Sjögren’s syndrome (SS) is an autoimmune disorder affecting primarily the exocrine glands, leading to keratoconjunctivitis sicca (KCS) and xerostomia, but that can also include extraglandular features. Due to the anatomical, physiological and pathological similarity between the pancreas and the salivary glands, it has been described that the pancreas is not exempt from the damage produced by this syndrome. Some authors have assessed pancreatic involvement of SS by analyzing the histopathological changes, evaluating the pancreatic endocrine and exocrine function (serum pancreatic enzymes, elastase, lipase or trypsin determinations, N-benzoyl-L-tyrosyl-para-aminobenzoic acid excretion test, etc), searching specific pancreatic antibodies (antiductal) or performing endoscopic retrograde colangiopancreatography or noninvasive imaging studies such as computed tomography or ultrasound. Herein we review the literature regarding the prevalence and type of pancreatic involvement in the SS and we discuss the differential diagnosis with multiorganic lymphoproliferative Syndrome.

**Clinical presentation**

Pancreatic manifestations in patients with pSS are diverse. For example, in the largest series of patients with pSS (1,010 patients),...
there was a 0.5% prevalence of acute pancreatitis of any aetiology. On the other hand, the coexistence of pSS with autoimmune pancreatitis, retroperitoneal fibrosis and sclerosing cholangitis is well-known, although its prevalence is unknown because the scientific literature includes only case reports. In addition, no information on the frequency of chronic pancreatitis in these patients is available. We evaluated the clinical records of 97 patients with pSS from our institution, a tertiary referral centre for patients with rheumatic diseases, and found that 3 patients (3%) presented autoimmune pancreatitis, of which 2 subjects progressed to chronic pancreatitis (unpublished data).

As for the time of presentation of both diseases (autoimmune pancreatitis and SS), in several of the cases reported in scientific literature, the diagnosis of SS was established after that of gastrointestinal autoimmune disease. However, it really is not known whether the patients presented prior sicca symptoms since they were not intentionally evaluated in relation to it. Some other reports have described simultaneous presentation of both autoimmune diseases.

Another presentation of pancreatic disease, although described in rare cases in these patients, is the presence of pancreatic pseudotumor. In these cases, the initial suspicion was of malignant pancreatic neoplasm given the presence of a pancreatic mass. However, after resection of the surgical specimen, an infiltration of mononuclear cells, lymphocytes and plasma cells was documented, as well as glandular atrophy and fibrosis.

Anti-ductal antibodies

Due to the similarity of the pancreas with other exocrine glands (salivary gland) and the bile duct and distal renal tubule, the presence of antibodies against antigens of ductal cells has been studied in patients with pSS, autoimmune chronic pancreatitis and in patients with both entities. Ludwig et al demonstrated the presence of antibodies against salivary duct epithelial cells in a study involving 12 patients with SS and 31 patients with rheumatoid arthritis. The authors found positivity for these antibodies in 41% of patients with SS and 33% of patients with rheumatoid arthritis. The presence of these antibodies was not detected in a control group. All sera positive for this antibody presented a positive intra- and inter-lobular immunofluorescence reaction to human and monkey pancreatic duct cells. These sera also presented positive staining in parotid, submandibular and lachrymal tissue from healthy controls and in tissue extracted from monkeys, suggesting the presence of a common antigen in the studied organs. In this same context, another study group reported the presence of a monoclonal antibody that recognised an antigen expressed in pancreatic ductal cells, salivary gland cells, bile duct and distal renal tubule cells in patients with pSS, SS associated with chronic pancreatitis and in patients with idiopathic chronic pancreatitis. This antibody was not found in patients with chronic pancreatitis related to other aetiologies, such as alcohol or lithiasis. These findings again suggested that an antibody could be directed against a common antigen in ductal cells. In fact, the term “dry gland syndrome” or “autoimmune exocrinopathy” was proposed, to include patients with positivity for this antibody regardless of the affected organ.

Pancreatic enzymes

There are also some studies on the behaviour of pancreatic enzymes in patients with SS. For example, in a study which included 25 patients with pSS, 24% presented hyperamylasemia of isotype P and S, probably indicating a moderate subclinical inflammatory process. Higher values of trypsinogen have also been documented in these patients. Consequently, since the elevation of pancreatic enzymes is a common finding, the monitoring of these values has been recommended in patients with SS to identify damage in its early stages; the most specific is the value of trypsin. Ostuni et al also found a relationship between the values of total amylase and pancreatic isoamylase with serum values of 2-microglobulin and they correlated pancreatic isoamylase with the presence of abnormalities in salivary gland scintigraphy.

