CASE REPORT

UDC: 616.441-008.61-085-06
DOI: https://doi.org/10.2298/VSP210429067B

Can propylthiouracil induce autoimmune-related immunotoxicity?

Može li propiltiouracil izazvati autoimunski posredovanu imunotoksičnost?

Ivana Bajkin*†, Sonja Golubović*‡, Tijana Ičin*†, Kristina Stepanović*†, Tatjana Ilić*‡

***University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; University Clinical Center of Vojvodina, †Clinic for Endocrinology, Diabetes and Metabolic Diseases, ‡Clinic for Nephrology and Clinical Immunology, Novi Sad, Serbia**

Abstract

Introduction. The use of propylthiouracil can be associated with mild adverse reactions, but severe complications such as agranulocytosis and vasculitis can also be seen. Direct toxicity and immune-mediated induction of anti-neutrophile cytoplasmic antibodies have been described as possible mechanisms responsible for agranulocytosis. The majority of vasculitis is antimyeloperoxidase antibodies associated, but the exact mechanism for anti-neutrophile cytoplasmic antibodies-associated vasculitis as an adverse effect of propylthiouracil treatment is still unclear. **Case report.** We presented a 61-year-old female patient with Graves' disease who experienced a fever and throat pain two weeks after propylthiouracil therapy was initiated. Agranulocytosis alongside basal left-sided pneumonia was noted. Propylthiouracil was discontinued, and the treatment with broad-spectrum antibiotics was started, as well as Lugol's solution, methylprednisolone, and granulocyte-colony stimulating factor. Further course of treatment was complicated by the occurrence of a generalized erythematous-papillomatous rash. The patient was diagnosed with agranulocytosis and antimyeloperoxidase, anti-neutrophile cytoplasmic antibodies positive vasculitis as an adverse effect of propylthiouracil. **Conclusion.** Patients presenting with concomitant agranulocytosis and anti-neutrophile cytoplasmic antibodies-associated vasculitis as a complication of propylthiouracil therapy for Graves' disease are rare in clinical practice. Prompt discontinuation of the antithyroid drug is of great importance to reduce damage to target organs. Similarities in the pathogenesis of both conditions could be the potential explanation for these two adverse events occurring at the same time, which points out the need for a deeper understanding of this topic.

Key words:
agranulocytosis; anti-neutrophil cytoplasmic antibody-associated vasculitis; drug-related side effects and adverse reactions; graves disease; propylthiouracil.

Apstrakt

Uvod. Propiltiouracil može biti povezan sa blagim neželjenim efektima, ali se u praksi mogu videti i ozbiljne komplikacije, poput agranulocitoze i vaskulitisa. U literaturi je kao mogući mehanizam nastanka agranulocitoze opisana direktna toksičnost i imunski posredovana aktivacija antineutrofilnih i anticitoplazmatskih antitela. Većina vaskulitisa je udružena sa antitelima na mijeloperoksidazu, ali nije poznat tačan mehanizam nastanka vaskulitisa udruženih sa antineutrofilnim citoplazmatskim antitelima kao neželjenim dejstvom terapije propiltiouracilom. **Prikaz bolesnika.** Prikazana je bolesnica sa Bazedovljevom (Grejsovom) bolesti, stara 61 godinu, koja se javila lekaru zbog povišene telesne temperature i bolova u grlu, dve nedelje nakon započinjanja terapije propiltiouracilom. Verifikovana je agranulocitoza kao i levostrana bazalna pneumonija. Obustavljena je primena propiltiouracila, a započeta terapija antibioticima širokog spectra, uz Lugolov rastvor, metilprednizolon i faktor stimulacije kolonije granulocta. Dalji tok se komplikovao pojavom generalizovane, eritematozno-papulomatozne ospe. Kod bolesnice je postavljena dijagnoza agranulocitoze i vaskulitisa udruženog sa antitelima na mijeloperoksidazu i antineutrofilnim citoplazmatskim antitelima, kao neželjenim dejstvima propiltiouracila. **Zaključak.** Bolesnici koji imaju Grejvsovu bolest, sa istovremenom agranulocitozom i vaskulitisom udruženim sa antineutrofilnim citoplazmatskim antitelima kao komplikacijom terapije propiltiouracilom, su retki u kliničkoj praksi. Hitan prekid terapije antitiroidnim lekom je od velikog značaja za smanjenje oštećenja ciljnih organa. Sličnost u patogenezi oba stanja mogla bi objasniti istovremenu pojavu ta dva neželjena dejstva, što zahteva dalja istraživanja.

