Editorial

The importance of studying the parotid glands in primary Sjögren's syndrome: the right tissue at the right time

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Introduction

The study of the parotid glands in primary Sjögren's syndrome (pSS) has gained importance and become the subject of intense debate in recent years. Two main factors can explain this. First, in pSS, the parotid is a target tissue where autoimmune-related lymphoid expansion results in mucosa-associated lymphoid tissue (MALT) acquisition (1-4) and is a major predictor of non-Hodgkin lymphoma (NHL) (5-7). Second, assessment of the parotids is now much more feasible, either indirectly by salivary gland ultrasonography (SGUS) (8-13) or directly by tissue biopsy (14-19). Both of these tools are likely to be more widely used in the years ahead. Independently, translational studies of the affected target tissue, and innovative treatments including the identification of treatment response, were developed. As such, pSS offers unique opportunities to monitor autoimmunity in the target tissue, *i.e.* "the right tissue at the right time". The implications for clinical practice and research are of outmost importance.

Parotid involvement in the clinical history of pSS

Historically, clinical, histological and molecular studies have indicated that parotid glandular swelling (PSW) in pSS is usually persistent and is associated with local inflammation and expansion of certain B-cell clones, both in pre-lymphomatous and lymphomatous parotid lesions (1, 20, 3, 21-25). Conversely, in other diseases, PSW is linked to local infection, which, if controlled physiologically or pharmacologically, is usually associated with a more rapid resolution of the swelling. PSW not associated with pSS can also be attributed to malformations, malignancies, obstructions or mixed causes (26). Notably, clinical data indicate that pathogenic events leading to pSS and lymphoma in predisposed individuals may occur within the parotid glands, even in the very early clinical stages of pSS. A recent study of the parotid glands found that they are involved from the very early clinical manifestations of pSS to the final stages of lymphoma (27), and NHL showed usual parotid NHL localisation at onset in the same series, consistent with prior reports (28, 29). This large multicentre case-control cohort (27) has demonstrated the need for much greater precision in the clinical assessment of PSW, one of the two key predictors of lymphoma in pSS (the other being mixed cryoglobulinaemia) (5, 30). In particular, patients frequently reported that they had noticed PSW well before their pSS diagnoses, and the occurrence also of such very early PSW was significantly higher in pSS-related NHL patients compared to pSS controls who did not develop lymphoma. Interestingly, this NHL risk was also related with the duration of PSW (2-12 months or ≥12 months), while transient PSW (<2 months) was not associated with a significantly increased lymphoma risk (27). These findings highlight the importance of evaluating PSW much more precisely then currently done in pSS, possibly also by ultrasound, and histological assessment of the parotid tissue when indicated. In addition to NHL localised in the parotid glands ab initio, pSS-related MALT lymphoma may arise at other sites, although much more rarely. It should be noted that in pSS, NHLs of the gastric mucosa and of the lung, the next most common sites to the parotids in most series, may be sustained by the same B-cell clone previously documented within the parotid glands of a given patient, this clone having been

subjected to local antigen stimulation in the parotid (31, 32). The non-parotid MALT NHLs may therefore be related to parotid lymphoproliferation in pSS. The frequency of this phenomenon is unknown, however.

In contrast to the parotids, the minor salivary glands (MSGs) appear to be extremely rarely affected by swelling, and they are typically not the primary localisation of NHL in pSS. To avoid invasive biopsies in certain patients, asymptomatic lymphoma localisation may indeed be assessed in the MSGs in pSS; however, although available data are very limited, the sensitivity of this procedure appears quite low (33). Lymphoma dissemination in MSGs from another site (*e.g.* the parotids themselves) is likely to occur (34). Additional studies are in any case required to address this interesting topic.

Previous biological and molecular data have established that the parotid glands are a key site of B-cell expansion in pSS. In this context, histological evaluations of pSS cases have indicated that germinal centre (GC)-containing lip biopsies have increased a NHL risk in most though not all studies (35, 36), that GCs are well represented in parotid biopsies (14, 15), and that same may occur as regards lymphopepithelial lesions (15, 27); this has pathogenic as well as potential clinical implications. Overall, more studies of the parotids should begin as soon as possible in pSS. Studies among undifferentiated/suspect pSS cases with PSW, and potential pre-clinical pSS, have been planned within the pSS ESSENTIAL/EULAR Group.

Infection within the parotid microenvironment

Infection of the local microenvironment is considered a key pathogenic event in MALT lymphomas; the infectious triggers in pSS-related lymphomagenesis and how they interact with autoimmune epitheliitis remain to be determined, and both autoimmune tissue involvement and B-cell expansion are linked and characterise pSS (1-3). Notably, the eradication of local infectious triggers of lymphoproliferation, such as *H. pylori* in the gastric mucosa, has proven clinically effective for the regression of low-grade MALT lymphomas (37). In addition, the T-cell compartment, and not the lymphomatous B-cell component, has been reported to be antigen-stimulated by infectious local triggers, such as *H. pylori* in the stomach, and to promote lymphoma progression. B-cell proliferation is here antigen-driven, and seemingly autoreactive (37), as in the case of parotid prelymphomatous and lymphomatous lesions in pSS (3, 25). Overall, pSS-related B-cell lymphoproliferation, usually localised in the parotid microenvironment, shares relevant biologic characteristics with pSS-unrelated lymphomas of MALT, although potential infectious agents have not been identified in pSS (37-40). Interestingly, among the different salivary glands, the parotids display the most infection and inflammation; sialolitiasis prevails in the submandibular glands, while ranula and mucocele characterise the sublingual and minor salivary glands, respectively. The parotids produce lower salivary flow at baseline and less mucinous saliva, both of which may predispose them to infection (41).

