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Anti-neutrophil cytoplasmic antibody-associated mucocutaneous allergic vasculitis with oral manifestations caused by propylthiouracil

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Abstract
A 49-year-old woman treated with increasing dosage of propylthiouracil (PTU) in order to control hyperthyroidism, developed progressive necrotic ulcers in the oral cavity, oropharynx and rhinopharynx and vasculitic ulcers on both auricular pinnae after a few days. The PTU treatment was immediately discontinued and the mucosal and skin manifestations resolved promptly. Laboratory findings, including anti-neutrophil cytoplasmic antibodies (ANCA), suggested allergic vasculitis. This is to our knowledge the first reported case of oral manifestations of PTU-induced allergic vasculitis.

Key words: Vasculitis, allergic cutaneous; Oral ulcer; Drug therapy; Antibodies, antineutrophil cytoplasmic

Introduction

Propylthiouracil (PTU) is a drug used to control hyperthyroidism. The most common side-effects are allergic reactions, e.g. leukopenia, exanthema, fever, hepatitis, arthralgia and lupus-like syndrome and they are encountered in up to five per cent of patients treated with PTU. An unusual complication of PTU treatment is vasculitis. In the literature there are several reports on PTU-associated allergic vasculitis with cutaneous manifestations, glomerulonephritis and respiratory failure (Wing and Fantus, 1987). We report a case of PTU-associated allergic vasculitis with manifestations in the oral cavity, oropharynx, rhinopharynx and on both auricular pinnae. To our knowledge this is the first report of mucous membrane manifestations associated with PTU treatment.

Case report

A 49-year-old Danish woman had been successfully treated with PTU because of hyperthyroidism for three and a half years. The treatment was stopped for eight months but the thyrotoxicosis relapsed when PTU treatment was started again. She received no other drugs. The starting dosage was 100 mg three times daily which was insufficient thus the dosage was increased after two weeks to a total of 1400 mg a day. Two weeks later the patient developed a mucosal ulcer on the inside of the right cheek, which was treated with local anaesthetic mouth washing. Because of progression of the symptoms, the patient was admitted to the ENT-department one week later.

At admission, the patient had a fever of 39.3°C, and appeared quite ill. She had difficulty eating and drinking. Clinical examination revealed, apart from the original mucosal ulcer on the inside of the right cheek (Figure 1), necrosis of the gingiva, including necrosis of the alveolar process surrounding the posterior molar (+7) (Figure 2), which was loose, necrotic ulcers at the right side of the

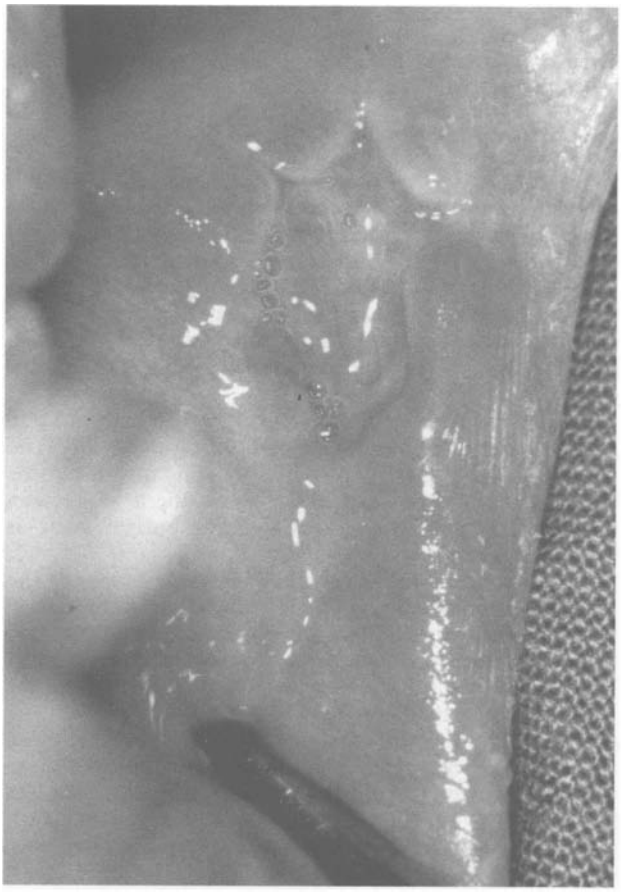

Fig. 1
Six days after admission. Mucosal ulcer on the inside of the right cheek with typical sharp margins.

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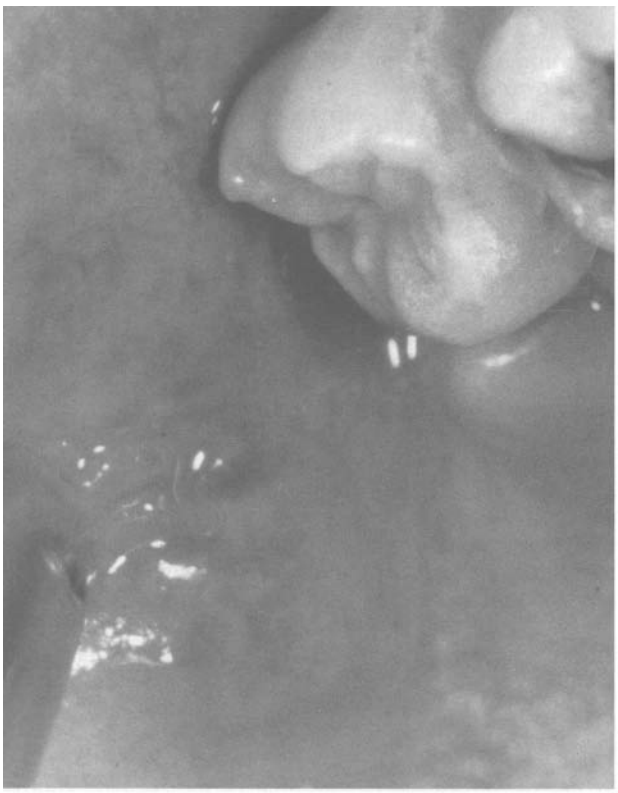

