Letter to the Editor

The diagnostic insights of immunoglobin G4-related Mikulicz disease: a case description and literature analysis

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Introduction

Mikulicz disease (MD) is a chronic, nonspecific inflammatory disease characterized by bilateral, painless, symmetrical, and persistent swelling of the salivary glands. MD has been considered a subtype of Sjogren syndrome (SS) since Morgan's report in 1953 (1). Both entities, MD and SS, present similar histological and clinical symptoms, and this can lead to misdiagnosis and the implementation of inappropriate therapy (2). Recently, a novel concept for MD as an immunoglobulin G4-related disease (IgG4-RD) was able to demonstrate differentiation capacity between MD and SS (3). MD involves elevated serum levels of lgG4 and infiltration of lgG4 cells in tissues (4). Notably, MD shows good responsiveness to glucocorticoids. Compared with the general population, patients with IgG4-RD appear to have a higher risk of overall cancer, especially pancreatic cancer and lymphoma (5), and thus early identification of MD is important for the treatment strategy and prognosis. However, the diagnosis of MD is challenging because MD is relatively rare, complex, and heterogeneous in terms of clinical symptoms.

Multimode ultrasonic techniques, including high-frequency ultrasound, power Doppler, sonoelastography, and contrast-enhanced ultrasound (CEUS), constitute a readily available, repeatable, noninvasive, versatile modality that can directly assess glandular structure. CEUS can easily and effectively provide an accurate depiction of microvascularity by using microbubble-based contrast agents. CEUS has been used to differentiate autoimmune pancreatitis from pancreatic cancer in IgG4-RD (6). However, to the best of our knowledge, the CEUS features of MD have yet to be characterized. In this paper, we describe a misdiagnosed case of MD and share our diagnostic insights for distinguishing MD from SS, especially via CEUS.

Case presentation

A 51-year-old female patient was admitted to Zhejiang Hospital with bilateral upper palpebral swelling and itchy skin, with a history of dry eyes and mouth, symptoms which had persisted for 3 years. Cranial magnetic resonance imaging (MRI) demonstrated an occupying lesion at the outer superior margin of the right orbit (*Figure 1*). A physical examination showed bilateral swelling of the upper eyelids. There were nodules 2 cm × 1 cm in size in the patient's bilateral upper eyelids, nodules 3 cm × 1 cm in size in the bilateral submandibular glands, and no nodule in the bilateral parotid glands. The patient had previously visited a local hospital due to dryness in her eyes and was diagnosed with xerophthalmia. She received artificial tears for dryness of the eyes and antiallergic agents for swelling and itching of the upper eyelids, which had little effect on the clinical symptoms.

On ultrasound examination of the lacrimal and submandibular glands, diffuse enlargement of the lacrimal and submandibular glands with multiple hypoechoic areas