Ključne reči:
agranulocitoza; vaskulitis, povezan sa antineutrofilnim antiplazmatskim antitelima; lekovi, neželjeni efekti i neželjene reakcije; gušavost, egzoftalmička; propiltiouracil.

Correspondence to: Ivana Bajkin, University of Novi Sad, Faculty of Medicine, University Clinical Center of Vojvodina, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Hajduk Veljkova 1-9, 21 000 Novi Sad, Serbia. E-mail: ivana.bajkin@mf.uns.ac.rs

Introduction

Propylthiouracil (PTU) is a thiourea antithyroid drug (ATD) used in the treatment of hyperthyroidism. It acts as an inhibitor of thyroid hormone synthesis by competitive inhibition of the enzyme peroxidase and conversion of thyroxine (T4) to triiodothyronine (T3) [1–3]. Even though systemic complications like gastric intolerance, pruritus, and arthralgia can be found in only about 1% to 5% of patients, severe complications like agranulocytosis and vasculitis have also been identified [1–4]. Patients with autoimmune thyroid diseases may have other autoimmune conditions and are more prone to the development of drug-induced autoimmune diseases [5, 6]. Direct toxicity and immune-mediated induction of anti-neutrophile cytoplasmic antibodies (ANCA) have been described as possible mechanisms responsible for agranulocytosis. It mostly occurs within the first 3 months of the ATD treatment in 0.2–0.5% of patients with Graves' disease and is potentially life-threatening due to an increased susceptibility to infection [7]. The exact pathogenesis of ANCA-associated vasculitis as an adverse effect of PTU treatment remains a matter of debate, even though it is widely known that the majority of these vasculitides are anti-myeloperoxidase (MPO) antibodies associated [8]. The prevalence of ANCA positivity in patients treated with PTU varies across literature between 4% and 64%, with a median prevalence of 30% [9–13]. It is hypothesized that these antibodies are induced by frequent and prolonged PTU therapy and occur more frequently in women, probably due to a higher prevalence of thyroid dysfunction in women [9, 14–16]. It should be emphasized that some patients have ANCA positivity even prior to PTU therapy [5].

This case report describes a patient who experienced two adverse events secondary to PTU treatment: agranulocytosis and ANCA-associated vasculitis. Similarities in the pathogenesis of both conditions could be the potential explanation for these two adverse events occurring at the same time, which points out the need for a deeper understanding of this topic.

Case report

A 61-year-old female with Graves' disease was admitted to the Department of Endocrinology with a 3-day history of fevers, throat soreness, arthralgia, myalgia, and fatigue.

