plasmacytes [11]. These were novel characteristics, prompting the recognition that MD is quite different from SS. The concept of MD has recently been expanded, with the recognition that it may be a systemic disease [12-14]. In this review, we summarize MD and its extraglandular lesions using both published and personal data.

CLINICAL CHARACTERISTICS

1. Definition and diagnostic criteria

As mentioned above, MD presents with bilateral, painless, and symmetrical enlargement of the lacrimal, parotid, and submandibular glands (**Fig. (1)**). Last year, the Japanese Medical Society for Sjögren's Syndrome determined the diagnostic criteria for IgG4-related MD (**Table (1)**). These consist of physical, imaging, serological, and histopathological factors; MD is diagnosed if item 1 and either item 2 or 3 are present.

We evaluated these criteria using our data and found them to be very useful for diagnosing MD. Sensitivity was 92.0%, specificity was 96.7%, and positive predictive value was 97.9%.

However, we often encounter cases which present with only lateral enlargement of the lacrimal or submandibular glands. These do not fulfill the diagnostic criteria for MD. The former have been treated as chronic dacryoadenitis by ophthalmologists, and the latter are conventionally classified as chronic sclerosing sialadenitis or Küttner's tumor by otolaryngologists. Recently it was reported that some of these cases had very similar serological and histopathological characteristics to MD [15-17]. They may therefore be considered subtypes of MD.

2. Etiology and demographics

The etiology of MD is unknown. We will explain later, in our serological analysis, hypocomplementemia and elevated levels of circulating immune complexes were often observed in MD patients, and its frequency and the concentrations raised more in MD with renal involvements. So we cannot remove autoimmune mechanism from the origin at the moment. On the other hand, the high frequency of comorbid parasinusitis and bronchial asthma [18] raises the possibility that MD results from a chronic allergic reaction to an unknown allergen. In terms of infection, Kawano

implicated an abnormal immunological reaction to tuberculosis as a causative factor in MD [19]. We may therefore have to consider a chronic infection in the etiology of this disease.

Peak incidence is between 50 and 70 years of age. Our patients with MD were mainly middle-aged or elderly women; the female:male ratio was 1.7:1, with an average age of 58 years. Recently reported gender ratios for SS are approximately 7-13:1 (female: male) [20, 21], so although both diseases show a tendency to affect women the gender ratio is quite different. Moreover, the average age at onset was higher in MD than in SS.

We do not know whether there is racial disparity in the distribution of MD. At present, there are many case reports and analysis from Asia including Japan, but those from America and Europe are also increasing [22, 23]. We therefore believe MD is a worldwide disease.

The overall population prevalence is also unclear. A nationwide survey of autoimmune pancreatitis (AIP), another IgG4-related disease, was carried out in 2002 in Japan. The prevalence of AIP was estimated to be 0.82 per 100,000 [24]. We have constructed a database of MD for approximately 2.5 million inhabitants around Sapporo. This database shows an incidence of MD of 0.48 per 100,000 per year.

3. Cardinal findings

The clinical findings of MD (our 49 cases) are shown in **Table 2**. The frequency of these findings is based on our database. Persistent swelling of the lacrimal and submandibular glands was noted in all cases of MD. A quarter also had bilateral enlargement of the parotid gland, which was painless and elastic-firm. SS differs from MD in that glandular swelling is mainly confined to the parotid glands and is usually transient but recurrent. MD usually had low frequency of constitutional symptoms, such as fever, malaise and weight loss.

An important finding is the low frequency of sicca symptoms compared with SS; while nearly all SS patients have dry eyes and mouth, about half of those with MD did not, and only a third of MD patients had keratoconjunctivitis sicca. Quantitative tests on our MD patients support these conclusions. Schirmer's test, which reflects lacrimal gland function, was not severely abnormal at 5.68±7.04 (SD) mm/5 minutes (normal = >10 mm/5 minutes; dry eye is suggested by < 5 mm/5 minutes). Saxon's test,

which reflects salivary function, was also only mildly abnormal at 2.37±1.96 g/ 2 minutes (dry mouth is suggested by <2.00 g/ 2 minutes).