Histopathology

Pancreatic morphological changes have been described in post mortem studies of patients with pSS in whom pancreatic problems had not been previously documented. These changes include moderate levels of chronic pancreatitis, atrophy, replacement of pancreatic tissue by vascular connective tissue and lymphocytic infiltration. In a report of 3 autopsied patients with pSS who were known to suffer pancreatic dysfunction, histopathological findings were similar to those reported previously in cases of asymptomatic patients.

Furthermore, biopsies from patients with autoimmune pancreatitis reported findings similar to those described in salivary glands from patients with autoimmune sialadenitis.

Imaging studies of the pancreas

There are few studies that have evaluated the pancreas in patients with autoimmune diseases in general through imaging techniques. Sahani et al conducted a study that assessed patients with autoimmune pancreatitis (4 of them with other autoimmune diseases, including SS) via computed tomography (CT) prior to steroid therapy. The CTs showed diffuse pancreatic inflammation with loss of lobularity in most patients. Moreover, the presence of an enlarged pancreatic size in 90% of cases was documented in a series of patients with chronic pancreatitis and SS who were evaluated by CT or ultrasound.

When evaluating a group of 20 patients with SS by endoscopic retrograde cholangiopancreatography (ERCP), abnormalities were located in the pancreatic duct in 27% of patients, although these alterations were mild in the pancreatic duct branches and absent in the main pancreatic duct. Conversely, in a study which included a group of patients with SS and elevation of pancreatic enzymes, none of them presented any alteration in the morphology of the pancreas assessed by CT.

Recently, an evaluation of 12 asymptomatic pSS patients by magnetic resonance cholangiography reported that 3 of them presented morphological changes in the pancreatic duct and 2 of them presented abnormalities suggestive of chronic pancreatitis.

Pancreatic function

Exocrine function

Given the anatomical, physiological and pathological similarities between the salivary and pancreatic glands, it has been postulated that pancreatic function is likely to be also impaired in patients with SS. However, the presence of symptoms of pancreatic failure has rarely been documented, so it is suggested that in these patients, if pancreatic failure is indeed present, it is mild.

In this regard, several authors have studied patients with SS, either primary or secondary (associated with rheumatoid arthritis), using various diagnostic tests: stimulation with secretin and ERCP quantification of the volume of duodenal secretion, with or without measurement of bicarbonate concentration, determination of fat in faeces, N-benzoyl-L-tyrosyl para-amo benzic acid (PABA) excretion test and measurement of elastase, lipase or trypsin (Table 1). It is noteworthy that the secretin stimulation test is the test of choice for the detection of exocrine pancreatic failure. It consists
of the collection of duodenal and/or pancreatic juices by ERCP after stimulation with secretin. Because it is an invasive procedure as well as technically difficult and not free from complications, other alternatives have been sought, such as faecal elastase measurement, chymotrypsin, determination of lipase, pancreolauryl test, bentiomide test or PABA excretion. Unfortunately, the results of these tests are variable and we must not forget that, in general, they are mainly useful for detecting cases of advanced pancreatic failure.31

Those pancreatic function studies in SS mentioned previously (Table 1) have shown variable and sometimes contradictory results; for example, findings have included an absence of involvement in pancreatic exocrine function16 minimum involvement,23,24,28 or involvement in up to 50% of patients.28,29,22 In addition, limiting factors have included the recruitment of a small number of patients or, in some cases, having used alternative tests instead of the secretin stimulation test, so that sensitivity and/or specificity may vary.31

It has recently become possible to integrate imaging studies (ultrasound or magnetic resonance cholangiography) in the secretin stimulation test to evaluate the morphology and function of the pancreas in the same study. So far, only one study has used this method (secretin test by magnetic resonance cholangiography) in the evaluation of patients with pSS. By studying 12 patients with pSS, it was found that 25% presented abnormalities in pancreatic morphology and 2 patients presented changes similar to those described in cases of chronic pancreatitis. Up to 80% of patients presented normal exocrine function and 100% normal duodenal filling.34