Table 1

Biochemical analyses of the presented patient with Graves' disease

Parameter	Normal range	On admission	After therapy
Leukocytes, $\times 10^9$/L	4.0–10.0	0.51	10.43
Erythrocytes, $\times 10^{12}$/L	3.9–5.4	4.0	3.83
Hemoglobin, g/L	120–160	117	118
Hematocrit, L/L	0.370–0.470	0.346	0.369
Thrombocytes, $\times 10^9$/L	140–400	126	184
Neutrophils, $\times 10^9$/L	2.0–7.0	0.04	5.88
Urea, mmol/L	2.2–7.1	11.1	4.2
Creatinine, µmol/L	49–97	85	63
Uric acid, µmol/L	154–357	291	244
Total protein, g/L	60–83	51	68
Albumin, g/L	35–55	26	41
Total bilirubin, µmol/L	3.0–21.0	25.8	6
Direct bilirubin, µmol/L	0.1–4.2	12.3	3.4
AST, U/L	1–31	8	16
ALT, U/L	5–50	17	19
GGT, U/L	3–38	18	23
K, mmol/L	3.5–5.1	3.7	3.5
Na, mmol/L	135–150	134	139
Cl, mmol/L	96–112	101	109
CRP, mg/L	< 5.0	325.6	9.4
Fibrinogen, g/L	2.20–4.96	6.0	2.98
PCT, ng/mL	< 0.05	41.33	0.06
APTT, R	0.83–1.30	1.28	0.91
PT, R	0.83–1.30	2.03	1.16
FT3, pmol/L	2.6–5.7	4.4	14.9
FT4, pmol/L	9.0–19.0	25.7	31.9
TSH, mIU/L	0.35–4.94	< 0.01	< 0.01
ESR, mm/h	< 37	39	15
C3, g/L	0.75-1.75	0.87	-
C4, g/L	0.15-0.45	0.18	-
Anticardiolipin IgG, GPLU/mL	< 12	8.7	-
Anticardiolipin IgM, MPLU/mL	< 12	6.4	-
Anti β2 glycoprotein IgG, AU/mL	< 12	4.5	-
Anti β2 glycoprotein IgM, AU/mL	< 12	< 3	-
Anti dsDNA IgG, IU/mL	< 20	12.6	-
Anti PR3, AU/mL	< 12	7.5	2.3
Anti MPO, AU/mL	< 12	30.2	78.6
ANA	negative	Positive, homogenous, mild intensity	negative

AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; CRP-C – reactive protein; PCT – procalcitonin; APTT – activated partial thromboplastin time; PT – prothrombin time; FT3 – free triiodothyronine; FT4 – free thyroxine; TSH – thyroid stimulating hormone; ESR – erythrocyte sedimentation rate; Anti dsDNA IgG – anti-double stranded DNA IgG antibodies; Anti PR3 – anti-proteinase-3 antibodies; Anti MPO – anti-myeloperoxidase antibodies; ANA – antinuclear antibody.

She was diagnosed with Graves' disease 13 years prior to this admission and was initially treated with thiamazole followed by two doses of radioactive iodine, after which her symptoms resolved, and she had not used any ATD since. Thirteen years later, during a regular visit, the patient presented with palpitations, excessive sweating, and mild hand thrill. Her eye finding was unremarkable. She had been diagnosed with recurring hyperthyroidism, and PTU treatment was started. On a regular check-up after two weeks, the patient complained of fever and throat pain. Laboratory tests showed agranulocytosis. The patient was admitted to the hospital. On initial examination, the patient presented with tachycardia, normal breathing rate, and normal body temperature. The mucosa of the soft palate was edematous and hyperemic, and the tonsils were swollen and covered with a white coating. Lung crackles were present in the lower right lobe. There was no evidence of thyroid enlargement, vasculitis, or any other skin and joint lesions. Her family history revealed one of her sisters had primary hypothyroidism. Previous medical history and lifestyle habits were unremarkable, and the patient reported no allergies.

PTU was stopped immediately, and the patient was put on empirical antibiotic therapy.

Additional biochemical analyses were done, and they are presented in Table 1. A basal right-sided pneumonia with a small pleural effusion was described on the chest radiograph (Figure 1). Treatment included broad-spectrum antibiotics for community-acquired pneumonia (ampicillin-sulbactam, 1.5 g *iv* every 8 hrs, q8hr), Lugol's solution (15 drops, q8hr), and methylprednisolone (1 mg/kg). Exogenous granulocyte-colony stimulating factor (G-CSF) (Zarzio®, 30 MU/0.5 mL) was administered on the fifth day. The response was satisfactory, which was confirmed by the normalization of white blood cell count, proinflammatory markers, and thyroid function tests (Table 1). However, the following course of treatment was complicated by the occurrence of a generalized erythematous-papillomatous rash with areas of urticaria (Figure 2), which was