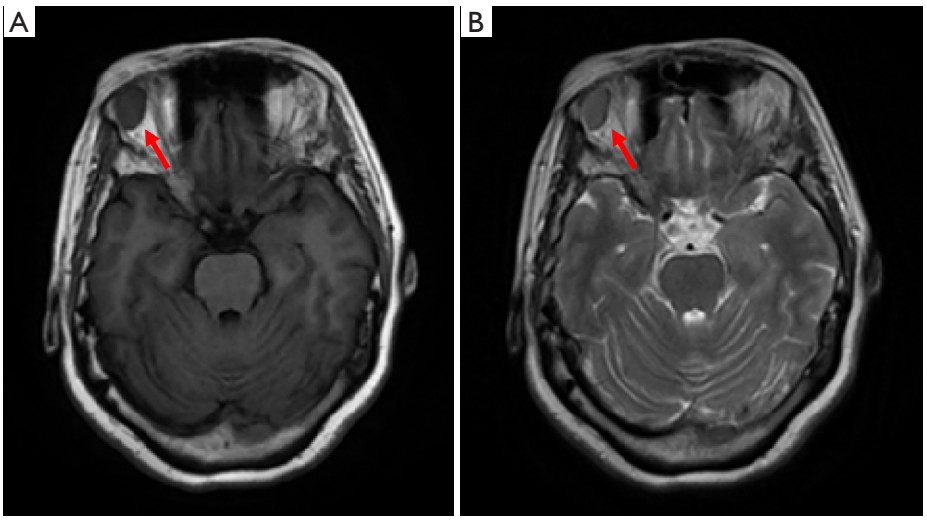


Figure 1 Cranial magnetic resonance imaging. (A) T1-weighted imaging showing hypointensity in the occupying lesion. (B) T2-weighted imaging showing isointensity in the occupying lesion. The red arrows show the lesion at the outer superior margin of right orbit.

was observed. Color Doppler ultrasound showed abundant blood flow in the right lacrimal and left submandibular gland, with resistance indices of 0.57 and 0.66, respectively (*Figures 2*,*3*). According to a scoring system described by Itoh *et al.* (7), in which elastic imaging is used on the basis of routine ultrasound, the stiffness of lesions was slightly higher, and the scores of bilateral lacrimal and submandibular glands were 3 and 4, respectively (*Figure 4*). No abnormalities were found in the parotid gland or superficial lymph nodes throughout the body. The ultrasound examination seemed to indicate a benign condition. Upon considering the combined clinical findings, we strongly suspected SS, after which we conducted the relevant examinations. The Schirmer/fluorescent dye test was positive, but blood samples taken were negative for both SS-A and SS-B antibodies, which excluded SS. To further determine whether lesions were benign or malignant, CEUS examination was performed by an experienced interventional ultrasound physician using a Resona 7 (Mindray Biomedical Electronics, Shenzhen, China) color ultrasonic diagnostic instrument and a superficial probe (5–14 L). The contrast agent used for injection was sulfur hexafluoride microbubbles (SonoVue, Bracco, Italy), which was quickly injected into the elbow and followed by a 5-mL injection of normal saline. Subsequently, the imaging mode was activated to observe the filling process of contrast agent in the tumor, and the images were stored. The contrast agent perfused from the center to the periphery of the lesions, rapidly enhanced, and subsided after reaching the peak; the details perfusion times are displayed in *Figure 5*. The lesions of the lacrimal gland and submandibular gland both showed a "fast-in and fast-out high enhancement" mode (*Figure 5*; *Videos 1*,*2*), which was consistent with the blood perfusion characteristics of malignant tumors.

The conflicting nature of the findings did not permit a definitive diagnosis. After reviewing the literature, IgG4-related MD was considered a possibility, and the IgG4 levels were measured. Additionally, after obtaining written informed consent, we performed ultrasound-guided puncture biopsy on the submandibular glands (*Figure 6*) but not the lacrimal glands, as this may accidentally injure the eyes. Notably, a high serum IgG4 level of >1.35 g/L was observed [total immunoglobulin E (IgE): 216.80 IU/mL↑ (<100 IU/mL); IgG4: 8.54 g/L↑ (<1.35 g/L)]. Results of histopathologic examination included marked diffuse plasma cells and lymphocyte infiltration at low magnification, immunohistochemical IgG4-positive plasma cells >40 at high magnification, slight vascular wall thickening, and no obvious fibrosis (*Figure 7*).

According to the above findings and the latest revised IgG4-RD comprehensive diagnostic criteria from 2020 (8), the final diagnosis was IgG4-related MD.

Treatment

The patient was treated with methylprednisolone at 24 mg/day for 2 weeks, which significantly reduced eyelid swelling and improved the symptoms of itchy skin.