Human "model diseases"

Besides animal models, some human "model diseases" may support the study of the parotid-associated infection and lymphoproliferation of MALT in pSS. In one such disease, hepatitis C virus (HCV) infection, the infectious agent is sialotropic; in addition, it often induces a mild oral and ocular sicca syndrome in the absence of overt pSS, may be associated with pSS itself and is significantly associated with lymphoma development in the liver and in the parotid glands themselves (42, 43). Notably, HCV-related lymphomas may significantly benefit from HCV antiviral therapy (44). Recurrent juvenile parotitis, another potential "model disease", usually resolves after years of short-term episodes of PSW and is not followed by lymphoma, despite recurrent parotid inflammation and likely infection (41). Adult recurrent parotitis is infrequent. In rare cases, juvenile or adult pSS may follow after juvenile or adult recurrent parotitis (45), representing a further subset of interest to be characterised. Another very important model is juvenile pSS, where PSW is much more common than in adult pSS and where a higher prevalence of fever is observed (46, 47), but where lymphoma evolution seems much rarer than in adults (48, 49). On the other hand, very little is known about the long-term follow-up of juvenile pSS or about the subset of adult pSS following juvenile pSS, and further investigation of this topic is warranted.

Finally, recurrent PSW soon after vaccination with live attenuated and sialotropic rubella paramyxovirus, followed by pSS, has been observed (50), again suggesting the possible pathogenic role of initial parotid infection in pSS. Indeed, mumps, together with juvenile recurrent parotitis, are the two most common causes of PSW in paediatric sialadenitis, and viral antigens elicit augmented immune responses in pSS (51).

Feasibility of studying the parotid glands in pSS

Improvements in SGUS and parotid biopsy, either surgical (52) or SGUS-targeted with core needle biopsy (CNB) (16, 18), are the most compelling developments supporting a more intensive investigation of the parotid glands in pSS.

The importance of SGUS and its main alteration in pSS, parenchymal inhomogeneity by ultrasound, was asserted 30 years ago (8); however, scarce attention was given for a long time to this diagnostic tool, which is still not included in pSS classification criteria and is still the object of reliability and accuracy studies (53). Recent data demonstrate the clinical value of SGUS and its remarkable intra- and inter-rater reliability among sonographers (13). The OMERACT (9) and EULAR ESSENTIAL working groups, as well as the HARMONICss pSS project (54), also significantly contributed to SGUS developments in pSS, and the application of artificial intelligence to the automatic detection and scoring of glands is now feasible (13). Glandular studies on sonoelastography and hypervascularization might be of value (55, 56).

As a second point, the availability of parotid tissue, *i.e.* of the target tissue to better investigate the etiopathogenesis of pSS-associated autoimmune epithelitis, emergence of MALT, and lymphomagenesis, allows crucial insights in the aetiopathogenesis and possibly in the diagnosis of pSS, as well as of related NHL/NHL risk. Few groups regularly employ parotid biopsy in the management of pSS. One such team, at the University of Groningen, The Netherlands (15, 52), has made great strides in the use of open surgical biopsy to study parotid histopathology. They have shown that open biopsy of the parotid gland is a relatively simple technique with no permanent morbidity reported.

Our group has also been employing parotid biopsy for a long time in pSS, mainly in patients with PSW (3). Recently, we proposed the use of ultrasound-guided CNB (US-guided CNB) of the parotid gland for the diagnosis of glandular lymphoma in this subset of pSS with PSW. We demonstrated that US-guided CNB can provide adequate sampling for histological examination, immunohistochemical staining and flow cytometry (16, 18). In the case of PSW, this procedure can be safely performed in the posterocaudal part of the gland, in a safe zone where facial nerve injuries are avoided. Additional investigation with promising results on the accuracy and safety of US-guided CNB, parotid or submandibular, and in the parotid "safe zone", *i.e.* also independently from the presence of PSW, are now completed by our group (16, 18). The correct disease diagnosis, the relevance and the choice of SGUS glandular areas in disease follow-up, and the analysis in detail of SGUS focal and diffuse areas, with particular reference to lymphoma and its risk, have been planned in larger and multicentric cohorts. It is also of great interest to investigate how SGUS and parotid biopsy may complement each other, as well as how they will provide precise answers relevant to pSS diagnosis and prognosis. In our opinion, these methods will likely contribute to improving clinical assistance and research dedicated to pSS patients.

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