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Systemic IgG4-Related Disease Masquerading as Cholangiocarcinoma: A Case Report Underscoring the Importance of Medical History

Authors' Contribution:

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 64-year-old
Final Diagnosis: Systemic IgG4 related disease
Symptoms: Painless jaundice • weight loss
Medication: —
Clinical Procedure: Contrast enhanced ultrasonography • endosonography • ERCP • histopathology • MRCP
Specialty: Gastroenterology and Hepatology • Rheumatology

Objective: Rare disease

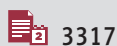
Background: Immunoglobulin (Ig) G4-related disease is a rare disease of unknown pathophysiology, which can affect multiple organs leading to tissue fibrosis and organ failure. The present case report describes a patient with systemic IgG4-related disease (IgG4-RD) that occurred over a 1-year period and affected multiple organs at different times. Imaging studies, interventional procedures, changes in laboratory parameters, and histopathology demonstrate the novel and known aspects of this disease before and during prednisolone monotherapy and in combination with azathioprine.

Case Report: A 64-year-old man presented with weight loss and painless jaundice, which was highly suspicious for cholangiocarcinoma. A thorough medical history together with laboratory tests, imaging procedures, and endoscopic interventions confirmed that surgery was not needed and led to the final diagnosis of histologically-confirmed, IgG4-related sclerosing cholangitis and autoimmune pancreatitis type 1. Other typical organ manifestations of systemic IgG4-RD were diagnosed through a thorough medical review, which led to immunohistochemical re-evaluation of past surgical specimens. Besides the IgG4-related organ manifestations, which can include peri-orbital xanthelasmas, our patient developed a pulmonary adenocarcinoma 6 years after the initial clinical onset of IgG4-RD. After immunosuppressive treatment with prednisolone alone and subsequently in combination with azathioprine, the patient's IgG4-RD resolved.

Conclusions: Interdisciplinary collaboration is required to diagnose IgG4-RD that involves multiple organs. Patient medical history remains crucial for diagnosis and attention should be paid to avoiding unnecessary surgery. Tumors (lung adenocarcinomas) and xanthelasmas can develop because of IgG4-RD. Glucocorticoids and additional azathioprine may be advisable for maintenance treatment.

Keywords: Cholangitis, Sclerosing • Pancreatitis • Xanthomatosis • Autoimmune Pancreatitis • Adenocarcinoma of Lung

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/930729>



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Background

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a chronic inflammatory disease with a prevalence of about 4.6 people per 100 000 [1], which can affect multiple organ systems [2,3], leading to tissue fibrosis and failure of organs and systems such as the pancreas, biliary tract, salivary and lacrimal glands, lymph nodes, the retroperitoneum, kidneys, and the aorta. Clinically, IgG4-RD presents as unspecific organ swelling or pseudotumors, which can mimic many malignant, infectious, or chronic inflammatory diseases [4]. Serologically, serum IgG4-levels may be increased to >135 mg/dL [4,5].

The criterion standard method for diagnosing IgG4-RD is histology [4]. Different diagnostic criteria exist for systemic- or single-organ involvement, based on the disease's clinical appearance, serology, histology, and imaging studies [5-10].

We present a report about a patient with IgG4-related sclerosing cholangitis (IgG4-SC) that masqueraded as cholangiocarcinoma. He was retrospectively diagnosed with systemic IgG4-RD based on evaluation of his medical history.

Case Report

A 64-year-old man was admitted to the Department of Gastroenterology with acute painless jaundice, a 4-kg weight loss in the last 3 months, dark-colored urine, and gray stools. The patient had noticed the painless jaundice <1 week before admission. He had no episodes of fever, night sweats, diarrhea, steatorrhea, abdominal pain, or dysuria but complained of pruritus. He was White, was born and lived in Germany, and had not traveled abroad. He rarely drank alcohol, did not smoke, and had never consumed illegal drugs. He was married, had 2 children, and worked as an electrician. His family history was positive for gastric and colonic cancer in his father.

On presentation, the patient was in good general condition, with a slender habitus and a body mass index of 23 kg/m². He was alert and oriented to self, location, and time. His skin was light brown with evident scleral jaundice and he had a few superficial scratch marks, associated with itching. Bilateral xanthelasmas were visible under his eyelids.