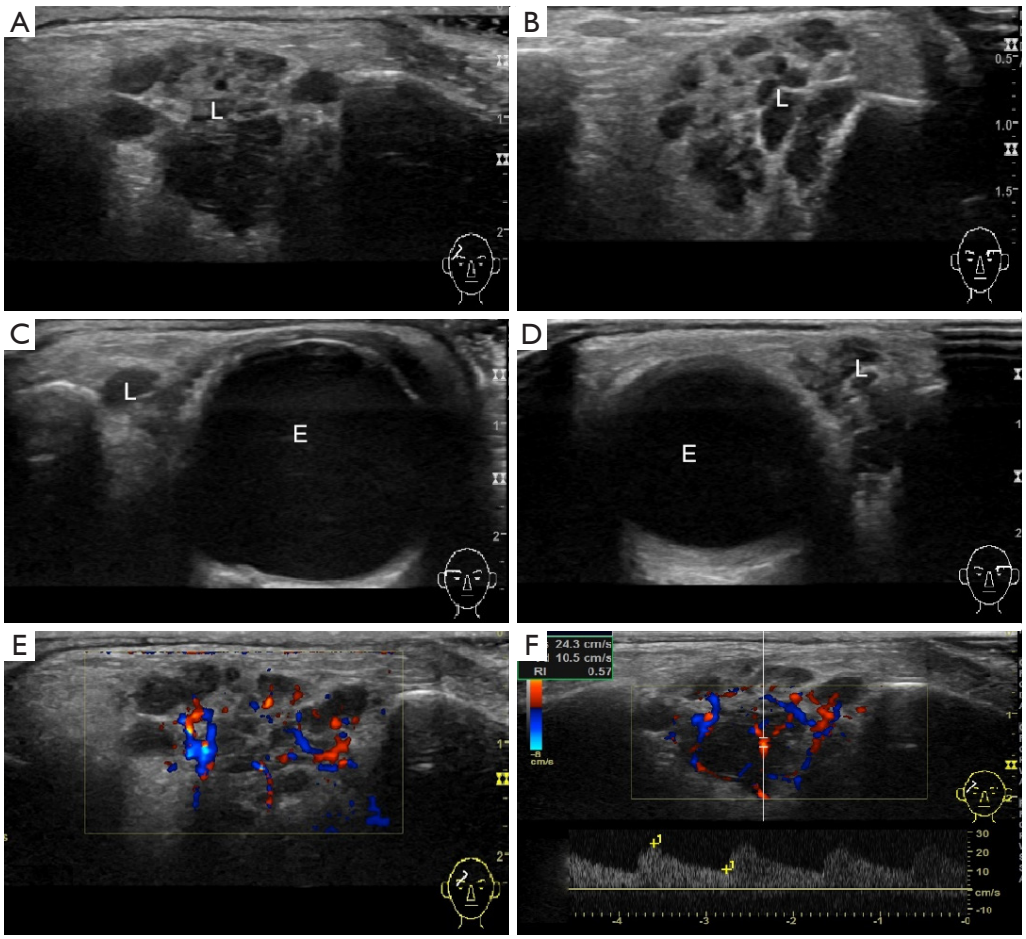


Figure 2 Ultrasound of the lacrimal glands. The right lacrimal gland (A,C) and the left lacrimal gland (B,D) were enlarged with multiple hypoechoic areas (right: 23 mm × 17 mm; left: 19 mm × 15 mm). (E,F) Color Doppler ultrasound showed abundant blood flow in the right lacrimal gland, with a resistance index of around 0.57. E, eyeball; L, lacrimal gland.

Consequently, the dose was decreased to 4 mg/week until it reached 8 mg/day. At the last follow-up visit, the serum IgG4 level had markedly decreased to 2.1 g/L, and the gland sizes had reduced.

All procedures performed in this study were in accordance with the ethical standards of the Medical Ethics Committee of Zhejiang Hospital (No. 2019KY003) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

IgG4-related disease can cause swelling and enlargement of multiple organs or tissues, such as the lacrimal gland, submandibular gland, pancreas, and retroperitoneum, with involvement of the lacrimal and salivary glands being referred to as IgG4-related MD. MD usually occurs in middle-aged or older adult men, but sialadenitis and dacryoadenitis typical to MD are more common in women than in men (2). Its main manifestation is the enlargement of the lesion salivary glands, accompanied by different degrees of eye and oropharyngeal dryness (4), which is quite similar to the clinical manifestation of SS, but with the symptoms of dry eyes and dry mouth in SS being more obvious. Serologically, patients with MD lack anti-SS-A and anti-SS-B antibodies and elevated serum IgG4 concentrations. Biopsy studies of patients with MD revealed infiltration of plasmacytes expressing IgG4 in the lacrimal and salivary glands (3). One of the

