Review
Clinicopathological characteristics of Mikulicz’s disease and Küttner’s tumor

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Abstract: Mikulicz's disease (MD) has been considered part of primary Sjögren's syndrome (SS) since Morgan's report in 1953. However, MD shows a unique condition involving persistent swelling of the lachrymal and salivary glands characterized by good responsiveness to glucocorticoids, leading to the recovery of gland function. Recently, it has been revealed that MD patients show elevated serum immunoglobulin G4 (IgG4) concentrations and prominent infiltration of IgG4-positive plasma cells. The complications of MD include autoimmune pancreatitis, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis, and Riedel's thyroiditis, all of which show IgG4 involvement in their pathogenesis. Thus, MD is a systemic IgG4-plasmacytic disease. On the other hand, Küttner's tumor (KT) is chronic sclerosing sialadenitis that presents with asymmetrical firm swelling of the submandibular glands. Immunohistochemical analyses have revealed that a proportion of IgG4-positive plasma cells was also elevated in KT. MD and KT differ from SS and are thought to possibly form a singular systemic IgG4-related plasmacytic disease.

Key words: hyposmia, IgG4-related disease, Küttner's tumor, Mikulicz's disease, Sjögren's syndrome

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Introduction

In humans, the serum immunoglobulin G (IgG) subclasses are defined as IgG1, IgG2, IgG3, and IgG4. In healthy adults, a mean level for IgG4 subclass is less than 5% (1). Generally, the amount of IgG4 does not vary with sex or age, and the quantity of IgG4, as well as the IgG4/total IgG ratio, tends to remain constant (2). Although the physiological role of IgG4 still remains unclear, several diseases, including Mikulicz’s disease (MD) and Küttner’s tumor (KT), were recently reported to be associated with elevated IgG4 concentrations in the serum and with prominent infiltration of plasma cells expressing IgG4 (3-4).

MD refers to idiopathic, bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands. Since MD and Sjögren’s syndrome (SS) are histologically similar, MD has been considered as a subtype of SS (5). However, there are some clinical differences between MD and typical SS. In MD, the enlargement of lachrymal and salivary glands is persistent, and secretory dysfunction is either not detectable or slight. Further, MD shows good responsiveness to steroids. Serologically, MD patients exhibit normal or hypergammaglobulinemia and normal or hypocomplementemia, but they lack anti-SS-A and anti-SS-B antibodies. Recently, it has also been confirmed that MD patients show elevated serum immunoglobulin G4 (IgG4) concentrations and infiltration of plasma cells expressing IgG4 into the lachrymal and salivary glands (3). Thus, MD apparently differs from SS. Attention has also been paid to the pathological similarities between MD and autoimmune pancreatitis (AIP), particularly the role of IgG4, and new developments are expected to clarify the pathogenesis of both diseases.

On the other hand, KT is chronic sclerosing sialadenitis that presents with asymmetrical firm swelling of the submandibular glands (6). The histological characteristics of KT are severe fibrosis, atrophic acinus, and mononuclear cell infiltration. While immune-mediated processes are suspected in its pathogenesis, and KT is occasionally reported to be associated with sclerosing pancreatitis (7),
IgG4-related disease (8-9), the exact immunopathologic processes of KT remain speculative.

In this review, we summarize the results of recent studies and provide an overview of MD and KT.