Regarding other symptoms, although most of our MD patients did not experience diplopia or visual loss, orbital computed tomography (CT) disclosed swollen mass in orbit except for lacrimal glands in 6.1% of these patients. No auricular symptoms were detected. Surprisingly, half of these patients had allergic rhinitis and a third experienced hyposmia, which was improved by oral glucocorticoids [25]. We encountered only one case with disseminated skin rash similar to that seen in systemic plasmacytosis [26]. In rare cases arthralgia or arthritis of the proximal interphalangeal joints was a presenting symptoms, and early rheumatoid arthritis had to be ruled out. Superficial lymphadenopathy was observed in 57% of the patients. This was nearly always cervical, but was occasionally retroauricular or axillary.

INVESTIGATIONS

1. Laboratory testing

Hematological tests were usually normal in MD patients, with the exception of eosinophilia in 26.5%. Leucopenia (WBC count <3,000 /mm^3) and thrombocytopenia (platelet count <100,000 /mm^3) were occasionally encountered. Hepatic and renal function was normal in patients without pre-existing organ failure. The majority of patients (85.7%) were negative for C-reactive protein, and those who did test positive had values less than 10 mg/L.

Serological analysis showed that autoantibodies were uncommon in MD. Antinuclear antibody was detected in only 14.3% of our patients, and the pattern was often diffuse or speckled. Rheumatoid factor was observed in 24.5%, but anti-cyclic citrullinated peptide (CCP) antibody, which is specific to rheumatoid arthritis, was not detected. Only one patient (2.0%) had anti-SS-A antibody, but this patient did not satisfy with the European-American criteria for SS [27] because sicca symptoms were absent. None of our patients demonstrated anti-SS-B antibody. Elevated levels of IgE occurred in 73.5% of patients, but there was no tendency for specific IgE on MAST testing.

In 2004, we were the first to report that all of a series of patients with MD had

elevated concentrations of IgG4 [10]. This was confirmed by analysis of our database, showing that MD was characterized by hypergammaglobulinemia (271.7±162.7 mg/L); this was in the majority (73.5%) of our patients. Detailed results for IgG subclasses were as follows: IgG1, 120.2±56.9 mg/L (normal range, 32.0-74.8 mg/L); IgG2, 83.5±24.6 mg/L (20.8-75.4 mg/L); IgG3, 6.7±5.8 mg/L (0.7-8.8 mg/L); and IgG4, 91.4±73.9 mg/L (0.5-10.5 mg/L) (**Fig. (2)**). Elevated levels of IgG4 are not observed in any other connective tissue disease, including SS, systemic lupus erythematosus, rheumatoid arthritis, and polymyositis [10] (**Fig. (3)**). Generally, IgG4 does not vary with sex or age, and the level remains constant [28], so a finding of an elevated level is useful in diagnosing MD.

Hypocomplementemia and elevated levels of circulating immune complexes in MD are very interesting findings. The former was observed in about a quarter of the patients, and the latter was detected in half of them [29]. It is important to differentiate such cases from systemic lupus erythematosus.

2. Diagnostic imaging

When we encounter a suspected case of MD, it is important to investigate the glandular enlargement and to perform systemic screening with imaging studies. CT and ultrasonography are convenient for evaluating the glands. CT generally revealed severe, symmetrical enlargement of the lacrimal and submandibular or parotid glands (**Fig. (4)**). Local lymphadenopathy was usually also seen. Ultrasonography of the enlarged glands revealed irregular, hypoechoic, and multilocular foci, while power Doppler showed hypervascular masses. Sialography was often normal, and the "apple-tree sign," which is typical for SS, was not observed in MD [13]. Gallium-67 scintigraphy and F-18 fludeoxyglucose (FDG) positron emission tomography (PET)-CT is useful for systemic screening [30]. Both modalities are helpful in showing latent lesions outside the lacrimal and salivary glands. **Fig. (5)** shows bilateral hilar lymphadenopathy in the same patient. The PET image was clearer than the gallium-67 scintigraphy image and allowed us to evaluate response to treatment.