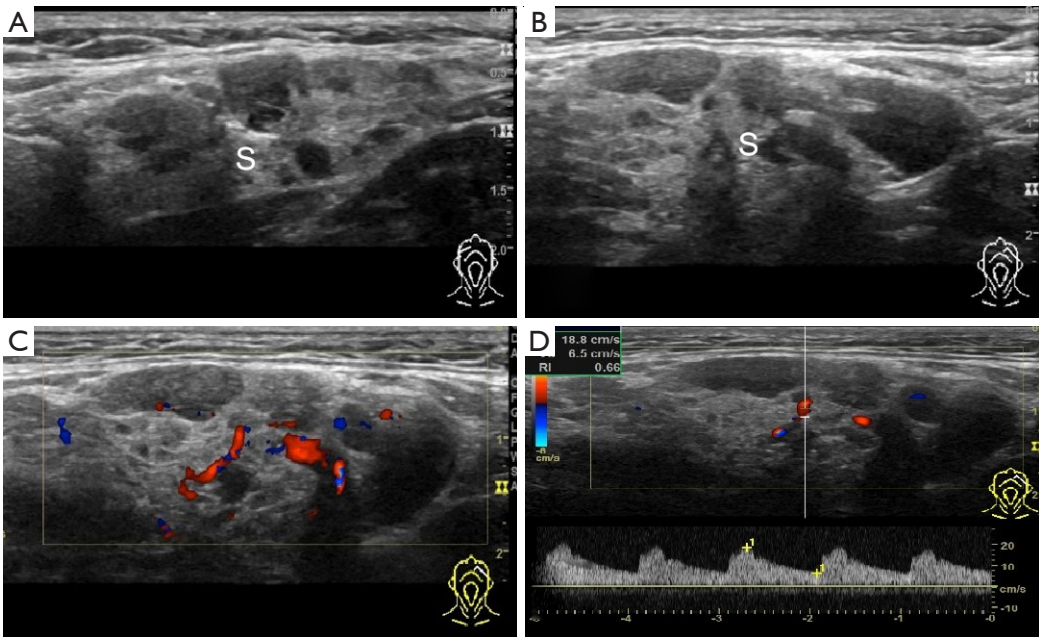


Figure 3 Ultrasound of the submandibular gland. The right submandibular gland (A) and the left submandibular gland (B) were enlarged with multiple hypoechoic areas (right: 35 mm × 12 mm; left: 37 mm × 14 mm). (C,D) Color Doppler ultrasound showed abundant blood flow in the left submandibular gland, with a resistance index of around 0.66. S, submandibular gland.

