

Correspondence between minor salivary glands ultra-high frequency ultrasonography and histology: a case report of severe/atypical lymphoid infiltrate in Sjögren's syndrome

Sirs,

Sjögren's syndrome (SS) is a multifactorial systemic autoimmune disease of unknown aetiology characterised by lymphocytic infiltration of the exocrine glands and a wide range of different clinical manifestations (1). The spectrum of lymphoproliferation extends from an increased frequency of circulating monoclonal immunoglobulins to an increased frequency of salivary glands non-Hodgkin's lymphoma (NHL) (2). The purpose of the present case report is to describe the potential usefulness of ultra-high frequency ultrasonography (UHFUS) to differentiate benign inflammatory infiltrate from severe/atypical infiltrate lesion in minor salivary glands of SS patient undergoing ultra-high frequency ultrasonography (UHFUS)-guided lip biopsy.

A 58-year-old female, previously in good health and with negative family history for autoimmune disease, was admitted to our outpatient Rheumatology Unit due to worsening xerostomia and xerophthalmia. She also presented right parotid salivary gland enlargement. There were no complaints of "B" symptoms or a poor performance status, no history of other symptoms related to SS and the patient was otherwise in good health. On physical examination, signs of severe xerostomia (oral mucosal dryness, angular cheilitis), moderate xerophthalmia (serious keratoconjunctivitis, blepharitis) and limited swelling of the right parotid

gland were detected. Blood tests showed normal value of CRP 0.17 mg/dL (n.v. <0.5 mg/dL) and increased values of ESR (74 mm/h), gamma globulins 32.6 % (n.v. <18%) and β -2 microglobulin 3600 μ g/L (n.v. 200-2000 μ g/L.) On immunofixation IgG kappa M-protein was identified whereas complements levels and blood cell count were normal. Immunological tests displayed high titre positivity of anti-Ro52, anti-Ro60, anti-La/SSB and rheumatoid factor 126 U/mL (n.v. <15 U/mL). The cryoglobulins test was negative. Ophthalmological assessment revealed a positive Schirmer's test (3 mm right eye, 2 mm left eye; n.v. >5mm) with a normal break up time. Major salivary glands ultrasonography showed multiple hypoechoic areas in submandibular and parotid glands (OMERACT score 3) though focal lesions were excluded. To fulfil diagnostic work-up, lip biopsy of minor salivary gland was performed. Ultra-high frequency ultrasonography (UHFUS), equipped with a 70 MHz probe, was used to locate the labial salivary glands biopsy, scanning both left and right peripheral compartments. Notably, in each compartments ultrasonography of minor salivary glands showed an unusual and distinctive pattern: very hypoechoic areas and hyperechoic septa (Fig. 1 A-B) with high perilesional Doppler (Fig. 1 D-E). Biopsy was then performed in the right compartment with the worst ultrasonographic features, no external changes of the lip were identified. Minor salivary gland histology revealed multiple lymphoid aggregates of variable sizes, sometimes confluent and replacing glandular parenchyma, mainly constituted by B-lymphocyte (CD20+). A diffuse plasma cells (CD138+, CD20-) infiltrate (composed by elements polytypical at immunohistochemical staining for immuno-

globulin light chains κ and λ) was also detected within collateral and surrounding parenchyma (*i.e.* mucous acini and ducts). Biopsy was consistent with atypical lymphoid infiltrate of undetermined significance of minor salivary glands (Fig. 2 A-H).