3. Pathology

Specimens of the minor salivary glands from both MD and SS patients showed severe mononuclear cell infiltration (**Fig. (6)**), but Tsubota reported that the frequency

of apoptosis of lacrimal gland cells was significantly lower in MD [8, 9]. We noted few apoptosis in salivary glands from MD patients using a terminal deoxynucleotidyl transferase-mediated dUTP digoxigenin nick-end labeling (TUNEL) method [31]. These findings are associated with the reversibility of lacrimal and salivary impairment, which we describe in the next section.

Anti-IgG4 antibody staining of minor salivary gland specimens from MD patients revealed numerous IgG4-producing plasmacytes infiltrating near acinar and ductal cells. On the other hand, labial specimens from SS patients showed no IgG4-producing cells (**Fig. (6)**). These cells were identified as plasmacytes because they expressed CD138 molecules on their surfaces. Numerous plasmacytes producing IgG4 were also seen in the lacrimal and submandibular glands in MD (**Fig. (7)**) [11]. These histological findings are also specific characteristics of MD.

THERAPY AND PROGNOSIS

MD is mainly treated with steroids. We start prednisolone at 20-30 mg/day for patients without organ failure. This leads to rapid improvement in glandular swelling as well as in lacrimal and salivary secretion. Administration of glucocorticoid for 2 months led to a significant increase from 5.7 mm/5 minutes to 8.2 mm/5 minutes on Schirmer's test, reflecting improved lacrimal secretion, and an increase from 2.4 g/2 minutes to 3.6 g/2 minutes on Saxon's test, reflecting improved salivary secretion [32].

Glucocorticoid administration also improved serological abnormalities including hypergammaglobulinemia and hypocomplementemia. Among MD patients in our database, 6 months of glucocorticoid therapy decreased serum IgG levels from 2455.3 mg/dl to 1231.1 mg/dl. Serum IgG4 levels also decreased from 845.4 mg/dl to 254.5 mg/dl but did not normalize. Nevertheless, there were some cases (6.1%) with complete remission of symptoms, but most patients experienced recurrence of lacrimal and salivary gland enlargement when steroid was discontinued or excessively reduced. Serum IgG4 concentrations also rose to their former levels during these recurrences. It therefore appears necessary to continue prednisolone at 5-10 mg/day. In the future, we will consider the use of biologic agents, such as tocilizumab and rituximab for complete remission without steroid.

The prognosis of MD remains uncertain. Lymphoma is a concern because, like SS, MD is a lymphoproliferative disorder. Of the rheumatic autoimmune diseases, SS is the most strongly associated with B cell lymphomas [33]. An initial report that patients with SS have up to a 44 times increased risk of developing lymphoma compared with the general population was based on a highly selected group of patients in a study that was not population based [34]. Theander found about a 16-fold increased risk of developing lymphoma in patients with SS [35]. Up to 10% of patients with SS may develop malignant lymphoma [35, 36]. In a multicentre European study, lymphoma occurred in 4.3% of patients with SS, and this was mostly low grade B cell lymphoma of the mucosa associated lymphoid tissue (MALT) type [34]. Recently, the number of reported cases of MD or a related disease complicated by lymphoma is increasing [37, 38]. We have also encountered a MD patient with MALT lymphoma. At the diagnosis of breast lymphoma, the lacrimal glands were enlarged bilaterally, and the submandibular glands later developed swelling. Histological analysis of these glands revealed abundant infiltration of IgG4-bearing plasmacytes. It is uncertain whether MD or lymphoma was the pre-existing pathology in this case, but we consider that lymphoma can develop secondary to MD in a certain proportion of patients. Shortly after we encountered this patient, two reports of IgG4-associated lymphoma were published. Sato reported that lymphoma can occur in the setting of systemic IgG4-related disease [39], and Takahashi conducted 331-patient-years of observation in 111 patients with systemic IgG4-related disease and found that three patients were diagnosed with non-Hodgkin lymphoma (mainly diffuse large B cell lymphoma) 3 to 5 years after diagnosis of systemic IgG4-related disease. It also was found a 16-fold increased risk of non-Hodgkin lymphoma in patients with systemic IgG4-related disease [40]. It is important to further clarify the relationship between MD and lymphoma, and to elucidate the molecular mechanism of lymphoma development in MD.

