Case Report

Propylthiouracil induced ANCA-associated vasculitis in a 14-year-old girl

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Background: Antineutrophil cytoplasmic antibodies (ANCAs) are the serologic hallmark of ANCA-associated primary small-vessel vasculitides (AAVs), but these antibodies have also been described in other autoimmune diseases such as inflammatory bowel diseases. Furthermore, different drugs are linked to the induction of ANCA, including propylthiouracil (PTU). However progression into clinical overt vasculitis is less common.

Case-diagnosis/treatment: We describe the case of a young girl with Graves' disease presenting with fatigue, fever, episcleritis and arthritis. The unexpected double myeloperoxidase/proteinase 3-ANCA positivity triggered a multidisciplinary diagnostic work-up and resulted in the diagnosis of a clinically overt PTU-induced AAV. After PTU-withdrawal and treatment with high-dose corticosteroids, a favorable clinical and biochemical evolution was obtained.

Conclusions: The use of PTU in the management of hyperthyroidism is not considered first-line treatment in Europe and is even less commonly used in children. Nevertheless, pediatricians should be aware of the possibility of PTU-induced AAV, especially in the presence of multiple ANCA reactivities. Therefore, the use of this drug should be weighed carefully in children.

Keywords: Graves' disease, Propylthiouracil, Anti-neutrophil cytoplasmic antibodies, Drug-induced, Small vessel vasculitis

Background

Antineutrophil cytoplasmic antibodies (ANCAs) are the serologic hallmark of ANCA-associated primary small-vessel vasculitides, with myeloperoxidase (MPO) and proteinase 3 (PR3) being identified as the two major target antigens. Other specificities against various neutrophil components have been demonstrated in disorders other than ANCA-associated vasculitides (AAVs) including other autoimmune disorders like inflammatory bowel disease and infections.[1] Furthermore, various drugs have been linked to the induction of ANCA.[1]

Propylthiouracil (PTU) and methimazole (MMI) are antithyroid drugs widely used as first-line treatment in children with Graves' disease. Within the class of antithyroid agents, PTU is known to induce ANCA in 15–64% of patients with Graves' disease, but only a minority of these patients show clinical overt vasculitis. In contrast to Asian countries and the USA, the use of PTU is less common practice in the management of hyperthyroidism in Europe.[2] In addition, reporting on PTU-induced AAV in children is scarce. We report a case of PTU-induced AAV in a young girl with double MPO/PR3-ANCA positivity, an uncommon finding that triggered a multidisciplinary diagnostic work-up.

Case-diagnosis/Treatment

A 14-year-old Caucasian girl presented with a one week history of worsening fatigue and pallor. At the age of nine she was diagnosed with Graves' disease and treated with PTU since. She was euthyroid with levothyroxine substitution therapy. Besides pallor, her clinical exam was unremarkable. Palpation of the thyroid gland was normal. The only abnormal laboratory finding was profound ferropenic anemia (Table 1). She denied gastrointestinal symptoms or blood losses.

Work-up for anemia showed a reticulocyte count of 3%, normal vitamin B12 and folic acid. Hemolysis and hemoglobinopathies were excluded. Haptoglobin and liver function tests with direct and total bilirubin and lactate dehydrogenase levels were normal. Blood smear demonstrated poikilocytosis and few fragmented red blood cells; the direct Coombs test was

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negative. Furthermore, both fecal occult blood test and radioisotope Meckel's scan were negative. A diagnosis of Iron deficiency anemia was made and the patient received oral iron treatment.

Four weeks later she developed low grade fever, arthritis of the left ankle and elbow without evidence for septic arthritis. She was referred to the pediatric rheumatology department of our centre for further diagnostic work-up.

Physical examination revealed pallor, unilateral red eye, defined as episcleritis by the ophthalmologist, and swelling of the right elbow without warmth or tenderness. On further inquiry, occasional morning stiffness and one previous episode of uveitis and episcleritis were withheld. In addition, two episodes of minor hemoptysis occurred, suggesting pulmonary vasculitis as well. There was no history of mucocutaneous abnormalities and family history for autoimmune diseases was negative. Laboratory investigations showed significant changes for the following parameters: hemoglobin (9.2 g/dl), erythrocyte sedimentation rate (21 mm/hour), creatinine (1.25 mg/dl), urine protein/creatinine (0.66 g/g) and hematuria (300/μl) (Table 1). Complement factor C3 and C4 were within the normal range, as were thyroid function tests. Serologic work-up showed the presence of antinuclear antibodies (homogeneous 3+/4+, anti-dsDNA negative, anti-ENA negative) and a mixed perinuclear/cytoplasmic ANCA pattern (intensity 5+) with MPO- and PR3-ANCA positivity (Table 1). Further testing, demonstrated no additional ANCA-reactivities (antibodies against lactoferrin, elastase, cathepsin G, and BPI were tested). Renal biopsy showed pauci-immune focal segmental glomerulonephritis with cellular crescents in 4 out of 12 glomeruli.