The patient's vital signs were normal. Auscultation of the heart revealed no pathological findings. Auscultation of the lungs revealed decreased breath sounds above the right upper lung, associated with a lobectomy that had been performed for lung cancer. The patient's other lung lobes had normal breath sounds. His bowel sounds were normal. His liver was slightly enlarged (13 cm) in the midclavicular line. The Courvoisier

sign was negative and no lymph nodes, abdominal resistance, or renal angle tenderness were noted on palpation.

Neurological examination revealed a left peripheral facial nerve palsy, which the patient had acquired after submandibulectomy with lymphatic node resection 7 years before. At that time, he experienced tender neck lymphadenopathy and salivary gland swelling; ultrasonography showed signs of cysts and masses in his submandibular and parotid glands. Because of suspicion of cervical lymphoma and a malignant salivary gland tumor, he underwent a left-sided submandibulectomy with neck lymphadenectomy. Histologically, the specimens were described as sialadenitis with inflammatory hyperplastic lymph nodes as well as follicular lymphatic hyperplasia with no signs of malignancy.

Seventeen months before the current clinical admission, the patient had a curative resection of his upper-right lung lobe for non-small cell lung cancer (NSCLC) (pT1b, pN0 (0/26), L0, V0, G2, R0, KRAS mutation in Exon 2).

Thirteen months before admission, he underwent right-sided parotidectomy for right parotid swelling and a left-sided neck dissection of Levels IB, IIA, III, IV, and V for recurrent, tender, left-sided lymphadenopathy because of suspicion of metastatic metachronous NSCLC. The removed parotid gland showed a lymphoplasmacellular and inflammatory infiltrate and was diagnosed as a cystadenolymphoma (Warthin tumor) with necrotic parotid tissue and no evidence of malignancy. The resected lymph nodes were described on histology as non-caseating epithelioid-cell granulomas with no signs of malignancy.

Nine months before admission, the patient underwent dilatation of his left iliac artery. He was treated with acetylsalicylic acid (100 mg orally/d), which he took regularly. He took no other prescription or nonprescription drugs, depot injections, or herbal preparations and had no history of allergies.

The serum parameters that were found to be abnormal on the patient's admission are listed in **Table 1**. The patient's total bilirubin was elevated at 294.12 µmol/L, consisting of about 70% of the direct-acting fraction (215.46 µmol/L). His transaminases, in contrast, were only slightly elevated, whereas his alkaline phosphatase (AP) (400 U/L) and gamma-glutamyl transpeptidase (γGT) (300 U/L) were increased. This constellation of findings indicated the presence of cholestatic jaundice. Elevation of C-reactive protein (CRP) suggested that cholangitis also might be present. Protein electrophoresis revealed a lowered albumin concentration but increased α₁, β₂, and γ fractions. A >10-fold increase in IgG4-plasma concentration (22.9 g/L) could be responsible for hypergammaglobulinemia. Furthermore, a slight hypertriglyceridemia and a pronounced decrease in the high-density lipoprotein fraction were present.

Table 1. Serum parameters found to be abnormal on patient's admission.

Parameter	Unit	Reference range	Results
Total bilirubin	μmol/L	<20.5	294.12
Conjugated bilirubin	μmol/L	<8.55	215.46
AP	U/L	40-150	400
γGT	U/L	12-64	300
AST	U/L	<35	51
ALT	U/L	<45	61
IgG4	g/L	0.0300-2.0100	22.9
HDL	mg/dL	>40	5
Triglycerides	mg/dL	<200	279
CRP	mg/L	<5	32.6
Protein electrophoresis			
Protein	g/dL	6.6-8.3	7
Albumin	%	55.8-66.1	37.7
α ₁ -globulin	%	2.9-4.9	5.7
α ₂ -globulin	%	7.1-11.8	13.0
β ₁ -globulin	%	4.7-7.2	5.9
β ₂ -globulin	%	3.2-6.5	14.6
γ-globulin	%	11.1-18.8	23.1
Immunoglobulins			
IgG	g/L	5.4-18.2	8,9
IgM	g/L	0.22-2.93	2.6
IgA	g/L	0.63-4.84	2.0

ALT – alanine aminotransferase; AP – alkaline phosphatase; AST – aspartate transaminase; CRP – C-reactive protein; γGT – gamma-glutamyl transpeptidase; HDL – high-density lipoprotein.