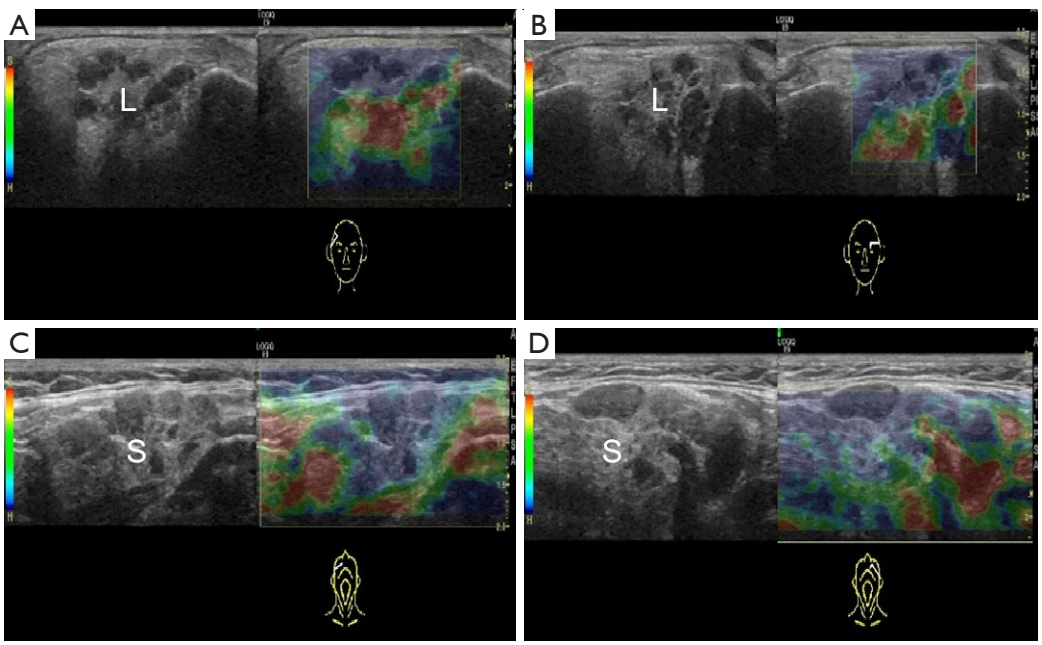


Figure 4 Ultrasonic elastography of the lacrimal and submandibular gland. (A,B) Bilateral lacrimal gland elastic imaging showed similar blue and green lesions, with a score of 3. (C,D) Bilateral submandibular gland elastography showed mostly blue lesions and a little green, with a score of 4. L, lacrimal gland; S, submandibular gland.

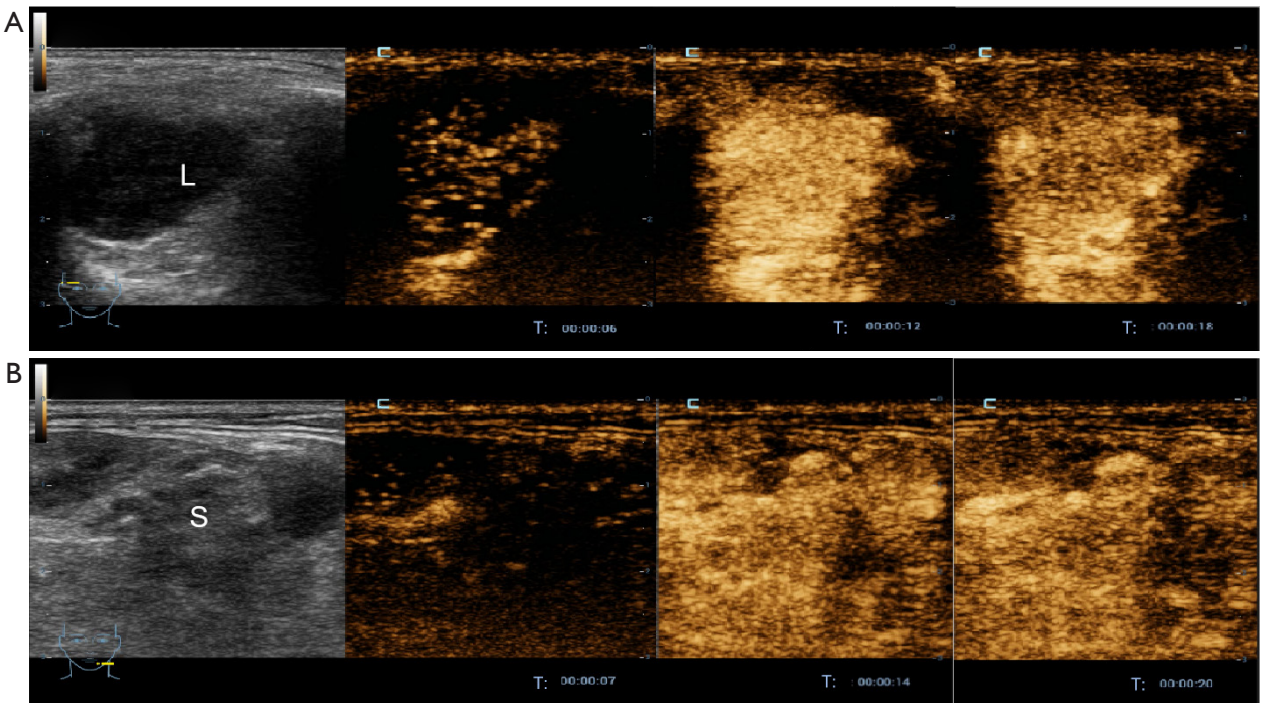
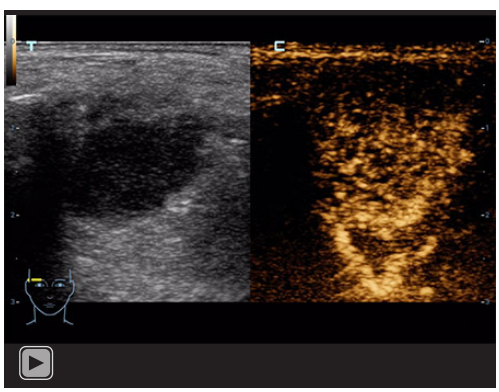
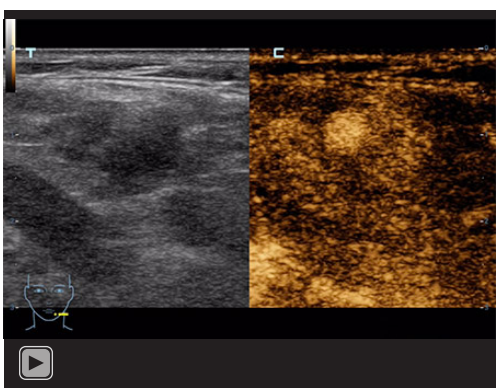