1. Histological details of Mikulicz’s disease and Küttner’s tumor

In 1888, Mikulicz-Radecki (Fig. 1) reported a case of bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands (Fig. 2) (10). In 1927, Schaffer compared this case with known diseases that show obvious similarities to this case, such as sarcoidosis and lymphoma, and reported that the symptoms in this case constituted Mikulicz syndrome and designated Mikulicz syndrome of idiopathic origin as MD (11). In 1933, Sjögren summarized the findings of 19 cases of keratoconjunctivitis sicca; in 2 of these cases, swelling of the major salivary glands was observed (12). The concept of SS was established after this report. In 1953, Morgan and Castleman examined specimens obtained from 18 patients diagnosed with MD. They concluded that the histological findings in both MD and SS were similar and reported that most patients diagnosed with MD could be considered to be suffering from SS (5). Since then, MD has been recognized as a subtype of SS, and no cases of MD have been reported. However, many studies on the relationship between MD and SS have been conducted in Japan. In SS, the minor salivary glands are infiltrated by mononuclear cells; this infiltration resolves with corticosteroid administration, but salivary function does not recover (13). It has also been confirmed that in patients with MD, the serum IgG4 concentration is elevated, and IgG4-expressing plasma cells infiltrate the lachrymal and salivary glands (3). Thus, MD appears to differ from SS and is now thought to be a systemic IgG4-related plasmacytic disease.

On the other hand, KT, which was first described as chronic sclerosing sialadenitis by Küttner in 1896 (6), is a rare and chronic inflammatory disorder of the salivary glands and most commonly affects the submandibular gland (16-17). Patients with KT present with firm swelling of the salivary glands, and clinical differentiation of KT from neoplasia is difficult (16-17), hence the name Küttner’s “tumor” (18). Although KT is not infrequently associated with sialoliths, sialolithiasis may be a secondary process in KT (18-19). Monoclonal and oligoclonal cytotoxic T cell populations found in the affected salivary gland of KT patients suggest an immune reaction to intraductal agent(s) (20-22). It has also been suggested that secretory dysfunction of the salivary glands leads to inspissation of saliva in the ducts and chronic inflammation of the salivary glands in patients with KT (20-22). KT is occasionally associated with similar sclerosing lesions in extrasalivary glandular tissues such as those of the bile duct (sclerosing cholangitis) and the retroperitoneum (retroperitoneal fibrosis) (23-25). The concomitant occurrence of such lesions is referred to as multifocal fibrosclerosis, and KT could be regarded as a manifestation of multifocal fibrosclerosis. In addition, there have been several reports of an association between KT and sclerosing pancreatitis (7-8). Recent studies have shown that sclerosing pancreatitis, which is also called autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis, is a unique IgG4-related disease (9, 16).
2. Clinical features between Mikulicz’s disease and Küttner’s tumor

Diagnostic criteria

We examined 39 patients with MD (15 men, 24 women) and 6 patients with KT (2 men, 4 women). All patients had previously consulted doctors at Sapporo Medical University and its related facilities between April 1997 and October 2008. MD was diagnosed according to the following criteria: i) persistent (> 3 months) symmetrical swelling of more than two lacrimal and major salivary glands; ii) prominent mononuclear infiltration of lacrimal and salivary glands; and iii) exclusion of other diseases that present with glandular swelling, such as sarcoidosis and lymphoproliferative disease. KT was diagnosed according to the following criteria: i) persistent (> 3 months) unilateral or bilateral hard swelling of only the submandibular glands; ii) histological findings similar to those reported in previous studies (16-21); and iii) absence of preceding lesion(s) such as sialolith or mechanical obstruction of the salivary duct.

Differences between MD, KT and SS

Background characteristics of the patients with MD and KT are shown in Table 1. The mean age of the patients with MD was 55.2 ± 14.7 years (range, 23-87 years), and that of the patients with KT was 61.8 ± 9.4 years (range, 50-74 years). Our cases of MD and KT patients displayed a sex ratio of approximately 2:1 in favor females. In SS, the ratio is about 20:1 (female: male) (14). Anti-SS-A and anti-SS-B antibodies were absent in all MD and KT patients, except one. As shown in Fig. 3, the enlargement of the lacrimal and salivary glands in MD patients was found to be elastic, painless, and persistent (occurring for more than 3 months). KT patients showed unilateral or bilateral hard swelling of only the submandibular gland. With regard to salivary gland function, secretion by these glands in MD and KT patients was normal or slightly decreased, and this improved with steroid treatment. Sialography was also normal, and the “apple-tree sign”, which is typical of SS, was not observed in MD and KT patients. On the other hand, the lacrimal and salivary swelling in SS patients presented repeatedly and disappeared without treatment. The sicca symptoms were more severe in SS patients than in MD or KT patients. We prescribed glucocorticoids to SS patients for treating the swelling of the lateral submandibular gland, but the amount of saliva did not increase. The impact of steroids on the natural course of SS is not well established. The clinical features of MD and KT are thus quite different from those of typical SS (Table 1).