SYSTEMIC COMPLICATIONS

As previously mentioned, MD was originally thought to be localized to the lacrimal and salivary glands, but our data and recent reports have shown other complications (**Table (2)**).

Regarding respiratory complications, 10% of MD patients that we analyzed developed bronchial asthma. Pulmonary CT revealed bilateral hilar lymphadenopathy in 53% of MD patients (**Fig. (5)**), pulmonary fibrosis in 4%, and pulmonary nodule-like organizing pneumonia in 2% (**Fig. (8)**). Pulmonary involvement mainly shows two patterns: pulmonary fibrosis and pulmonary nodules. Both often disappear spontaneously, and are very responsive to glucocorticoid if required. However, pulmonary nodules must be differentiated from lung cancer. Patients with MD may present with asthma-like symptoms if the bronchial wall becomes thickened, and this can be mistakenly diagnosed as refractory asthma [41-43].

AIP is an important gastroenterological complication of MD [44-46], and was seen in 18% of our MD cases (**Fig. (8)**). CT revealed diffuse enlargement of the pancreas, and PET-CT imaging showed strong accumulation in the pancreas (**Fig. (8)**) [47]. About half of these AIP patients demonstrated impaired glucose tolerance. Urinary C-peptide level, which reflects insulin secretion, was suppressed before treatment, but was improved by glucocorticoid [46]. Pancreatic exocrine function was also improved by the same therapy. Sclerosing cholangitis with or without AIP was seen in 10% of our patients with MD and sometimes occurred with obstructive jaundice. The symptoms were also resolved by steroid.

Renal and urological complications were observed in patients with MD. Tubulointerstitial nephritis is typical in renal involvements [48, 49]. Increased levels of urine N-acetyl-β-D-glucosaminidase, a marker of tubular damage, were observed, but the concentrations of creatinine and blood urea nitrogen were normal in the early stage. Some patients in whom renal impairment was ongoing required dialysis. Enhanced-CT is very useful for detecting renal lesions, which are often demonstrated as heterogeneous areas of poor enhancement, like metastatic tumors (**Fig. (8)**). Membranous nephropathy was rarely found in MD patients (2.0%) [50]. We encountered hydronephrosis (10.2%), which was caused with retroperitoneal fibrosis [51], and this sometimes formed nodules at the renal pelvis (14.3%). Recently there have been reports of prostatitis associated with MD [52]. This must be differentiated from prostatic carcinoma.

Hypophysitis (2.0%) (**Fig. (8)**) [53, 54], Riedel's thyroiditis (2.0%), and pericardial thicking (4.1%) were also encountered as systemic complications. Periaortitis (10.2%) and inflammatory aortic aneurysm were also noted as forms of

vascular involvement [55, 56], but those conditions are difficult to differentiate from retroperitoneal fibrosis.

It is important that these complications can occur at different times and sites. Patients with organ involvement require higher dose of glucocorticoid (prednisolone 30-40 mg/day) to attain remission. Moreover, MD and extraglandular lesions tend to recur more easily in patients with systemic complications.

As mentioned above, MD can have various systemic complications and these have common histological characteristics, namely the infiltration of IgG4-bearing plasmacytes and accompanying fibrosis. Hence, it seems preferable to consider these manifestations as a part of a systemic disease.

At the 10th Internal Symposium on Sjögren's Syndrome in October 2009, the concept of **IgG4-related systemic disease** was officially agreed upon [57]. The previously reported entities of 'systemic IgG4-related plasmacytic syndrome (SIPS)' [14] and 'IgG4+ multiorgan lymphoproliferative syndrome (MOLPS)' [18] will come under this umbrella term. According to this new concept, MD is the lacrimal and salivary glandular manifestation of IgG4-related systemic disease, and AIP is the pancreatic manifestation.