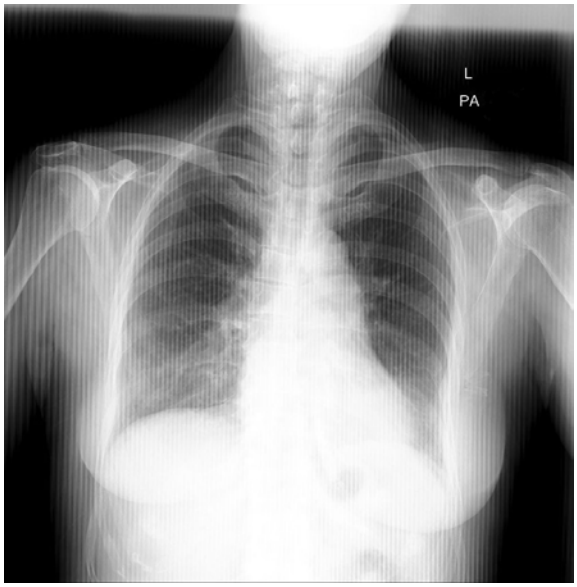

Fig. 1 – Chest X-ray of the presented patient reveals basal right-sided pneumonia with a small pleural effusion. PA – posterior-anterior projection.

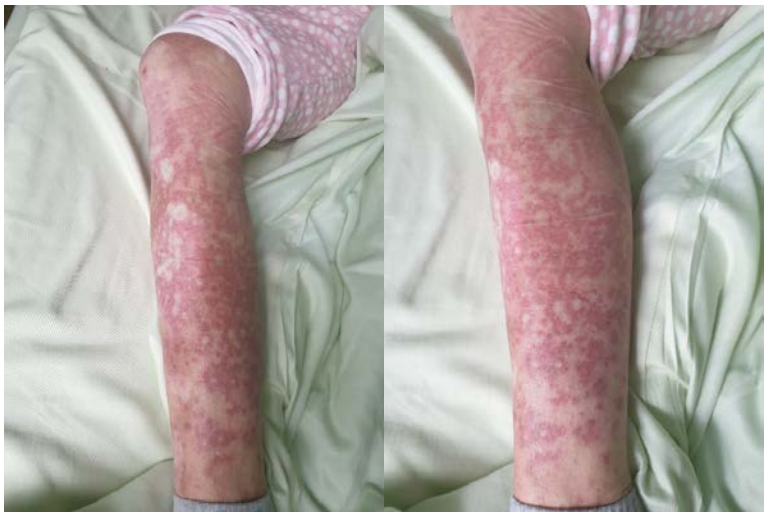

Fig. 2 – Generalized erythematous-papillomatous rash with areas of urticaria.

initially resolved by an escalation of methylprednisolone dosage together with antihistaminic treatment. As soon as the methylprednisolone dose was reduced, the generalized annular exanthematous rash and fever worsened again. Elevation of serum level of inflammatory markers was not seen. Microbiological testing, including blood, urine, and nasopharyngeal swab cultures, was performed again and came back negative; nevertheless, immunological testing revealed positive ANCAs with positivity for MPO. Antinuclear antibodies were identified as positive, homogenous, and of mild intensity. All other immunological testing was negative. Diagnosis of ANCA-positive vasculitis with a preserved kidney function was proposed probably as a side-effect of PTU treatment. Methylprednisolone and local treatment of skin lesions resulted in a resolution of skin changes and an overall improvement of the patient status. Primary hyperthyroidism was eventually treated surgically. The patient was discharged from the hospital and continued with ambulatory check-ups.

Biopsy of skin lesions was done too late, i.e., after the vasculitis-like lesion resolved and turned into simple hyperpigmentation. The reason for the late biopsy lies in prolonged prothrombin time at the time of florid skin lesions.

At follow-up visits, the patient was stable, with no recurrence of the skin rash. Substitute levothyroxine therapy was continued with a gradual reduction of corticosteroid therapy.

