid	12.5	29.6	2.65	0.21	0.9

(4) Changes in urinalysis and stool test before and after steroid therapy

	Urine blood	Urine RBC (/μL)	Fecal occult blood	ESR (mm/h)	CRP (mg/L)
Before steroid	3+	286	+	120	19.6
2 weeks after steroid	3+	19	−	/	5.72
2 months after steroid	2+	40	−	94	/
3 months after steroid	+	35	/	68	/
4 months after steroid	+	42	/	81	6.11
10 months after steroid	/	/	/	50	11.5
12 months after steroid	−	13	/	62	5.06

ANCA = antineutrophilic cytoplasmic antibody, APTT = activated partial thromboplastin time, CRP = C-reactive protein, D-D = D-dimer, ESR = erythrocyte sedimentation rate, FDPs = fibrin(ogen) degradation products, Fg = fibrinogen, Hb = hemoglobin, MPO = myeloperoxidase, NEUT = absolute neutrophil count, PLT = platelet, PT = prothrombin time, PR3 = proteinase 3, WBC = white blood cell.

* After subcutaneous injection of recombinant human granulocyte colony-stimulating factor.

Normal values: WBC 3.50–9.50, Hb 115.0–150.0, PLT 101–320, NEUT 1.80–6.30.

Normal values: PT 10.5–13.7, APTT 15.0–34.0, Fg 1.50–3.50, D-D 0.00–0.55, FDPs 0.0–5.0.

Normal values: ESR 2–38, CRP 0.00–8.00.

3. Discussion

Generally, PTU-induced AAV has the following characteristics:[3] (1) symptoms and signs occur after taking PTU and are alleviated after withdrawing PTU. But there has been no evidence that the onset of AAV was associated with dose or PTU-taken time.[4] (2) Serum ANCA, especially those can identify various target antigens, are positive. And antibody titers can decrease after PTU discontinues. (3) There may be systemic symptoms like

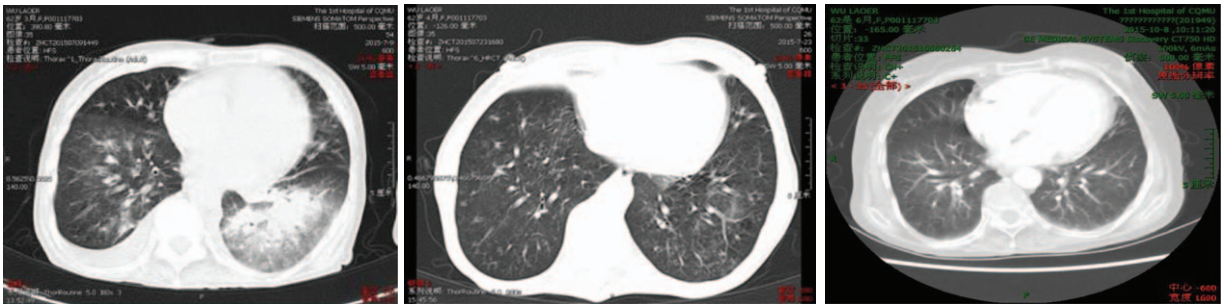
Table 2

Changes in thyroid function and related antibodies before and after lithium/RAI therapy.

	FT3 (pg/mL)	FT4 (ng/dL)	TSH (uIU/mL)	TRAb (IU/L)	TGAb (Iu/mL)	TPOAb (Iu/mL)
On admission	11.39	1.01	0.01	35.2	>2261	458.1
Before lithium	19.33	5.07	0.03	/	/	/
Before RAI	2.9	0.93	0.02	/	/	/
1 months after RAI	3.42	1.13	0.06	3.2	270.3	42.8
2 months after RAI	3.87	1.02	0.06	3.2	294.0	41.9
3 months after RAI	3.88	1.05	0.03	2.9	288.5	45.9
11 months after RAI	3.9	0.59	0.77	/	/	/

Normal values: FT3 2.19–3.9, FT4 0.61–1.12, TSH 0.35–3.5, TRAb 0.3–1.8, TGAb 0.00–4.00, TPOAb 0.00–9.00.

FT3 = free triiodothyronine, FT4 = free thyroxine, RAI = radioactive iodine, TGAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody, TRAb = TSH receptor antibody, TSH = thyroid stimulating hormone.



(1) before steroid (2) Two weeks after steroid (3) Three months after steroid

Figure 1. Change in HRCT before and after steroid therapy. HRCT = high-resolution computed tomography.

fever, fatigue, and weight loss. (4) There may be multiple organs injured such as kidney, lung, joints, skin, blood, brain, nerves,[5] and so on. (5) Biopsy indicates vasculitis. (6) Tumor, infection, and other types of vasculitis should be excluded.