Normal values were measured for hemoglobin, hematocrit, erythrocytes, thrombocytes, leukocytes, sodium, potassium, creatinine, lipase, haptoglobin, lactate dehydrogenase, IgG, IgM, IgA, antinuclear antibodies, anti-mitochondrial antibodies (AMAs), anti-smooth muscle antibodies, thyroid stimulating hormone (TSH), total cholesterol, low-density lipoprotein (LDL), apolipoprotein-A1 and -B, lipoprotein a, carbohydrate-antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA). Routine urinalysis and urine sediment examinations showed no pathological findings. Serum titers for hepatitis A, B, and C; cytomegalovirus; Epstein-Barr-virus; HIV1 and 2; and herpes simplex and varicella zoster viruses were negative.

Abdominal ultrasound showed bilateral intrahepatic cholestasis with a dilated common bile duct (CBD) that measured 7 mm, but no intrahepatic or extrahepatic masses. Because of a strong suspicion of cholangiocarcinoma in the liver hilus (Klatskin tumor), contrast-enhanced ultrasound (CEUS) was performed for a targeted transcutaneous bile duct biopsy.

Endoscopic ultrasound (EUS) showed sub-hilar stenosis of the proximal CBD. The pancreas was hypoechoic, which suggested autoimmune pancreatitis (AIP).

Endoscopic retrograde cholangiopancreatography (ERCP) confirmed the presence of a sub-hilar, contrast medium-sparing lesion of unknown origin in the CBD, with consequent intrahepatic biliary tree dilatation (**Figure 1**). Sphincterotomy, biopsy, and brush cytology were performed on the side with the stenosis and a pigtail stent was placed in the CBD.

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) also were performed. The imaging demonstrated multifocal strictures, partly dilated intrahepatic biliary tracts, and a central T2 signal-sparing lesion in the CBD. Axial T1-weighted, contrast-enhanced MRI demonstrated delayed enhancement of the pancreatic tail compared to the pancreatic head. This is a characteristic feature of AIP type 1 (**Figures 1 and 2A1-2A3**).

