Wegener's Granulomatosis and the Salivary Glands

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Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosisis, is a form of vasculitis that affects small and medium-sized vessels in various organs. In 1990, the American College of Rheumatology established classification criteria for Wegener's syndrome [1]. These criteria were not intended for diagnosis but for inclusion in randomized controlled trials. They included nasal or oral inflammation (painful or painless oral ulcers, or purulent or bloody nasal discharge); pathological changes in the lungs (abnormal chest X-ray with nodules, infiltrates or cavities); abnormalities in the kidneys (urinary sediment with microhematuria or red cell casts); and specific biopsy: granulomatous inflammation within the arterial wall or in the perivascular area. The salivary glands were not mentioned. In 1994, the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis established the diagnosis of WG, which was described as a granulomatous inflammation involving the respiratory tract and a vasculitis of small to medium-size vessels [2]. Again, the salivary glands were not mentioned. The current generally accepted description states that WG mainly affects blood vessels in the nose, sinuses, ears, lungs and kidneys [3]. Once again, the salivary glands are ignored.

Nevertheless, the salivary glands must be taken into account. It is correct that while ear, nose and throat symptoms are part of the upper respiratory tract manifestations in GPA/WG, salivary gland involvement has been rarely documented. But WG does not start in all the target organs at the same time. More often, the kidneys, the sinuses or the lungs are affected first and present enough symptoms for the correct diagnosis. When the diagnosis of WG is established, the treatment is administered and other organs might not be involved. But I suggest that if a patient with WG does not receive the proper treatment, the salivary glands would be the next target of the disease in many more cases. Why?

It brings us to the pathophysiology of the disease. It is now generally accepted that the antineutrophil cytoplasmic antibodies are responsible for the inflammation in WG [4]. In vitro studies have found that ANCAs can activate neutrophils, increase their adherence to the endothelium of blood vessels, and induce their degranulation which can damage endothelial cells. In theory, this phenomenon could cause extensive damage to the vessel wall, particularly of arterioles. But the WG is defined as a vasculitis. The arterioles are everywhere in the body but the frequent target organs are few: the nasal cavity, the sinuses, the lungs, the kidneys, the spleen, and the salivary glands. The brain and the muscles are very rare targets of the disease, for example. Wegener himself, who reported three cases briefly in 1937 [5] and in detail in 1939, postulated that they represented a pathological entity separable by the nature of the tissue reaction from the more usual forms of polyarteritis nodosa. He was impressed by the predominance in his cases of nasal and paranasal lesions and accordingly named the condition "rhinogenous granulomatosis." Inflammation with granuloma formation against a non-specific inflammatory background is the classical tissue abnormality in all organs affected by GPA/WG [4].

What do all the WG target organs have in common? They all have a significant amount of epithelial cells neighboring the endothelial cells that are the primary target of the WG. In renal glomerulus, for example, epithelium, basement membrane, endothelium and intercapillary cells are the main interacting components. In the salivary glands, endothelial cells interact chemically with ductal, acinar and serous cells [6]. Three major families of integral membrane proteins – namely, claudins, occludin, and junctional adhesion molecules – as well as the cytosolic protein zonula occludens can be expressed in all of them. Tubular epithelial architecture of the salivary glands depends on paracrine interactions via endothelium [7]. In the salivary glands, lipoxins are formed by leukocytes during cell-cell interactions with epithelial or endothelial cells. Cell adhesion molecules enhance lymphocyte binding to both the vascular endothelium and salivary epithelium [8]. These findings were reported in connection with the pathogenesis of Sjögren's syndrome, but the similar endothelium-epithelium interactions might be important in our understanding of how the inflammation of the endothelium becomes the inflammation of the whole gland.

Unfortunately, the salivary gland symptoms of the GPA/WG are non-specific and careful differential diagnosis is of paramount importance. Bacterial, viral, fungal, chlamydial and helminthic infections; rheumatoid arthritis, temporal arteritis, Sjogren's syndrome, sarcoidosis,

WG = Wegener's granulomatosis

GPA = granulomatosis with polyangiitis
ANCA = antineutrophil cytoplasmic antibodies

and malignancies should be taken into account. Fever, swelling of the gland and intractable pain are the usual symptoms. In most cases, the biopsy finding of necrotizing granuloma helps to establish the correct diagnosis [9]. The treatment is also non-specific.

What is intriguing, however, is that the parotid gland is a frequent target organ for the GPA/WG while the submandibular gland involvement is extremely rare. We might recall here that the salivary glands have a high blood flow. The facial artery enters the submandibular and sublingual glands along with the main ducts and nerves, thereby creating a hilum, although this hilum is not as clearly defined as in another WG target organ, the kidney. In contrast with the submandibular, the parotid gland – being mainly irrigated by the external carotid artery via the posterior auricular artery and the transverse facial – has no main supply route and depends on smaller arterioles and capillaries that give WG more room to express itself. In fact, parotitis can be the initial syndrome and the first indication of the developing WG.

In this issue of *IMAJ*, there are two articles on the subject that prove this point [10,11]. The authors' reports and analysis are equally important for specialists in oral and maxillofacial surgery, for ENT head and neck surgeons, and for specialists in rheumatology. These reports are very practical. If practitioners have more knowledge about possible WG development in the parotid gland, their swift response might minimize necrosis of the affected gland.

Within the glands, the vessels follow the subdivision of the secretory duct tree so that each lobule has a distinct and separate blood supply. Actually, only in cells where there is blood passage can there be saliva formation. The direction of the blood flow is countercurrent to the direction of the salivary flow. In the salivary glands, vascular changes attracted attention in cases of the rheumatoid vasculitis, the Sjögren's syndrome, and some other disorders [12]. In fact, any kind of vasculitis can affect salivary secretion severely and can damage the whole gland.

While salivary gland involvement in the WG is not yet well researched, some other salivary pathologies can contribute to WG. In fact, atypical endothelial cells were found in cases of angiosarcoma and adenoid cystic carcinoma of the parotid gland [13,14]. In Sjögren's syndrome, the relationship between clinical symptoms and the grade of histopathological damage is connected with vascular cell adhesion molecules in the endothelial cells [15]. Finally, the regulation of salivary gland function by autonomic nerves also involves endothelium. Non-adrenergic, non-cholinergic neuropeptides released from autonomic nerves evoke salivary gland secretion and parasympathetically derived vasointestinal peptide, acting through endothelial cell-derived nitric oxide [16]. All these facts could contribute to our understanding of salivary gland involvement in WG as well as our understanding of the pathophysiology of WG itself in other target organs where endothelium and epithelium closely coexist.

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"There may be times when we are powerless to prevent injustice, but there must never be a time when we fail to protest"

Elie Wiesel (born 1928), Romanian-born Jewish-American writer, professor, political activist, Nobel Laureate, and Holocaust survivor

"A man never stands as tall as when he kneels to help a child"

Anonymous