Figure 5 CEUS showed a "fast-in-fast-out-high enhancement" pattern in multiple hypoechoic areas of the right lacrimal land (A) and the left submandibular gland (B). L, lacrimal gland; S, submandibular gland; T, the entry time of contrast agent; CEUS, contrast-enhanced ultrasound examination.



Video 1 Contrast-enhanced ultrasound of the lacrimal gland.



Video 2 Contrast-enhanced ultrasound of the submandibular gland.

most distinct features of MD that differentiates it from SS is its good response to glucocorticoids (9); thus, in this way, MD may differ from SS. However, IgG4-MD is not common, and clinical physicians often miss its diagnosis. The patient in our case received antiallergic agents due to a misdiagnosis. Theoretically, early improvements in the swelling of the lacrimal and submandibular glands can be obtained if glucocorticoid treatment is initiated. In fact, a good responsiveness of the patient to glucocorticoids was observed in the follow-up after a correct diagnosis was made.

In the past, computed tomography (CT) and MRI were the main examination methods for MD. In recent years, it has been found that ultrasonography has high sensitivity

and specificity in the identification of IgG4-RD and SS (10). In high-frequency ultrasound, the salivary gland ultrasound imaging in both SS and MD show significant hypoechoic areas as well as reticular patterns, leading to misdiagnosis. However, more careful observation has revealed that changes in MD mainly affect the submandibular glands, and the appearance of the parotid gland is normal (2). Conversely, SS shows atrophic changes in both the submandibular and parotid glands. More notably, in Doppler mode, MD shows high vascularity in the lymph nodes and a reticular pattern, SS shows small punctate vessels in the parotid gland, which is also a hallmark of MD (11). Additionally, De Lucia *et al.* found that hypoechogenicity and linear hyperechogenicity were characteristic futures of lacrimal glands in SS, and the size and shape of lacrimal glands were similar to those of healthy controls (12). Unlike the features in SS, those in our case included swelling of the bilateral lacrimal glands and no enlargement of the parotid glands. Blood samples taken were negative for both SS-A and SS-B antibodies, which could exclude SS.