Extrasalivary gland lesions in MD and KT

Association of extrasalivary gland lesions of the patients with MD and KT are shown in Table 2. Autoimmune pancreatitis (AIP) was observed in 6 patients with MD and in 3 patients with KT. Interstitial tubulointerstitial nephritis and retroperitoneal fibrosis was observed in 7 and 6 patients with MD and KT, respectively (Table 2).

AIP has recently drawn attention in the field of pancreatology as a newly-proposed clinicopathological entity. Abdominal computed tomography shows diffuse or limited swelling of the pancreas, and endoscopic retrograde cholangio-pancreatography discloses sclerosing pancreatic ducts. Steroid therapy is usually effective for improving pancreatic swelling and pancreatic endocrine and exocrine secretion (26). AIP also exhibits hypergammaglobulinemia, particularly with regard to IgG4, and severe infiltration of

| Table 1. Clinical features compared between Mikulicz’s disease and Küttner’s tumor |
|---------------------------------|------------------|------------------|
| clinical features              | Mikulicz’s disease (n=39) | Küttner’s tumor (n=6) |
| mean age of disease onset      | 55.2 ± 14.7       | 61.8 ± 9.4       |
| sex ratio (M:F)                | 1:1.7             | 1:2              |
| hypergammaglobulinemia (mean serum IgG mg ± SD) | 29 (74.4%) (2848.7 ± 1788.7) | 3 (50.0%) (2344.0 ± 934.4) |
| anti-SS-A antibody             | 1 (2.5%)          | 0 (0.0%)         |
| anti-SS-B antibody             | 0 (0.0%)          | 0 (0.0%)         |
| antinuclear antibody           | 5 (14.4%)         | 1 (16.7%)        |
| Saxon test (g/2 min ± SD)      | 2.62 ± 2.10       | 2.24 ± 2.18      |
IgG4-positive plasma cells into the pancreas (9, 27). These characteristics are similar to those of MD or KT, i.e., There are elevated concentrations of serum IgG4, infiltration of IgG4-positive plasma cells into the glands, and recovery of secretion by steroid treatment. Thus, MD, KT, and AIP are considered to be related.

3. Mikulicz’s disease and Küttner’s tumor as an IgG4-related disease

Serum IgG subclasses in each group of MD, KT, and SS were measured by nephelometry. The IgG4 level was 931.1 ± 796.2 mg/dl in the MD patients, 756.6 ± 449.2 mg/dl in the KT patients, and 75.4 mg/dl in the SS patients (Fig. 4a). The IgG4 levels accounted for 26.4 ± 10.5% of the total IgG level in the MD patients, 25.3 ± 10.0% in the KT patients, and 2.6% in the SS patients (Fig. 4b).

The relative serum concentrations of human IgG subclasses in healthy adults are as follows: IgG1 > IgG2 > IgG3 > IgG4 (28-29). In normal human subjects, the mean levels of the IgG subclasses are reported as follows: IgG1, 64%; IgG2, 20%; IgG3, 13%; and IgG4, 3% (30). The Japanese population does not differ from other populations with regard to the connections of the IgG subclasses relative to the total IgG concentrations. IgG4 levels generally do not vary with sex and age, and both the IgG4 level and the IgG4/total IgG ratio are basically constant (31). The physiological role of IgG4 remains unknown, except for its role as a

