

Antineutrophil cytoplasmatic antibody positive systemic vasculitis in a patient treated with propylthiouracil

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ABSTRACT

The development of antineutrophil cytoplasmatic antibody (ANCA) during therapy with propylthiouracil (PTU) is not uncommon but occasionally has clinical significance. Risk factors associated with the development of ANCA associated systemic vasculitis when taking PTU have been described. We report and discuss a case with PTU-induced ANCA vasculitis with severe systemic manifestations.

Keywords: ANCA; systemic vasculitis; PTU.

RESUMO

O desenvolvimento de anticorpos anti-citoplasma de neutrófilos (ANCA) durante o tratamento com propiltiouracilo (PTU) não é raro, no entanto, apenas em alguns casos tem significado clínico. Alguns fatores de risco de desenvolvimento de vasculite sistémica associada a ANCA com a toma de PTU têm sido descritos. Apresentamos e discutimos um caso de vasculite associada a ANCA induzida pelo PTU com graves repercussões sistémicas.

Palavras-chave: ANCA; Vasculite sistémica; PTU

INTRODUCTION

Anti-neutrophil cytoplasmatic antibodies (ANCA) are significant markers for certain small-vessel vasculitis, like Wegener's granulomatosis, Churg-Strauss syndrome, renal limited vasculitis, anti-glomerular basement membrane antibody disease or inflammatory bowel diseases. Two patterns are recognized: a cytoplasmatic

(c-ANCA), almost exclusively caused by antibodies against proteinase 3, and a perinuclear pattern (p-ANCA) which can be caused by a variety of antibodies reacting with different neutrophil granule constituents as myeloperoxidase (MPO), human leucocyte elastase and lactoferrin¹. Etiology of ANCA-associated vasculitis is largely unknown. There is evidence that drugs^{2,3} from different classes, such as antibiotics, anti-thyroid, anti-tumor necrosis factor- α and psychoactive agents, can cause vasculitis in sporadic cases^{4,5}. Propylthiouracil (PTU) is one of the most frequent drug implicated. Despite the high prevalence of PTU-induced ANCA (estimated from 20-64% in cross sectional studies) only a subset of patients develop clinical significant ANCA-associated vasculitis (AAV)^{6,7,8,9}. The mechanisms involved in PTU-induced AAV are far from being fully understood. The spectrum of manifestations is wide and ranges from less specific syndromes to single organ involvement and life-threatening vasculitis⁶. We report a case of PTU-induced AAV with systemic involvement and life threatening manifestations.

CASE REPORT

A 65-year-old portuguese woman was admitted for uncontrolled hyperthyroidism in perspective for thyroid surgery. Ten years before she had a diagnosis of hyperthyroidism and since then she was treated with methimazole, which was suspended one year before with evidence of controlled disease. She had a past of smoking with chronic bronchitis, hypercholesterolemia, hypertension, venous insufficiency and a long history of hypersensitivity to many drug classes, described mostly as skins lesions. Eight weeks before the admission she was started on PTU (150mg/day) due to a relapse of hyperthyroidism (TSH<0.008 uIU/mL, NR 0,27-4,2uIU/mL, free T3=17.70 ng/dL, NR 2,0-4-4pg/mL, and free T4=4.93 ng/L, NR 0,93-1,7ng/dL).

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Six weeks later she developed fever and dry cough. She was admitted in the emergency department where she presented leucopenia (660/uL, NR 4000-11000/uL) with severe neutropenia (20/uL, NR 2000-7500/uL), without anemia or thrombocytopenia. Chest x-ray was clear, urine sediment and blood gas analyses were normal. Her MASCC risk score for febrile neutropenia was 24. She was diagnosed with agranulocytosis secondary to PTU and upper respiratory tract infection. PTU was suspended, blood cultures were collected and she was sent home in treatment with ciprofloxacin, prednisolone and propranolol.

Reevaluated three days later she had better neutrophils count (340/uL, NR 2000-7500/uL) and thyroid function (TSH=0.01uUI/mL, NR 0,27-4,2uUI/mL, free T3=6.1pg/mL, NR 2,0-4-4pg/mL and free T4=2.0 ng/dL, NR 0,93-1,7ng/dL), but she maintained fever and was proposed for admission as inpatient for clinical surveillance and subsequent thyroid surgery. She started on lugols solution for surgery preparation but at 48-72 hours she developed symptoms of sialoadenitis and a purpuric rash with papules, nontender or pruriginous, mostly in the face, trunk and upper limbs, with palmar and plantar involvement (Figures 1 and 2).

She then evolved with abdominal pain, in a belt pat-



FIGURE 1. Purpuric rash with papules, non tender or pruriginous, mostly in the face



FIGURE 2. Purpuric rash with papules, non tender or pruriginous, with palmar and plantar involvement



FIGURE 3. Chest radiography with bilateral multiple patchy opacities



FIGURE 4. Toraco-abdomino tomography (without iv contrast) with bilateral multifocal consolidation along the bronchovascular bundle with mild ground-glass opacity and splenic infarctions