However, it must be remembered that the correlation between structural dysfunction by imaging and by function is poor in patients with pancreatic failure from various aetiologies. This is because patients with significant exocrine failure may have a structurally normal pancreas and vice versa. These discrepancies range between 12%-29%.32

**Endocrine function**

It is known that the non-obese mouse model for diabetes mellitus type 1 (DM-1) also presents sialadenitis at 4-6 months of age. Deficiency of E2F1, regulator of the proliferation, differentiation and apoptosis of T cells, induces the early appearance of diabetes and SS in this animal model.33 However, although theoretically the
coexistence of SS with DM1 in humans is feasible, so far there have only been case reports. Moreover, in terms of the frequency of DM-2 in patients with pSS, this has been described as higher than in controls matched by age. When comparing patients with pSS and DM versus patients with pSS and without DM, it was found that diabetic patients presented increased steroid use and decreased antimarial use. A recent study evaluated 12 patients with pSS through the oral glucose tolerance test; 3 of them presented intolerance to carbohydrates and FERUM values of IgG4 Normal Very elevated

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<thead>
<tr>
<th>Gender</th>
<th>Mainly females</th>
<th>Both genders</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Xerostomia and xerophthalmia</td>
<td>Scarce symptoms</td>
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<tr>
<td>Anti-Ro and anti-La</td>
<td>Generally present</td>
<td>Absent</td>
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<td>Response to steroids</td>
<td>Normal</td>
<td>Very elevated</td>
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<td>Biopsy</td>
<td>Nodular infiltration of lymphocytic predominance with none or scarce presence of IgG4 cells</td>
<td>Infiltrates of IgG4+ plasma cells</td>
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**Mikulicz disease and IgG4-positive multi-organ lymphoproliferative syndrome**

Mikulicz disease is defined as the idiopathic painless, bilateral and symmetrical inflammation of the lachrymal, parotid and submandibular glands. This disease was traditionally considered as a subtype of SS; however, certain differences have been described between the two pathologies (Table 2). One of the main differences is the presence of elevated serum IgG4 values and infiltration of plasma cells and IgG4+ monocytes in gland biopsies in Mikulicz disease. Moreover, since an elevation of IgG4 has also been identified in about 70% of patients with autoimmune pancreatitis, the presence of IgG4+ plasma cell infiltrates is part of the diagnostic criteria for this pathology, and the use of steroids is the treatment for this entity; it has been considered that autoimmune pancreatitis and Mikulicz disease are related.

A new entity has recently been proposed to cover those pathologies that have documented elevations of serum IgG4 values, infiltrations of plasma cells and IgG4+ monocytes in the affected organs. This entity is known as IgG4-positive multi-organ lymphoproliferative syndrome and may be multisystem or affect a single organ. The most frequently involved organs are the pancreas, biliary tract, liver, kidneys, lungs, aorta and exocrine glands, etc.

With the introduction of this new concept, it is likely that some of the patients described previously in the scientific literature, in whom SS coexists with other autoimmune diseases (pancreatitis, cholangitis, thyroiditis, etc.), are in fact cases of IgG4 syndrome.

**Conclusions**

Although the pancreas is a gland very similar to the salivary glands, clinical involvement of the pancreas is one of the most infrequent manifestations of SS. Studies in this area are few and most of them were carried out more than two decades ago, with mixed results due to differing methodologies and having included only a small number of patients. The most frequently reported findings were alterations of pancreatic enzymes and pancreatic exocrine dysfunction; however, the latter was mild and, therefore, subclinical. These changes could not be correlated to morphological or imaging changes. In addition, pancreatic endocrine involvement has been attributed more to external factors than to the autoimmune disease itself. Common antibodies that recognise the pancreas and salivary glands have also been identified; however, the detection of these antibodies has not yet become widespread in clinical practice.

Lastly, the relationship between autoimmune pancreatitis and Mikulicz disease has been highlighted, encompassing both pathologies in a new entity: IgG4-positive multi-organ lymphoproliferative syndrome. Consequently, this new concept requires consideration of the idea that the coexistence of autoimmune pancreatitis in patients with SS represents, in fact, a single entity.

**Conflict of interest**

The authors declare no conflict of interest.

**References**