As double ANCA positivity is uncommon and frequently associated with drug-induced AAV,[2] PTU-induced AAV was suspected. PTU was withdrawn and high-dose oral corticosteroids were started (2 mg/kg/day) with satisfactory clinical and biochemical response (Fig. 1). Upon follow-up, no more arthritis

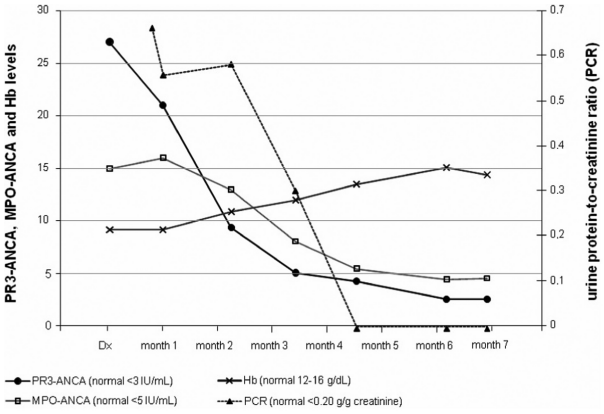

Figure 1 Biochemical evolution of laboratory parameters upon PTU-withdrawal. Dx, diagnosis; ANCA, antineutrophil cytoplasmatic antibodies; MPO, myeloperoxidase (normal <5 IU/ml); PR3, proteinase 3 (normal <3 IU/ml); Hb, hemoglobin (normal 12–16 g/dl); PCR, protein-to-creatinine ratio (normal <0.20 g/g creatinine).

appeared and exercise tolerance improved significantly. Anemia resolved and renal function ameliorated. In parallel, a decline in MPO/PR3-ANCA positivity was observed and seven months after cessation of PTU therapy, ANCA antibody titers normalized. Apart from the cushingoid facial characteristics and increased glucose levels, she did not experience other side effects of the high-dose systemic corticosteroids. A careful corticosteroid tapering schedule was followed based on clinical and biochemical disease evolution. She was treated with oral steroids for a period of nine months. Recently, our patient underwent thyroidectomy because of relapse of hyperthyroidism.

Discussion

In patients treated with antithyroid drugs, the reported prevalence of ANCA varies from 4 to 46% with clinical overt AAV in 0–1.4% of these patients.[2] For PTU, ANCA-positivity is seen in 15–64% of patients and systemic vasculitis in approximately one-fourth to one-third of them,[2,3] with similar findings in adult as well as pediatric patient populations.[2]

Table 1 Laboratory data

	First presentation	At diagnosis	After 3 months CS	Normal range
Haemoglobin (g/dl)	6.9	9.2	12.0	12.0–16.0
MCV (fl)	67.1	84.5	84.8	82.3–96.4
Iron (μg/dl)	14	67	178	50–150
Ferritin (μg/dl)	43	137	94	13–150
ESR (mm/hour)	20	21	5	<10
CRP (mg/l)	2.1	2.0	<0.6	<5.0
Serum creatinine (mg/dl)	0.77	1.25	0.96	0.50–0.95
Urine protein/creatinine (g/g)	0.18	0.66	0.30	<0.20
Haematuria (RBC/μl)	2000	300	180	<25
MPO-ANCA (IU/ml)	N/A	15.0	8.1	<5.0
PR3-ANCA (IU/ml)	N/A	27.0	5.1	<3.0

Note: MCV, mean corpuscular volume; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RBC, red blood cells; PCR, protein-to-creatinine ratio; ANCA, antineutrophil cytoplasmatic antibodies; MPO, myeloperoxidase; PR3, proteinase 3; N/A, not available; CS, corticosteroids.