Several issues remain to be clarified. We first have to explore and confirm the field of IgG4-related systemic disease. Infiltration of plasma cells bearing IgG4 was recently detected in multicentric Castleman disease [26, 58], Rosai-Dorfman disease [59], hypertrophic pachymeningitis [60], and plasmacytosis [26, 58, 61]. This can lead to confusion in clinical practice. Typical cases of MD and AIP have less inflammatory factors on laboratory investigations and fewer manifestations of fever, malaise and weight loss, while the above-mentioned diseases have a high frequency of inflammation. Can this be explained by the presence of elevation of interleukin (IL)-6? Second, the pathogenesis of IgG4-related systemic disease is uncertain, especially the role of autoimmunity. Immune complexes are often detected in IgG4-related systemic disease including MD, and our proteomic analysis revealed that a 13.1 kDa protein is one of the candidate antigens [29]. It is possible that the pathogenesis also involves allergic reactions to other outside antigens.

We have summarized the features of MD and its extraglandular complications in this review. We hope that the concept of IgG4-related systemic disease including MD is recognized by all clinicians and researchers so that this disease can be correctly

recognized and optimal treatment given.

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Figure and Table

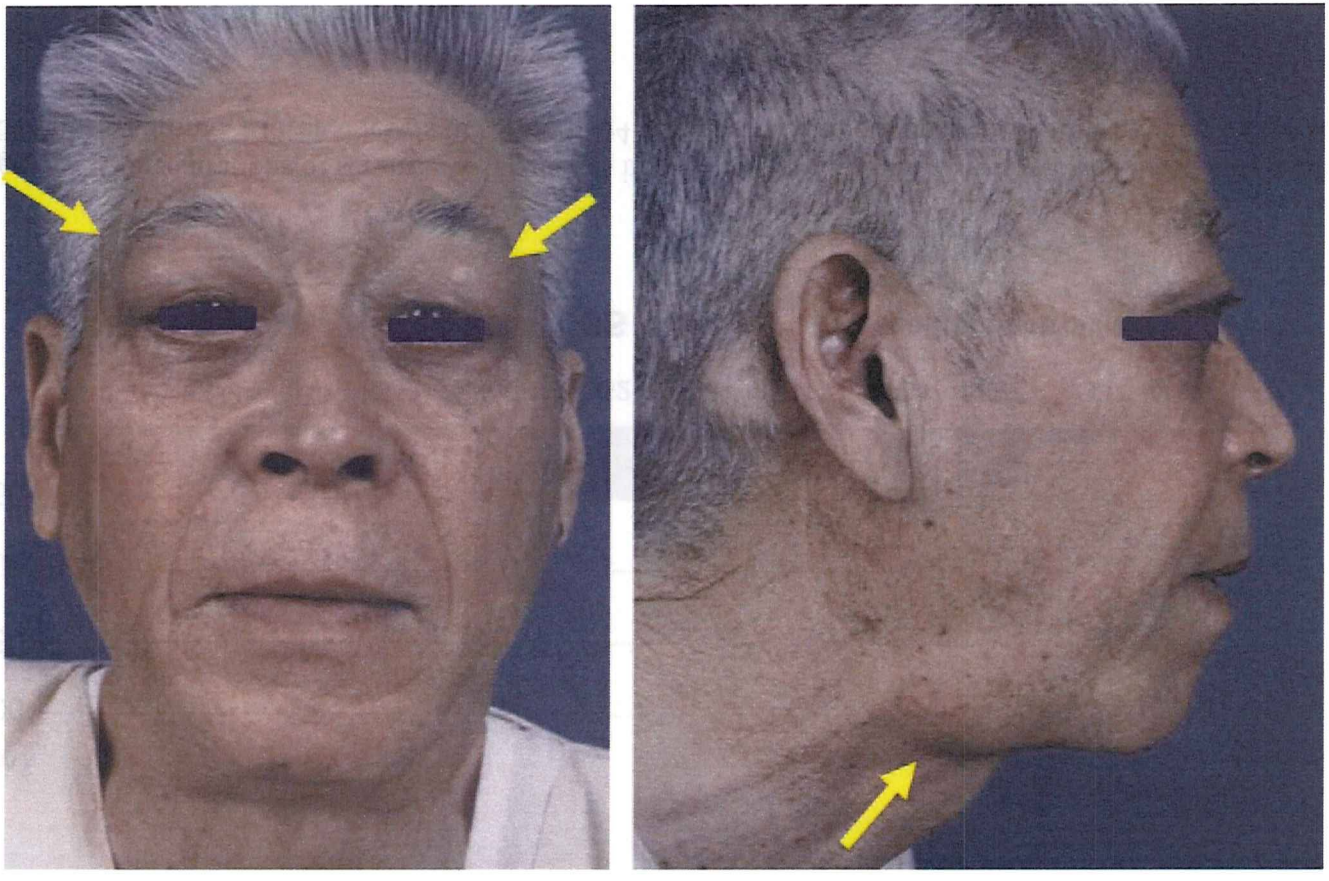

Figure 1. Typical facial appearance in a patient with Mikulicz's disease. The bilateral upper eyelids and submandibular regions were enlarged without tenderness (arrow).

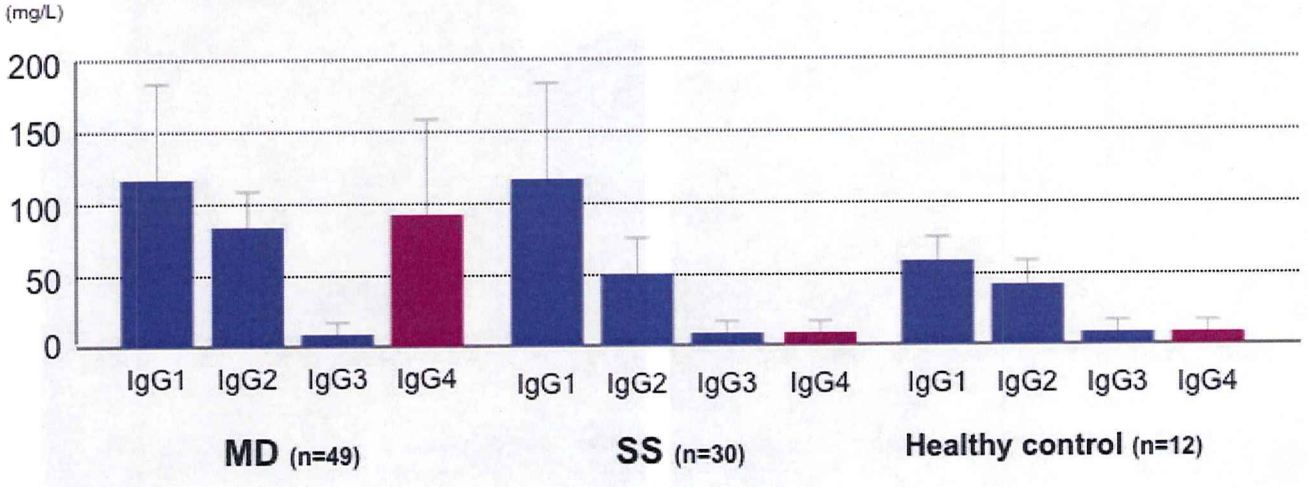

Figure 2. Concentrations of serum IgG subclasses in patients with Mikulicz's disease and those with primary Sjögren's syndrome. Elevated levels of serum IgG4 was observed in only patients with Mikulicz's disease.