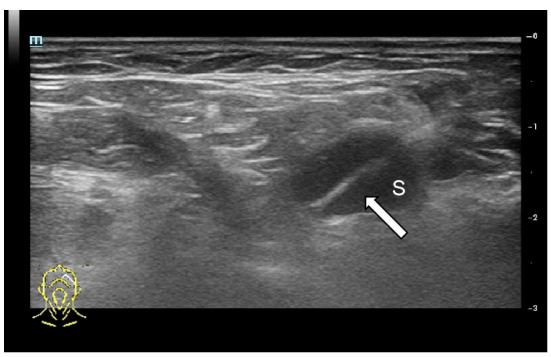


Figure 6 Ultrasound-guided puncture biopsy in the hypoechoic areas of the left submandibular gland. The white arrow indicates puncture needle. S, submandibular gland.

To our knowledge, this is the first case in which CEUS was applied for examining MD. Surprisingly, it showed a "fast-in-fast-out-high enhancement" pattern in the lacrimal and submandibular gland lesions, which was similar to the perfusion characteristics of malignant tumors. CEUS is used to evaluate the microvascularity of lesions in different tissues with an objective angiographic index, eliminating the observer-dependent defect of ultrasound (6). The result in this case indicated that the MD lesion had an abundant blood supply, which was consistent with a previous study (11). We speculate that abundant blood supply and inflammatory cell infiltration leads to an increase in glandular blood flow velocity, which accelerates the entry and disappearance of contrast agent. In a previous study, CEUS of the submandibular gland in patients with primary SS showed a low enhancement pattern (13), whereas this case of MD showed a "fast-in-fast-out-high enhancement" pattern. This finding can to distinguish IgG4-MD from SS in CEUS; however, the sample size for the application of CEUS in IgG4-MD and SS was small and could not exclude occasionality. A larger sample size and prolonged follow-up should be taken into account in the future. In addition, the CEUS presentation of orbital occupying lesions is "fast-in and fast-out" and should not be limited to malignant tumors such as orbital lymphoma (14), and the possibility of inflammatory lesions should also be considered. In one case report, a patient with bilateral ophthalmic IgG4-RD had mucosa-associated lymphoid tissue lymphoma (15), but the association between ophthalmic IgG4-RD and ocular IgG4 mucosa-assisted lymphoid tissue (MALT) lymphomas

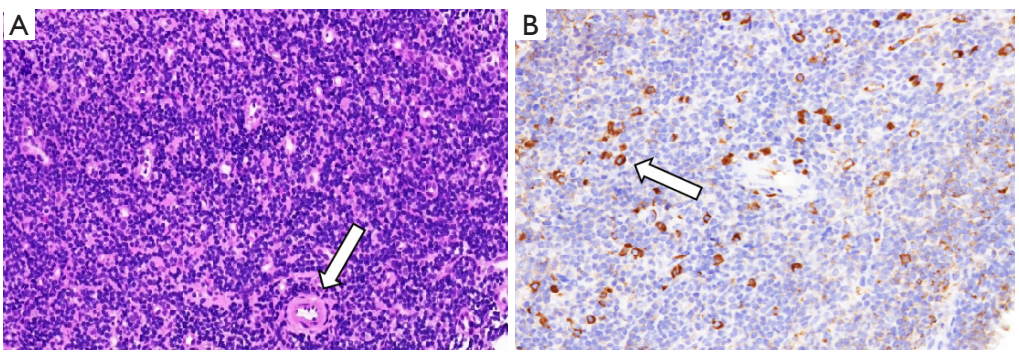


Figure 7 Histopathological findings of submandibular gland biopsy. (A) Hematoxylin and eosin staining (200×) showed a massive infiltration of lymphocytes and plasma cells, slight vascular wall thickening (white arrow), and no obvious fibrosis. (B) IgG4 immunostaining (400×) showed IgG4 plasma cell (white arrow) >40 cells/HPF. IgG4, immunoglobin G4; HPF, high-power field.

remains uncertain. Therefore, changes in the patient's condition must be closely monitored in follow-up.

Conclusions

This report describes a case of misdiagnosing MD, exemplifying the challenges of high-frequency ultrasound in discriminating MD from SS. However, our experience in this case suggests that CEUS may be expected to provide a new means of diagnosis for these diseases in future clinical decision-making.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-563/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Medical Ethics Committee of Zhejiang Hospital (No. 2019KY003) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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