FIG. 2

Six days after admission. The right side of the gingiva and alveolar process. The tooth 7+ has not yet been removed, but was so loose, that it could be removed with a forceps. A small area of the necrosis of the alveolar process can barely be seen. A bone sequester could later be removed from this site.

oropharynx and rhinopharynx and punctual necrotic ulcers on both auricular pinnae (Figure 3). There was slight leucopenia 2.1 $\times$ 10^9 and elevated sero-reactive protein (CRP) 1335 mmol/l. Anti-nuclear antibody (ANA) screening three days later was positive for specific MPO-ANCA (myeloperoxidase-antineutrophil cytoplasmic antibodies) and P-ANCA (perinuclear-antineutrophil cytoplasmic antibodies).

The PTU treatment was immediately discontinued and substituted by thiamazol 10 mg four times a day. The progression of the mucosal and skin manifestations stopped during the next day. The patient was given chlorhexidine solution mouth washing, but no local or systemic steroid treatment.

Six days after the PTU-treatment was stopped, the patient underwent surgical revision under general anaesthesia. There were sharp margins to the necrotic tissue and healing granulation tissue formation had already started. The loose molar could be removed with a forceps and the necrotic bone surrounding it was removed.

Biopsies from the margins of the ulcers showed inflammation with light eosinophilia in one site, but there were no signs of vasculitis. The rhinopharyngeal changes had vanished. The white blood cell count was normalized together with CRP. The ANA-screening has not been repeated. Five weeks after admission all the oral ulcers were healed as well as the changes on both auricular pinnae. The defect in the hard palate was covered with normal mucosa, but the sixth molar was loose as a result of the impaired vascular supply.

We can report that the patient is still well and has no symptoms from the mouth and has developed neither lupus nor a systemic vasculitis.

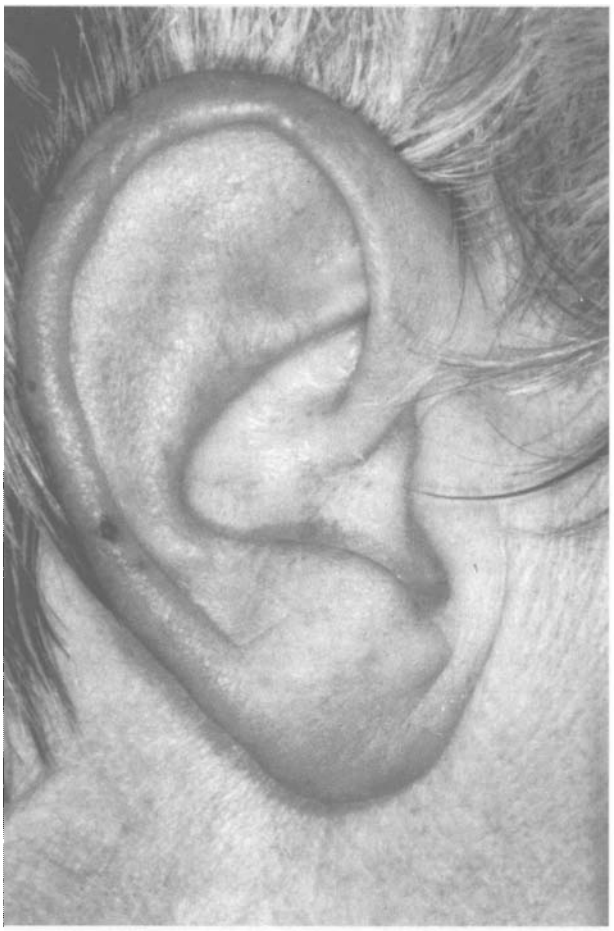

FIG. 3

Six days after admission. The right pinna with typical punctual necroses on the helix.

Discussion

Vasculitis is an unusual complication of PTU therapy. In previous reports ANCA has been found associated with vasculitis induced by anti-thyroid drug treatment (Dolman *et al.*, 1993; Tanemoto *et al.*, 1995). It usually arises within weeks after initiation of the therapy, but can also be seen after months or even years. Our patient showed typical vasculitis changes on both auricular pinnae. To our knowledge oral mucous membrane manifestations of PTU-induced vasculitis have not been reported by others. We believe that the fact that lesions appeared after increasing the PTU doses, that they resolved promptly on the discontinuation of the PTU therapy and the positive MPO-ANCA and P-ANCA reactions is indicative of PTU-induced vasculitis, even though the biopsies taken showed inflammation but no typical histological signs of vasculitis. The pathogenesis of PTU-induced vasculitis is unknown. Actual deposition of immunoglobulins and complement activation has been demonstrated by immunofluoroscence studies (Vasily and Tyler, 1980). The detection of ANCA in association with vasculitis suggests other pathogenic mechanisms. ANCA may activate neutrophils causing vascular injury through their proteolytic granules. The immune complex deposition producing vasculitis is possibly secondary. We have found several reports on the subject of ANCA-associated vasculitis caused by PTU (Dolman *et al.*, 1993; Tanemoto *et al.*, 1995; Yuasa *et al.*, 1996).

Patients treated with PTU because of hyperthyroidism are running a small risk of developing allergic vasculitis.

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Should patients treated with PTU develop oral necrotic ulcerations, the drug should be discontinued immediately. ANA-screening and possibly biopsies taken in the acute stage may verify the diagnosis. The prognosis for the oral manifestations depends on the severity of the necrosis.

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