Discussion

This case report describes a patient who experienced concomitant agranulocytosis and ANCA-associated vasculitis as an adverse effect of PTU treatment for Graves' disease. Only 0.1–1.75% of patients with Graves' disease receiving ATDs are estimated to develop agranulocytosis, mostly within the first 12 weeks of the start of treatment, as was the case with our patient [17–20]. However, according to some reports, it can also occur up to eight courses of treatment later (with either the same or a different ATD) [20, 21]. Even though it is defined as an absolute neutrophil count less than 500/μL, most patients present with a count < 100/μL [22]. PTU-induced activation of circulating antibodies against differentiated granulocytes might be held accountable for the development of agranulocytosis, which is a possible explanation of an underlying immune-mediated mechanism [23]. ANCAs are the most commonly found antibodies. ANCAs react against neutrophil granules, induce complement-mediated opsonization and cytotoxicity, reduce neutropoiesis, and induce apoptosis [7, 24], but neither has been clearly proven. Various cytokines, sometimes facilitated by an underlying bacterial infection, may lead to an increase in ANCA expression and translocation of these antibodies from the intracellular region to the plasmatic membrane of neutrophils [25, 26]. It should be noted that vasculitis could be associated with acute infection, but the underlying mechanism is not fully understood [27].

The most frequent symptoms are fever, which is present in almost 80% of cases, and sore throat, reported in 72.8% of cases, followed by a lower incidence of skin and gastrointestinal infections [28]. Immediate discontinuation of the drug is imperative in order to prevent further damage, followed by *iv* administration of broad-spectrum antibiotics. In some cases, hematopoietic growth factors such as G-CSF might be used. Yet, the reports on the benefit of this treatment vary [29]. A recent study by Yang et al. [27] showed that recovery time in the G-CSF-treated group did not differ from that in the group not treated with G-CSF. However, in our patient, a complete recovery was identified after the administration of the drug. Surgery or radioactive iodine are effective options for further treatment of primary hyperthyroidism [18, 30]. Due to having already received radioactive iodine, our patient successfully underwent a total thyroidectomy.

It is now also widely known that certain drugs are responsible for the development of ANCA-associated vasculitis, with PTU, hydralazine, sulfasalazine minocycline, penicillamine, and interferon being the most common [31, 32]. However, it should be mentioned that 2.9% of patients have ANCA positivity prior to PTU therapy, whereas 22% on PTU are ANCA positive [5]. PTU-induced ANCA vasculitis is characterized by the recognition of multiple target antigens, including MPO, proteinase 3, cathepsin G, lactoferrin, neutrophil elastase, and azurocidin [33, 34]. The exact mechanism of MPO-ANCA-associated vasculitis is still unclear. Possible mechanisms for this phenomenon include degranulation and apoptosis of neutrophils caused by PTU or its metabolites, which, in return, produce oxygen radicals and interact with MPO enzyme activity [14]. Production of p-ANCA is thought to occur through a direct effect of PTU itself or its metabolites [15, 16]. PTU might also serve as an MPO substrate, which may result in an autoimmune response of activated lymphocytes toward self-material [35]. According to Harper et al. [13], PTU-induced ANCA vasculitis might also be a result of polyclonal B cell activation. Some studies have shown that patients with PTU-induced ANCA vasculitis had significantly higher titers and avidity of MPO-ANCA antibodies than those patients without clinical vasculitis. These antibodies are less pathogenic, which might partly explain why the severity of PTU-induced vasculitis is usually milder than in primary vasculitis [36].

Upon initiating PTU treatment, vasculitis usually develops several months after the treatment. Nonetheless, a great variety has been reported ranging from a single week up to 13 years [3, 14]. Patients typically present with systemic symptoms, such as fever, myalgia, arthralgia, sore throat, and malaise [1, 14, 37]. However, in PTU-associated ANCA vasculitis, severe, even life-threatening symptoms, including pulmonary hemorrhage and acute kidney injury, might also occur [37, 38]. If skin involvement is present, it affects subcutaneous parts of the skin and mostly consists of acral, purpuric plaques or nodules defined as "retiform purpura" [39–42]. Similarly, our patient exhibited purpuric urticarial plaques on the lower extremities. Skin lesions in our patient are most probably the consequence of PTU-induced ANCA vasculitis since the period between the cessation of the drug and the occurrence of the skin lesions was very short.