In patients with SS, major salivary glands NHL, especially mucosa-associated lymphoid tissue (MALT) lymphoma, is a relatively frequent complication. In fact, SS patients have a 16-times higher risk of developing NHL compared to the normal population (3). In contrast, in SS patients, NHL affecting minor salivary glands are extremely rare localisation, with only few dozen documented cases reported in literature (4). However, performing labial salivary gland biopsies as a routine part of SS diagnostic work-up, may lead in some instances to early diagnosis of labial salivary gland NHL in asymptomatic patients. In a recent study by Parreau *et al.* (5) a diagnosis of minor salivary glands NHL was reported in 13 SS patients; in 10 out of them (76.9%) labial salivary glands were the only site enabling NHL diagnosis. In major salivary glands ultrasonography is currently used to identify suspicious lymphoproliferative lesions and to perform a US-guided biopsy (6). Recently, a growing interest has arisen in last generation UHFUS that, with a resolution up to 30 μ m, allows minor salivary glands visualisation (7, 8). Ferro *et al.* (9) have recently found that minor salivary gland UHFUS inhomogeneity was significantly higher in patients with SS than in no-SS subjects. In our patient UHFUS suspicious findings were represented by very hypoechoic areas, presence of septa, perilesional Colour-Doppler vascularisation (Fig. 1 A-B, D-E). These features are generally not detectable in benign inflammatory SS

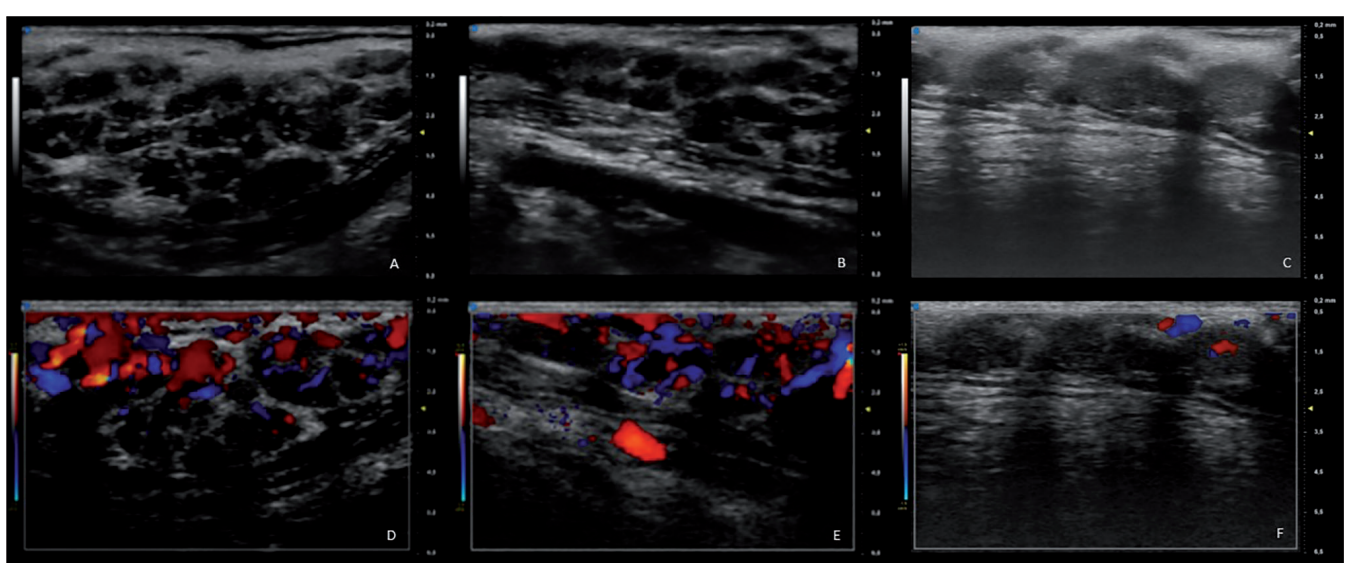


Fig. 1. Minor salivary glands, right (A) and left (B) compartment, UHFUS grey scale showing very hypoechoic areas surrounded by hyperechoic septa; C) Minor salivary glands, left compartment, UHFUS grey scale showing normal appearance of minor salivary gland with normal echostructure; minor salivary glands, right (D) and left (E) compartment, UHFUS Colour Doppler showing high perilesional vascularisation; F) minor salivary glands, left compartment, UHFUS Colour Doppler showing normal vascularisation.