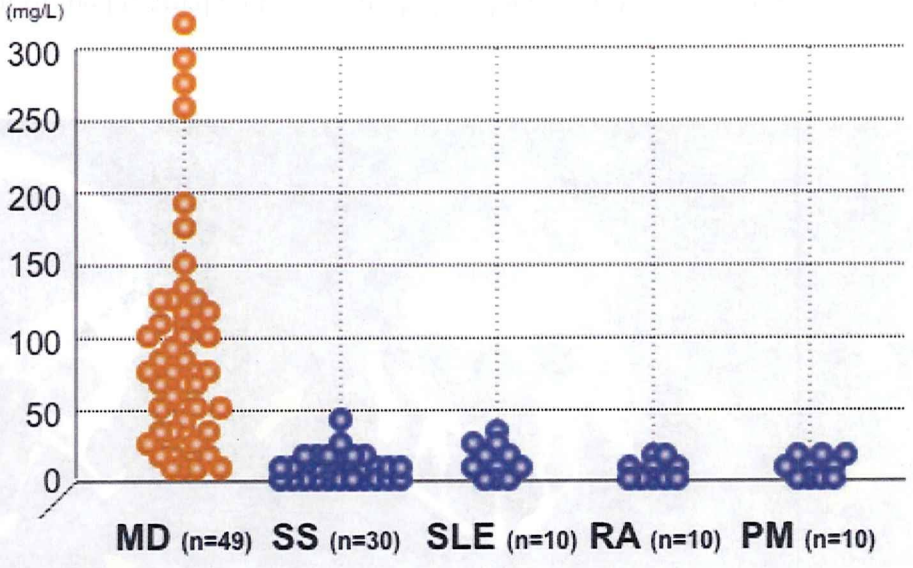

Figure 3. Concentrations of serum IgG4 in patients with Mikulicz's disease and those with other rheumatic diseases. The elevated level of serum IgG4 was specific to Mikulicz's disease.