Most patients affected by this condition achieve the resolution of most symptoms upon withdrawal from PTU therapy. In some cases in which severe impairment of one or

multiple organs is present, other treatment modalities must be started as well, with corticosteroid and immunosuppressive agents (especially cyclophosphamide) being feasible options. No consensus on the duration of immunosuppressive therapy has been achieved yet, especially for maintenance therapy. Normally, once PTU is discontinued and remission of vasculitis is achieved, relapses most commonly do not occur [43]. Our patient underwent a skin biopsy too late, so the diagnosis was not pathologically proven. The biopsy was performed after the correction of prolonged prothrombin time which could be explained by changes in coagulation and fibrinolysis on the ground of hyperthyroidism itself [44]. Pathologists described chronic inflammatory infiltrates, and at the time of the biopsy, only hyperpigmentation was present in the affected areas of the skin.

Conclusion

This is an exceedingly rare case of a patient presenting with concomitant agranulocytosis and anti-neutrophile cytoplasmic antibodies-associated vasculitis as a complication of propylthiouracil therapy for Graves' disease. We would like to emphasize the importance of prompt discontinuation of antithyroid drugs in order to reduce end-organ damage and the possible mutual pathogenesis responsible for the occurrence of these adverse events.

REFERENCES

1. *Jacobs EM, Hartkamp A, Kaasjager HA.* PTU-associated cutaneous vasculitis with ANCA anti-MPO and anti-PR3 antibodies. Neth J Med 2003; 61(9): 296–9.
2. *Sato H, Hattori M, Fujieda M, Sugihara S, Inomata H, Hoshi M*, et al. High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset Graves' disease treated with propylthiouracil. J Clin Endocrinol Metab 2000; 85(11): 4270–3.
3. *Rodrigues R, Jorge PT.* Vasculite leucocitoclástica: uma rara manifestação associada ao metimazol. Arq Bras Endocrinol Metab 2002; 46(6): 716–9. (Portuguese)
4. *Karincaoglu Y, Esrefoglu M, Aki T, Mizrak B.* Propylthiouracil-induced vasculitic oral ulcers with anti-neutrophil cytoplasmic antibody. J Eur Acad Dermatol Venereol 2006; 20(1): 120–2.
5. *Aloush V, Litinsky I, Caspi D, Elkayam O.* Propylthiouracil-induced autoimmune syndromes: Two distinct clinical presentations with different course and management. Semin Arthritis Rheum 2006; 36(1): 4–9.
6. *Weetman AP.* Non-thyroid autoantibodies in autoimmune thyroid disease. Best Pract Res Clin Endocrinol Metab 2005; 19(1): 17–32.
7. *Vicente N, Cardoso L, Barros L, Carrilho F.* Antithyroid Drug-Induced Agranulocytosis: State of the Art on Diagnosis and Management. Drugs RD 2017; 17(1): 91–6.
8. *Gao Y, Zhao MH.* Review article: Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton) 2009; 14(1): 33–41.
9. *Wall AE, Weaver SM, Litt JS, Rae L.* Propylthiouracil-Associated Leukocytoclastic Necrotizing Cutaneous Vasculitis: A Case Report and Review of the Literature. J Burn Care Res 2017; 38(3): e678–85.
10. *Wada N, Mukai M, Kohno M, Notoya A, Ito T, Yoshioka N.* Prevalence of serum anti-myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA) in patients with Graves' disease treated with propylthiouracil and thiamazole. Endocr J 2002; 49(3): 329–34.