![Fig. 4. Comparison of serum concentrations of IgG subclasses (a) and ratios of each IgG subclass/total IgG (b) between Mikulicz’s disease, Küttner’s tumor, and Sjögren’s syndrome. The statistical significance was determined by Mann-Whitney U test. Serum IgG4 levels were significantly higher in Mikulicz’s disease (MD) and Küttner’s tumor (KT) than in Sjögren’s syndrome (SS) by its concentrations (a) as well as ratios (b). *P<0.005 compared to the IgG4 level of SS.]
blocking antibody in allergic reactions (32). IgG4 usually responds to allergens, especially to polysaccharides (32). However, the antigen responsible for the increased IgG4 levels in MD and KT patients remains unidentified. The IgG4 levels may be increased in only some cases.

Immunohistochemically, as shown in Fig. 5, the infiltration of numerous IgG4-positive plasma cells near acinar and ductal cells in the submandibular glands of patients with MD (a) and KT (b), while no infiltrating IgG4-positive cells were observed in the labial salivary glands of those with SS (c).

**Fig. 5.** Immunohistochemistry for IgG4 in salivary glands in MD (a), KT (b), and SS (c). Immunoperoxidase stain, hematoxylin counterstain, × 200. There were abundant IgG4-positive cells infiltrating around acinar and ductal cells in the submandibular glands of patients with MD (a) and KT (b), while no infiltrating IgG4-positive cells were observed in the labial salivary glands of those with SS (c).

These characteristics, i.e., elevated concentrations of serum IgG4, infiltration of IgG4-bearing plasma cells into the glands, and recovery of secretion on glucocorticoid treatment, are similar to those found in MD and KT. Furthermore, AIP is occasionally complicated by MD (39) or KT (30); this was observed in our patients. Other complications associated with MD and KT include autoimmune hypophysitis (40), Riedel’s thyroiditis (41), interstitial pneumonia (8, 30), sclerosing cholangitis (42), retroperitoneal fibrosis (27, 42-43), and interstitial tubular nephritis (44). In our study, the concentrations of serum IgG4 tended to be proportional to the frequency of occurrence of these complications as shown in Table 2. It is possible that serum IgG4 concentrations reflect disease activity in systemic IgG4-related plasmacytic syndromes such as MD and KT.

4. Hyposmia associated with Mikulicz’s disease

We observed that MD patients often complained of olfactory disturbance. Of the 39 MD patients who were interviewed, 17 (44%) cases had this complication, even though no abnormalities, such as obstructive or inflammatory disease, were detected in their nasal cavities and sinuses. We were unable to determine the pathogenesis of this phenomenon in this study; however, we found abundant IgG4-positive plasma cells in the nasal mucosa of MD patients who complained of hyposmia (Fig. 6) (45). It is possible that infiltration by IgG4-positive plasma cells affects the secretory activity of the Bowman glands in the olfactory epithelium, as well as that of the lachrymal and salivary glands.

5. Treatment of Mikulicz’s disease and Küttner’s tumor

MD and KT are mainly treated by the administration of steroids. We initiate prednisolone at 30-40mg/day against...
MD and KT without organ failure. This leads to rapid improvement in glandular swelling as well as in salivary secretion. Glucocorticoid administration also improves hypergammaglobulinaemia (3). However, when steroids are discontinued, swelling of the lachrymal and salivary glands is observed, and the serum IgG4 levels increases. It is thus necessary to continue prednisolone administration at 5-10mg/day or combine it with an immunosuppressant.

**Conclusions**

Our study suggests that the serological and histopathological findings in MD and KT are very similar, and that both these diseases are IgG4-related. The abundance of IgG4-positive plasma cells in the affected salivary glands might be related to the pathogenesis of these diseases; however, the pathogenesis of MD and KT at the cellular and molecular levels should be studied further. Otolaryngologists or rheumatologists should initially administer corticosteroids to MD and KT patients in order to treat glandular swelling and improve exocrine and endocrine secretions. Based on the evidence presented here, we recognize the need to identify and manage the systemic complications of MD and KT.

**References**