In contrast to primary vasculitis, in which MPO-ANCA and PR3-ANCA are presumed mutually exclusive, multiple target antigens can be simultaneously encountered in PTU-induced AAV.[1,2] Moreover, this observation appears to be associated with an increased risk of the development of clinical signs.[3] The pathogenesis of PTU-induced AAV is not yet fully understood. PTU decreases thyroid hormone production by inhibiting the enzym thyroid peroxidase. The nucleotide and amino acid structures of the latter and MPO approach a similarity of 50%, which could explain an interaction between PTU and the target antigens of ANCA, in particular MPO, contributing to the development of PTU-induced AAV. On the one hand, PTU was found to alter the structure of MPO by decreasing its oxidation activity, which may serve as a neoantigen.[2] On the other hand, MPO itself might affect the structure of PTU and transform it into immunogenic cytotoxic metabolites, triggering ANCA production.

As only one-third of patients with PTU-induced ANCA develop clinical vasculitis,[2] several studies were performed to identify risk factors for the development of clinical signs. First, the antigenic specificity of ANCA seems to play a role. Gao and colleagues[3] showed that most patients with clinical overt PTU-induced vasculitis show multiple ANCA reactivities (92.6%) and/or MPO-ANCA positivity (92.6%). In both cases, these antibody profiles were significantly more common in patients with overt vasculitis compared to those without symptoms (multiple reactivities: 92.6 versus 31.6%; MPO-ANCA: 92.6 versus 36.8%).[3] Secondly, the immunological characteristics of the MPO-ANCA antibodies might be of particular importance. Both titers as well as avidity of MPO-ANCA were significantly higher in patients with clinical overt PTU-induced vasculitis compared to asymptomatic patients and epitope specificity against MPO-ANCA was different.[4] Thirdly, long-term exposure to PTU was found to be associated with an increased incidence of PTU-induced AAV although there are no clear data on the cumulative threshold dose of PTU that would induce vasculitis.[2]

At the time of diagnosis, our patient experienced long-term exposure to PTU (5 years) and showed serum ANCA against multiple targets including MPO. She fulfilled at least three out of six risk criteria for the development of overt PTU-induced vasculitis as proposed by Chen and Colleagues.[2] Furthermore, episcleritis as well as renal and pulmonary involvement were observed through the disease course.

Clinical manifestations of PTU-induced AAV are similar to those of primary AAV. However, disease severity is generally milder and the overall prognosis is better. In patients with organ involvement, the duration of immunosuppressive therapy is still inconclusive, but might be shorter than that in primary AAV. Moreover, maintenance therapy might not be necessary.[2] Despite discontinuation of the offending drug, immunosuppressive therapy and clinical and biochemical normalisation of vasculitis, ANCA might remain positive for up to multiple years.[2]

Fortunately PTU-induced AAV in patients is rare. PTU and MMI have been widely used for the treatment of hyperthyroidism in both children and adult, with minor side effects being itching, rash, urticaria, joint pain and swelling, fever, myalgia, paresthesia, vertigo and lymphadenopathy. Over the past 60 years of PTU and MMI use, reports of PTU-related liver failure and death have accumulated.[5] In contrast, this problem has not been reported with MMI use in children. Perhaps because of these concerns, there has been an important reduction in PTU use in the pediatric population over the past decade and it is suggested that PTU should no longer be used as first line treatment for Graves' diseases in children.

Conclusion

In summary, we report a case of drug-induced AAV in a 14-year-old girl during PTU treatment for Graves' disease. She presented with fatigue secondary to anemia, fever, episcleritis and pauciarticular arthritis. During the disease course, she developed glomerulonephritis and mild pulmonary vasculitis. Diagnostic work-up revealed a PTU-induced AAV as confirmed by the clinical and laboratory improvement on drug withdrawal. The presence of multiple target ANCA antigens is a risk factor for developing clinically overt vasculitis. Because of accumulation reports of PTU-related liver failure and death, PTU is no longer considered as a first-line treatment for Graves' disease in children.

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References

1 Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. Lancet. 2006;368:404–18.
2 Chen M, Gao Y, Guo XH, Zhao MH. Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated vasculitis. Nat Rev Nephrol. 2012;8:476–83.
3 Gao Y, Chen M, Ye H, Guo XH, Zhao MH, Wang HY. The target antigens of antineutrophil cytoplasmic antibodies (ANCA) induced by propylthiouracil. Int Immunopharmacol. 2007;7:55–60.
4 Fujieda M, Suzuki K, Sato H, Hattori M, Wada N, Tsuchiya M, *et al.* Epitope analysis of myeloperoxidase-specific antineutrophil cytoplasmic autoantibodies (MPO-ANCA) in childhood onset Graves' disease treated with propylthiouracil. Clin Nephrol. 2005;63:437–45.
5 Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil Era. Int J Pediatr Endocrinol. 2014;1:10.