11. *Slot MC, Links TP, Stegeman CA, Tervaert JW.* Occurrence of antineutrophil cytoplasmic antibodies and associated vasculitis in patients with hyperthyroidism treated with antithyroid drugs: A long-term followup study. Arthritis Rheum 2005; 53(1): 108–13.
12. *Fujieda M, Hattori M, Kurayama H, Koitabashi Y.* Clinical features and outcomes in children with antineutrophil cytoplasmic autoantibody-positive glomerulonephritis associated with propylthiouracil treatment. J Am Soc Nephrol 2002; 13(2): 437–45.
13. *Harper L, Chin L, Daykin J, Allahabadia A, Heward J, Gough SC*, et al. Propylthiouracil and carbimazole associated-antineutrophil cytoplasmic antibodies (ANCA) in patients with Graves' disease. Clin Endocrinol (Oxf) 2004; 60(6): 671–5.
14. *Criado PR, Grizzo Peres Martins AC, Gaviolli CF, Alavi A.* Propylthiouracil- induced vasculitis with antineutrophil cytoplasmic antibody. Int J Low Extrem Wounds 2015; 14(2): 187–91.
15. *Noh JY, Asari T, Hamada N, Makino F, Ishikawa N, Abe Y*, et al. Frequency of appearance of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) in Graves' disease patients treated with propylthiouracil and the relationship between MPO-ANCA and clinical manifestations. Clin Endocrinol (Oxf) 2001; 54(5): 651–4.
16. *Otsuka S, Kinebuchi A, Tabata H, Yamakage A, Yamazaki S.* Myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis following propylthiouracil therapy. Br J Dermatol 2000; 142(4): 828–30.
17. *Nakamura H, Miyauchi A, Miyawaki N, Imagawa J.* Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab 2013; 98(12): 4776–83.
18. *Franklyn JA, Boelaert K.* Thyrotoxicosis. Lancet 2012; 379(9821): 1155–66.
19. *Watanabe N, Narimatsu H, Noh JY, Yamaguchi T, Kobayashi K, Kami M*, et al. Antithyroid drug-induced hematopoietic damage: a retrospective cohort study of agranulocytosis and pancytopenia involving 50,385 patients with Graves' disease. J Clin Endocrinol Metab 2012; 97(1): E49–53.
20. *Kobayashi S, Noh JY, Mukasa K, Kunii Y, Watanabe N, Matsumoto M*, et al. Characteristics of agranulocytosis as an adverse effect of antithyroid drugs in the second or later course of treatment. Thyroid 2014; 24(5): 796–801.
21. *Mutharasan P, Oatis W, Kwaan H, Molitch M.* Delayed anithyroid drug-induced agranulocytosis. Endocr Pract 2012; 18(4): e69–72.
22. *Andrès E, Zimmer J, Affenberger S, Federici L, Alt M, Maloisel F.* Idiosyncratic drug-induced agranulocytosis: Update of an old disorder. Eur J Intern Med 2006; 17(8): 529–35.
23. *Fibbe WE, Claas FH, Van der Star-Dijkstra W, Schaafsma MR, Meyboom RH, Falkenburg JH.* Agranulocytosis induced by propylthiouracil: evidence of a drug dependent antibody reacting with granulocytes, monocytes and haematopoietic progenitor cells. Br J Haematol 1986; 64(2): 363–73.
24. *Wall JR, Fang SL, Kuroki T, Ingbar SH, Braverman LE.* In vitro immunoreactivity to propylthiouracil, methimazole, and carbimazole in patients with Graves' disease: a possible cause of antithyroid drug-induced agranulocytosis. J Clin Endocrinol Metab 1984; 58(5): 868–72.
25. *Csernok E, Ernst M, Schmitt W, Bainton DF, Gross WL.* Activated neutrophils express proteinase 3 on their plasma membrane in vitro and in vivo. Clin Exp Immunol 1994; 95(2): 244–50.