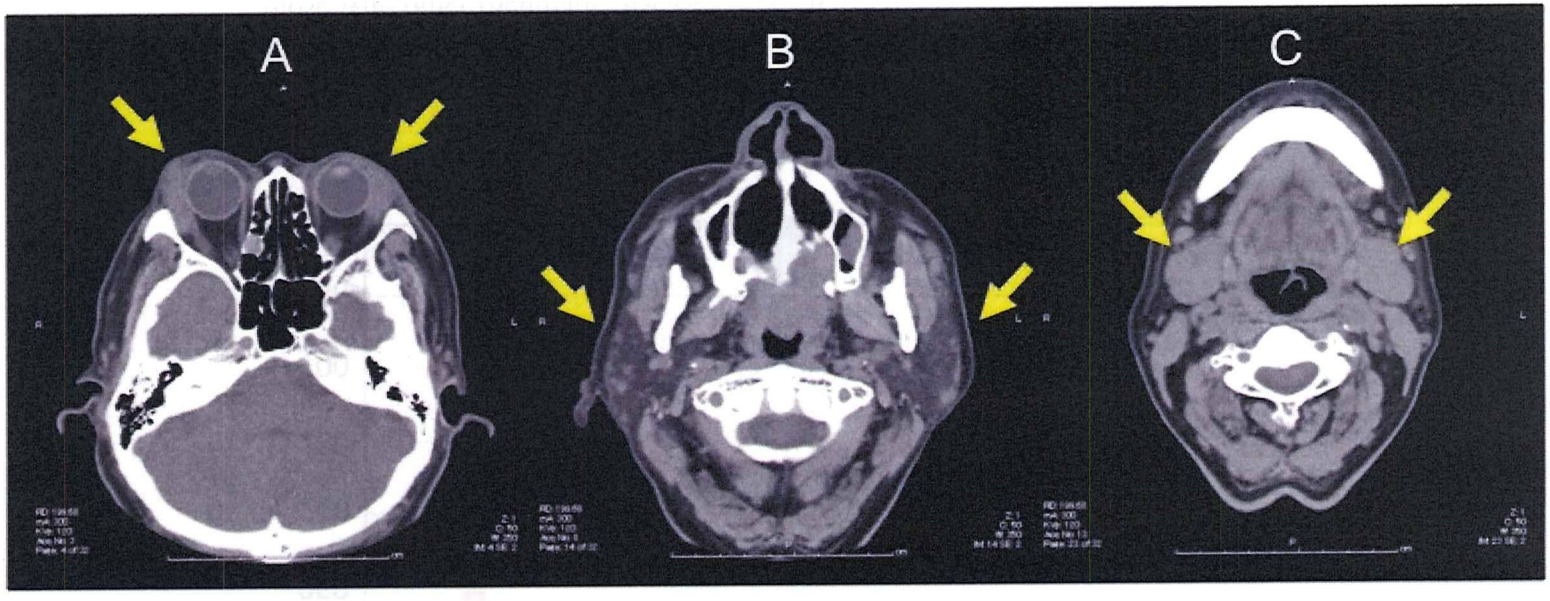

Figure 4. Enlargement of the lacrimal and submandibular glands shown by computed tomography. Marked, symmetrical enlargement of the lacrimal (**A**), parotid (**B**) and submandibular glands (**C**) (arrows) in Mikulicz's disease.

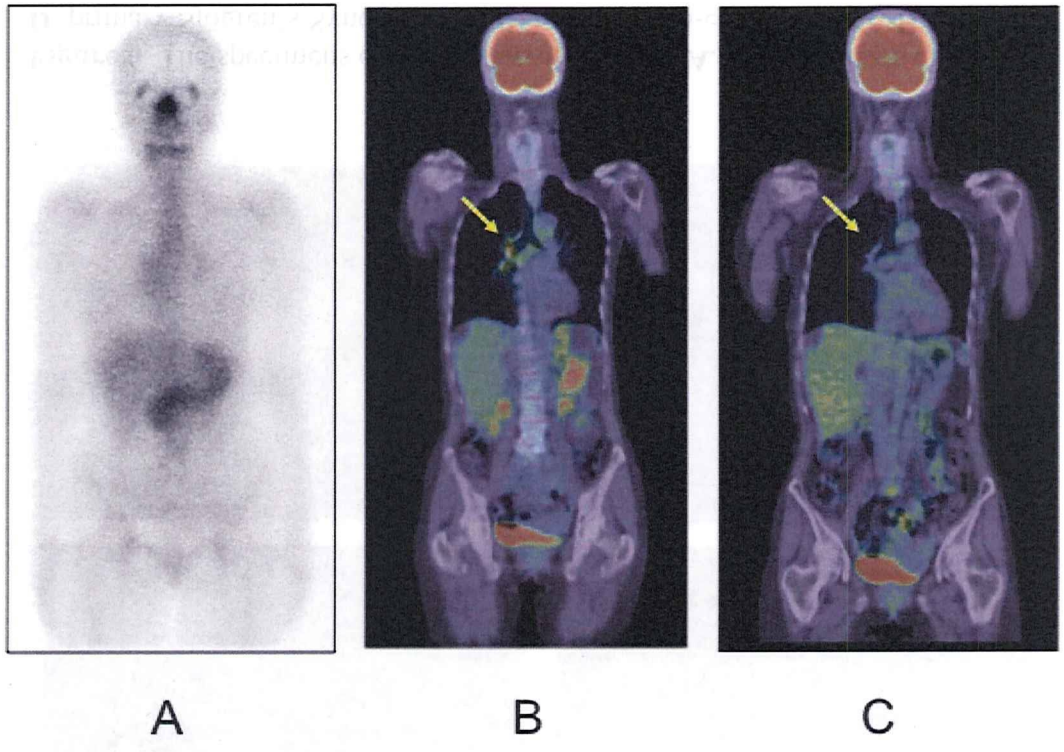

Figure 5. Whole body images with gallium-67 scintigraphy and F-18 fludeoxyglucose positron emission tomography (PET). Arrows show bilateral hilar lymphadenopathy in the same case. The PET image (**B**) is clearer than the gallium-67 scintigraphy image (**A**) and allowed us to evaluate response to treatment (**B**: before treatment, **C**: after treatment).