Based on the features above, PTU-induced AAV was diagnosed. P-ANCA positivity is more common in secondary vasculitis; sometimes c-ANCA increases slightly.[6] In our case, both p-ANCA and c-ANCA were positive, but the concentration of p-ANCA (titre: 1:320) was significantly higher than that of c-ANCA (titre: 1:100). Generally, we thought platelet was always increased in inflammation and blood was in a hypercoagulable state. In this case, we supposed that 2 causes might account for this results. One was the vasculitis itself, which caused endothelial injury, leading to a process of DIC. The other was the drug, imipenem-cilastatin. We noted that both drop of platelet and coagulation disorders occurred after the use of imipenem-cilastatin. However, no association between imipenem and DIC are reported in the literature so far. Now, whether its clinical manifestations were associated with DIC or not could not be determined, because use of steroid and withdrawal of imipenem-cilastatin were carried out at the same time.

In addition, another special point in our patient was the treatment of hyperthyroidism. Vasculitis improved after discontinuing PTU and giving steroid, but atrial fibrillation still troubled our patient. Therefore, we gave her lithium carbonate to control hyperthyroidism, and finally successfully completed RAI therapy. Lithium carbonate is a kind of drugs for the treatment of mania. Because lithium ions can inhibit the hydrolysis of thyroglobulin and release of thyroid hormones, it can effectively control the clinical symptoms of patients with hyperthyroidism. Meanwhile, lithium ions can also retain RAI in thyroid, raise RAI uptake rate, and then enhance the therapeutic effect of RAI therapy. It can also eased symptoms of thyrotoxicosis caused by destruction of thyroidal cells in the early stage of RAI therapy. Study by Bogazzi et al[7] showed that RAI therapy combined with lithium carbonate was more effective for hyperthyroidism than RAI therapy alone. Some other researchers suggested that lithium ion could stimulate bone marrow to generate white blood cells, so it was also quite suitable in hyperthyroidism combined with leukopenia.

The mechanisms of PTU-induced AAV mechanism are still not clear. The following factors were thought to be related:[8–10] (1) Some PTU metabolites could sensitize T-cells, and then activate B-cells which could produce autoantibodies. At the same time, PTU metabolites could inhibit the DNA synthesis of peripheral lymphocytes, resulting in abnormal immunoregulation. (2) PTU could bind with MPO, changing the structure of heme in enzymes. The changed enzymes became hapten, mediating vascular injuries. (3) In an inflammatory status, ANCA could directly activate neutrophils, making these neutrophils degranulation and releasing a large amount of MPO, reactive oxide species, B factor, and C3. These substances could damage blood vessels through activating pathways of complements. What's more, PTU-induced AAV might be genetically predisposed. HLA - DR3 was thought to be closely related.[11]

In general, PTU-induced AAV is mild compared with primary small vasculitis. Most patients can recover after stop using PTU. But for those with vital organs involvement, steroid, and (or) immunosuppressant drugs can be added. For those with severe kidney damage, they even need plasma exchange and hemodialysis. Anyhow, drug-induced vasculitis is relatively good prognosis. To strengthen the understanding of this, rare adverse drug reactions, early diagnosis, and timely withdrawal of associated drugs are the key to the treatment.

References

[1] Davies DJ, Moran JE, Niall JF, et al. Segmental necrotizing glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? BMJ 1982;285:606.

[2] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1–1.

[3] Gao Y, Zhao MH. Review article: drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrology 2009;14:33–41.

[4] Noh JY, Yasuda S, Sato S. Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. J Clin Endocrinol Metab 2009;94:2008–700.

[5] Li X, Zhao J, Wang Q, et al. ANCA-associated systemic vasculitis presenting with hypertrophic spinal pachymeningitis: a report of 2 cases and review of literature. Medicine 2015;94:e2053.

[6] Hagen EC, Daha MR, Hermans J, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int 1998;53:743–53.

[7] Bogazzi F, Giovannetti C, Fessehatsion R, et al. Impact of lithium on efficacy of radioactive iodine therapy for graves' disease: A cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal. J Clin Endocrinol Metab 2010; 95:0000–0000.

[8] Waldhauser L, Uetrecht J. Antibodies to myeloperoxidase in propylthiouracil-induced autoimmune disease in the cat. Toxicology 1996;114: 155–62.

[9] Aloush V, Litinsky I, Caspi D, et al. Propylthiouracil-induced autoimmune syndromes: two distinct clinical presentations with different course and management. Semin Arthritis Rheum 2006;36:4–9.

[10] Jiang XX, Khursigara G, Rubin RL. Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1994;266: 810–3.

[11] Griffith ME, Pusey CD. HLA genses in ANCA-associated vasculitides. Exp Clin Immunogenet 1997;14:196–205.