26. *Owen CA, Campbell MA, Sannes PL, Boukedes SS, Campbell EJ.* Cell surface-bound elastase and cathepsin G on human neutrophils: a novel, non-oxidative mechanism by which neutrophils focus and preserve catalytic activity of serine proteinases. J Cell Biol 1995; 131(3): 775–89.
27. *Yang J, Zhu YJ, Zhong JJ, Zhang J, Weng WW,* et al. Characteristics of Antithyroid Drug-Induced Agranulocytosis in Patients with Hyperthyroidism: A Retrospective Analysis of 114 Cases in a Single Institution in China Involving 9690 Patients Referred for Radioiodine Treatment Over 15 Years. Thyroid 2016; 26(5): 627–33.
28. *Sheng WH, Hung CC, Chen YC, Fang CT, Hsieh SM, Chang SC,* et al. Antithyroid-drug-induced agranulocytosis complicated by life-threatening infections. QJM 1999; 92(8): 455–61.
29. *Alexander EK, Larsen PR.* High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2002; 87(3): 1073–7.
30. *Fiorentino DF.* Cutaneous vasculitis. J Am Acad Dermatol 2003; 48(3): 311–40.
31. *Sera N, Yokoyama N, Abe Y, Ide A, Usa T, Tominaga T*, et al. Antineutrophil Cytoplasmic Antibody-associated Vasculitis Complicating Graves' Disease: Report of Two Adult Cases. Acta Med Nagasaki 2000; 45(1–2): 33–6.
32. *Gunton JE, Stiel J, Clifton-Bligh P, Wilmshurst E, McElduff A.* Prevalence of positive anti-neutrophil cytoplasmic antibody (ANCA) in patients receiving anti-thyroid medication. Eur J Endocrinol 2000; 142(6): 587.
33. *Gao Y, Zhao MH, Guo XH, Xin G, Gao Y, Wang HY.* The prevalence and target antigens of antithyroid drugs induced antineutrophil cytoplasmic antibodies (ANCA) in Chinese patients with hyperthyroidism. Endocr Res 2004; 30(2): 205–13.
34. *Jiang X, Khursigara G, Rubin RL.* Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1994; 266(5186): 810–3.
35. *Ye H, Gao Y, Guo XH, Zhao MH.* Titre and affinity of propylthiouracil-induced anti-myeloperoxidase antibodies are closely associated with the development of clinical vasculitis. Clin Exp Immunol 2005; 142(1): 116–9.
36. *Yang J, Yao LP, Dong MJ, Xu Q, Zhang J, Weng WW,* et al. Clinical Characteristics and Outcomes of Propylthiouracil-Induced Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in Patients with Graves' Disease: A Median 38-Month Retrospective Cohort Study from a Single Institution in China. Thyroid 2017; 27(12): 1469–74.
37. *Bilge NS, Kaşifoğlu T, Korkmaz C.* PTU-induced ANCA-positive vasculitis: an innocent or a life-threatening adverse effect? Rheumatol Int 2013; 33(1): 117–20.
38. *Tanaka R, Shimojima Y, Moteki H, Kishida D, Ueno KI, Sekijima Y.* Propylthiouracil-induced Otitis Media with Antineutrophil Cytoplasmic Antibody-associated Vasculitis. Intern Med 2018; 57(20): 3029–33.
39. *Flendrie M, Vissers WH, Creemers MC, de Jong EM, van de Kerkhof PC, van Riel PL.* Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005; 7(3): R666–76.
40. *Vasoo S.* Drug-induced lupus: an update. Lupus 2006; 15(11): 757–61.
41. *Sheen YS, Chu CY, Yu HS.* Antineutrophil cytoplasmic antibody-positive cutaneous leukocytoclastic vasculitis associated with propylthiouracil therapy. Arch Dermatol 2006; 142(7): 879–80.
42. *Khurshid I, Sher J.* Disseminated intravascular coagulation and vasculitis during propylthiouracil therapy. Postgrad Med J 2000; 76(893): 185–6.
43. *Gao Y, Chen M, Ye H, Yu F, Guo XH, Zhao MH.* Long-term outcomes of patients with propylthiouracil-induced antineutrophil cytoplasmic auto-antibody-associated vasculitis. Rheumatology (Oxford) 2008; 47(10): 1515–20.
44. *Erem C, Ersoz HO, Karti SS, Ukinç K, Hacihasanoglu A, Değer O,* et al. Blood coagulation and fibrinolysis in patients with hyperthyroidism. J Endocrinol Invest 2002; 25(4): 345–50.

Received on April 29, 2021
Revised on June 5, 2021
Accepted on June 16, 2021
Online First June 2021