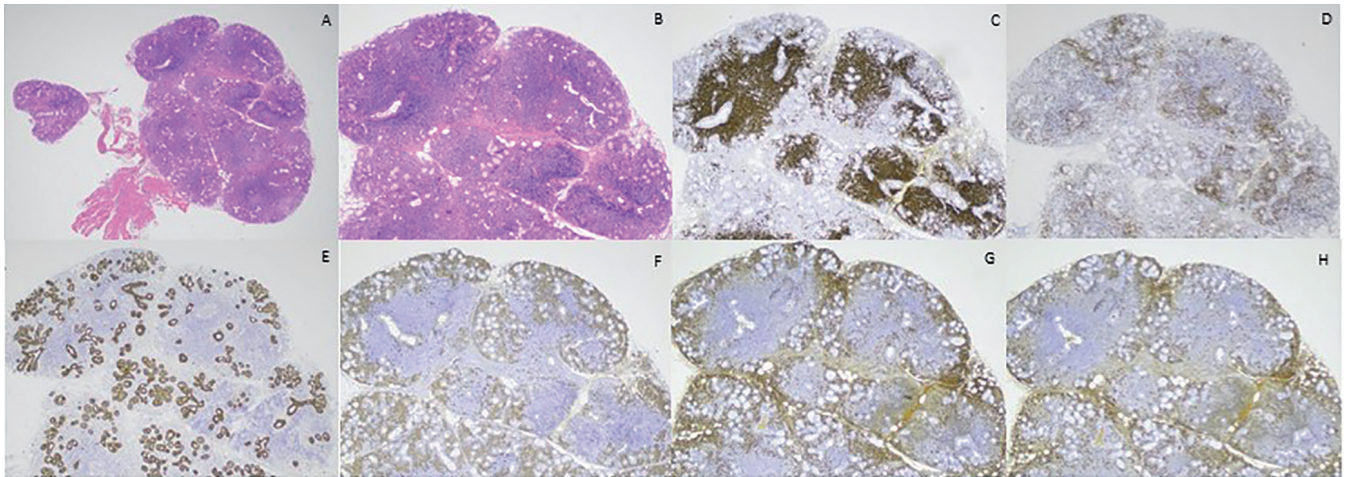


Fig. 2. Minor salivary gland biopsy, haematoxylin and eosin at 20x (A) and 40X (B) magnification; C) immunohistochemical staining for CD20 highlighting multiple and large aggregates of B-lymphocytes partly replacing glandular tissue (40x magnification); D) immunohistochemical staining for CD3 showing a smaller amount of T-lymphocytes in the lymphoid aggregates (40x magnification); E) immunohistochemical staining for pan-CK showing the epithelial component (40x magnification); F) immunohistochemical staining for CD138 displaying collateral diffuse plasma cell infiltrate, composed by elements polytypical at immunohistochemical staining for immunoglobulin light chains κ (G) and λ (H) (40x magnification).

lesions (Fig. 1 C, F) and closely resemble those recently described by Lorenzon M *et al.* (6) in major salivary glands NHL. Remarkably, we found strong correlations between radiological and histological findings suggestive for severe/atypical lymphoid infiltrate: UHFUS multiple hypoechoic areas, separated by hyperechoic septa, might be consistent with “atypical” CD20+ lymphoid aggregates. In conclusion, UHFUS may help to guide minor salivary gland biopsies in the most suspicious site of lip compartment and could be a promising non-invasive tool to accurately identify SS patients with an infiltrate severe or suspected of NHL, thus improving patients’ stratification and prognostic assessment.

G. FULVIO¹, MD
 V. DONATI², MD
 R. IZZETTI³, PhD
 S. FONZETTI¹, MD
 G. LA ROCCA¹, MD
 F. FERRO¹, MD
 C. BALDINI¹, MD PhD

¹Rheumatology Unit, University of Pisa;
²Unit of Pathological Anatomy 2, Azienda Ospedaliero-Universitaria Pisana, Pisa;
³Dentistry and Oral Surgery, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy.

Please address correspondence to:
 Giovanni Fulvio,
 U.O. di Reumatologia,
 Dipartimento di Medicina Clinica e Sperimentale,
 Università di Pisa,
 Via Roma 67,
 56126 Pisa, Italy.
 E-mail: giovanni.fulvio92@gmail.com

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