Salivary gland involvement as initial presentation of Wegener's disease

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Summary: We describe a case of Wegener's disease with massive painful bilateral submandibular gland enlargement as the presenting symptom. The diagnosis was based on histologically documented nasal mucosa involvement, focal necrotizing glomerulonephritis, episcleritis and anti-neutrophil cytoplasmic antibody.

Introduction

Wegener's granulomatosis is characterized by necrosis, granulomatous inflammation and vasculitis, and a classic triad of upper and lower respiratory tract involvement and glomerulonephritis. Other common clinical manifestations include fever, joint involvement, ocular abnormalities, skin lesions, central and peripheral nervous system involvement and pericarditis.^{1,2} Involvement of salivary glands in Wegener's disease is rare.^{1,3} We present a case with bilateral submandibular gland involvement as a major initial manifestation.

Case report

A 60 year old woman was admitted to another hospital because of trismus and swelling of both submandibular glands. She had had fatigue for 6 weeks and 3 weeks before admission painful enlargement of the left submandibular gland was noticed, followed one week later by swelling of the right submandibular gland. Sialography was normal but computed tomography (CT) showed diffusely enlarged submandibular glands with areas of decreased density suggesting necrosis. Treatment with amoxycillin–clavulanic acid plus metronidazole brought no relief. Epistaxis and episcleritis developed and the trismus became even more pronounced. One week after admission the right submandibular gland was excised. Histopathological examination revealed diffuse paren-

chymal necrosis and inflammation with abscess formation and many multi-nucleated giant cells. Considerable capillary proliferation was noticed associated with fibrinoid necrosis (Figure 1). The picture was considered as pyogenic necrotizing sialadenitis associated with giant cell reaction to contrast material. She was subsequently referred to our centre, 4 weeks after the onset of enlargement of the submandibular glands.

At admission, she complained of general malaise, anorexia and dysphagia for swallowing. Physical examination disclosed a firm painful left submandibular gland, bilateral episcleritis and swollen eyelids.

The erythrocyte sedimentation rate was 140 mm/hour, the haemoglobin value was 112 g/dl, the leucocyte count $14.1 \times 10^9/l$ (81% polymorphonuclears), the platelet count was $404 \times 10^9/l$. Serum creatinine was normal as well as amino-transferase values, creatine kinase and lactic dehydrogenase. Alkaline phosphatase and gammaglutamyltranspeptidase was elevated, 326 IU/l (normal to 130) and 92 IU/l (normal to 28), respectively. Urinalysis revealed erythrocyturia with morphologically abnormal erythrocytes but no proteinuria. Angiotensin converting enzyme value was normal, anti-nuclear antibody and anti-neutrophil cytoplasmic antibody (ANCA) tests were negative.

Chest X-ray was normal but sinus films showed signs of bilateral maxillar and ethmoidal sinusitis. There were no signs of bony destruction on computed tomography of the sinuses.

Examination showed an inflamed nose mucosa, and nasal mucosa biopsy revealed an intense

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Figure 1 Submandibular gland biopsy. (A) Inflammatory infiltrate with many multi-nucleated giant cells. (B) Vessel wall, infiltrated by polymorphonuclear leucocytes and surrounded by epithelioid histiocytes, polymorphonuclear leucocytes and lymphocytes. (Haematoxylin & eosin $\times 250$).

inflammation with microabscesses surrounded by lymphoplasmacytes and epithelioid-like cells but no vasculitis. Wegener's disease was suggested but the negative anti-neutrophil cytoplasmic antibody test and the extensive necrotizing purulent inflammation of the salivary glands were considered as arguments against the diagnosis. Renal biopsy showed focal necrotizing glomerulonephritis and a second ANCA test performed 14 days after referral to our institution was positive (c-ANCA, titre 1/64).

The diagnosis of Wegener's disease was made and treatment with corticosteroids and cyclophosphamide resulted in gradual regression of the signs of inflammation and the enlargement of the left submandibular gland.

Discussion

Wegener's disease is a systemic inflammatory disease and hence can affect almost any organ system. Ear, nose and throat symptoms are very common but salivary gland involvement is rarely reported.⁴ We could trace 16 cases of salivary gland involvement in Wegener's granulomatosis reported since 1960 and seven of which had involvement of the submandibular gland.^{3,5–12}

The rarity of salivary gland involvement in Wegener's granulomatosis is further demonstrated

by the prospective clinical and therapeutic study of Fauci, describing 85 patients with Wegener's granulomatosis followed over a 21 year period at the National Institutes of Health in the USA. Only one of these patients showed involvement of the parotid gland.¹ In the recent update of their experience these authors describe biopsy-proven involvement of the parotid gland in less than 1% of 158 patients.² A histopathological study from the same institute reporting on 126 head and neck biopsy specimens of 70 patients with Wegener's disease describes acute or chronic vascular changes, necrosis, microabscesses and poorly formed granulomas in salivary gland biopsies of three of the 70 patients.⁵ Salivary gland abnormalities were not discussed in a study emphasizing the ear, nose and throat symptoms in 22 patients.⁴

Salivary gland involvement seems to be an early feature of Wegener's disease which probably explains the sparing of the kidneys found in a number of these cases.³ Our case study also underlines the value of repeated anti-neutrophil cytoplasmic antibody testing with suspicion of Wegener's disease.¹³

Inflammatory conditions of the salivary glands encompass infections – viral, such as mumps, bacterial and chronic granulomatous diseases such as tuberculosis, actinomycosis, syphilis and others – in addition to noninfective inflammatory diseases. In this latter group Sjögren's syndrome

and sarcoidosis are by far the most common.¹⁴ Recent reports and our case emphasize the importance of Wegener's disease as a cause of salivary gland involvement particularly in a context of multi-system disease. The histopathologic findings are diffuse necrotizing inflammation with abscess formation in addition to granulomatous features such as giant cells and aggregates of lymphocytes and epithelioid cells. Vasculitis may also be seen. The vasculitis is described as necrotizing or granulomatous without many further details.^{3,7} Although these findings are not specific for Wegener's disease, knowledge of this picture should suggest the diagnosis in case of suspected multi-system disease and particularly when accompanied by involvement of the upper or lower respiratory tracts and the kidneys as in our case.¹⁷

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The differential diagnosis of granulomatous sialadenitis is shown in Table I.

Table I Causes of granulomatous sialadenitis

Granulomatous reaction to extravasation of mucus due to obstruction by calculi or tumour ¹⁵
Sarcoidosis
Infections (mycobacterial, toxoplasmosis tularemia, cat scratch disease, actinomycosis, fungi, syphilis)
Inflammatory diseases (Wegener's disease, Crohn's disease)
Foreign body granulomas due to sialographic contrast medium ^{15,16}

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