FIGURE 5. Toraco-abdomino tomography (without iv contrast) with bilateral multifocal consolidation along the bronchovascular bundle with mild ground-glass opacity and splenic infarctions

tern, accompanied by a rise in pancreatic enzymes, and a rapidly progressive respiratory distress and global respiratory failure associated with hypotension responsive to volume. At this time she was admitted in ICU department, with extensive areas of skin necrosis and respiratory failure (ratio $pO_2/FiO_2 < 200$). Laboratory values showed hypoproliferative anemia, elevation of pancreatic enzymes (amylase=600U/L, NR 0-53U/L, and lipase=624U/L, NR 30-190U/L), mild hematuria (2 to 5 erythrocytes/field of 400x, NR 0-2 erythrocytes/field of 400x) and subnephrotic proteinuria (protein/creatinine 1,0g/mmol, NR < 0,45g/mmol) without dysmorphic erythrocytes, elevated erythrocyte sedimentation rate and C-reactive protein. Culture tests were consistently negative. Immunologic studies showed hypergammaglobulinemia (IgM), complement consumption (C3=76,0mg/dL, NR 81-167mg/dL, and C4=7,0mg/dL, NR 11-43mg/dL), positive ANA with a speckled pattern (1/320, NR < 1/80) and ANCA (1/640, NR < 1/20) with a perinuclear pattern with elevated anti-MPO antibodies. Anti-double-stranded DNA, anti-Sm, anti-U1 ribonucleic protein, anti-SSA, anti-SSB and anti-histones) were all negative. Chest radiographs now showed bilateral multiple patchy opacities (Figure 3) and a chest-abdominal CT scan revealed bilateral multifocal consolidation along the bronchovascular bundle with mild ground-glass opacity and splenic infarctions (Figures 4 and 5). Histological examination of skin lesions biopsy showed leukocytoclastic vasculitis (Figure 6) - Direct and indirect immunofluorescence were not available.

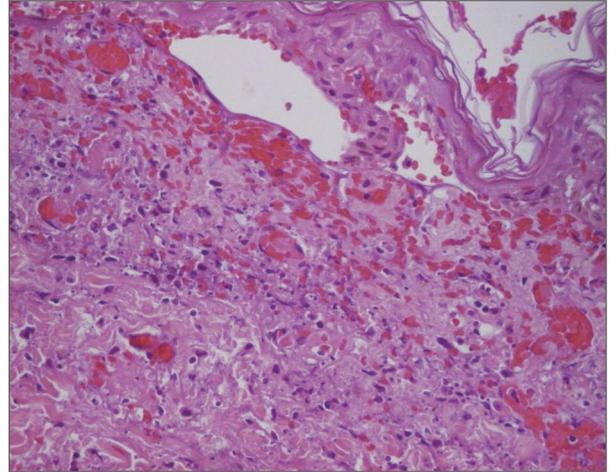


FIGURE 6. Skyn biopsy with leukocytoclastic vasculitis (x40)

At this point the diagnosis of systemic p-ANCA vasculitis was made, with polyglandular, lung, splenic and skin involvement, probably secondary to PTU. She went on a short course of high dose methylprednisolone (1g/day), following of 1mg/kg of prednisolone (two weeks with subsequent withdraw) and thyroid surgery, with complete vasculitis remission, with ANA and p-ANCA levels returning negative six months later.

DISCUSSION

The mechanisms of PTU-induced AAV are ill-defined and are probably multifactorial. PTU may play an immunogenic effect on T cells, which stimulates B cells producing ANCA, and also by binding to MPO, it may modify the configuration of the neutrophils resulting with triggered autoimmune response^{6,10}. This probably explains the p-ANCA pattern with production of anti-MPO classically described in these cases. PTU-induced AAV seem to develop mostly in younger females, probably because of greater prevalence of thyroid disease in young women⁶. Long-standing therapy using PTU might be a risk factor for developing clinically evident vasculitis and relapse of hyperthyroidism was reported as another risk factor¹¹⁻¹³, which occurred in our patient. The clinical manifestations of PTU-induced AAV are similar to those of other primary vasculitis. Kidney is the most common involved organ, featuring from mild hematuria and proteinuria to rapidly progressive glomerulonephritis. Cutaneous involvement is also common and may present as different patterns

of skin changes^{12,14}, while pulmonary manifestations more commonly occur as alveolar hemorrhage with some patients presenting interstitial pneumonia and acute respiratory distress syndrome⁶. In the presented case, our patient evolved mostly with skin involvement, confirmed by histology, and interstitial lung disease, from which we unfortunately did not get a bronchoalveolar lavage. In 1994 Chapell Hill Conference defined the criteria for AAV, which was updated by Gae et al⁶ at 2009 with three more criteria added: clinical findings related to the suspected drug and resolving with its discontinuation, serum ANCA positivity and exclusion of other conditions mimicking vasculitis. Systemic lupus erythematosus (SLE) was also considered, namely drug-induced SLE. This diagnosis was disregarded attending to the absence of musculoskeletal complains, serositis and other characteristic clinical findings in our patient and the absence of SLE antibodies other than low titer ANA. By opposite, the patient age, proeminent lung and skin involvement and serum p-ANCA high titer made AAV the most probable diagnosis^{15,16}. Regarding treatment, primary vasculitis pathogenesis is different from PTU-induced AAV, and treatment should be based on individual assessment. In PTU-induced AAV an immediate cessation of the drug after diagnosis will probably be enough for those with clinically limited disease. For patients with severe and active organ involvement intensive steroid therapy (with or without immunosuppressive agents) can improve organ function and prevent progression to severe, irreversible disease^{6,11}. Maintenance therapy may not be necessary¹¹. The overall outcome of PTU-induced AAV is much better than primary vasculitis probably because of cessation of the potential immunogenic stimulus.

CONCLUSION

Since many patients treated with PTU have ANCA positivity but only few develop systemic vasculitis syndromes, early recognition of signs and symptoms related to vasculitis is the best way to prevent the worst consequences⁶. ANCA screening without clinical manifestations showed no benefit¹⁰.

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