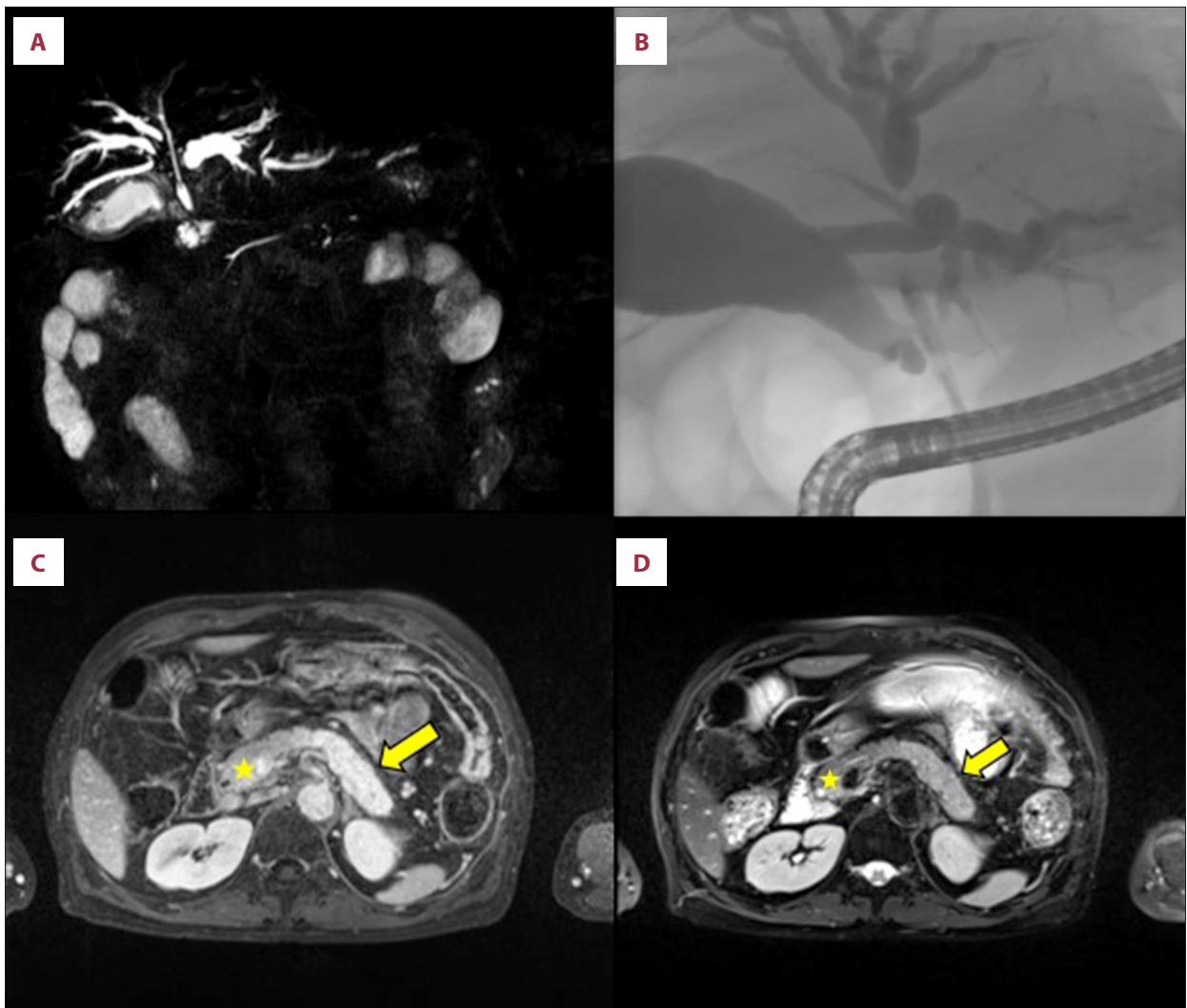


Figure 1. Magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) on admission (before treatment). **(A)** MRI and MRCP with contrast medium before treatment show multifocal strictures, partly dilated intrahepatic biliary tracts, and a central T2-signal-sparing lesion in the common bile duct (CBD). Those findings are usually indistinguishable from those of primary sclerosing cholangitis or hilar cholangiocarcinoma. There were no intrahepatic or pancreatic masses that could have caused an obstructive jaundice. In the contrast-enhanced, T1-weighted studies, no signs of pathological signal alterations were detectable in the pancreatic head. **(B)** ERCP on admission shows signs of intrahepatic and extrahepatic biliary tree dilatation and a subhepatic contrast medium-sparing lesion in the CBD. **(C)** Axial T1-weighted, contrast-enhanced MRI in a more delayed phase demonstrates a delayed enhancement of the pancreatic tail (arrow) compared to the pancreatic head (star). This is a characteristic feature of autoimmune pancreatitis. **(D)** Axial T2-weighted imaging reveals a slight but diffuse enlargement of the pancreatic tail and loss of normal fatty lobulation of the organ, along with a slim, hypointense halo around the pancreatic tail (arrow) compared to the head (star). The main pancreatic duct is tender and not dilated.

The brush cytology, performed by ERCP, showed normal epithelial cells with no signs of malignancy.

Histology of the specimen from the CBD biopsy, performed by CEUS, showed proliferating bile ducts with ascending cholangitis, compatible with a biliary obstruction. No malignant tumor cells were evident. Immunohistochemical staining for IgG and IgG4 revealed an increased IgG4-positive plasma-cell infiltrate

(>50/hpf) and an IgG4/IgG rate >40%, compatible with IgG4-SC (**Figure 3A**) [11].

With respect to these findings, past surgical specimens (left-sided neck dissection, left submandibular gland, right parotid gland) were retrospectively examined for IgG4-RD with immunohistochemistry (**Figure 3B, 3C**).

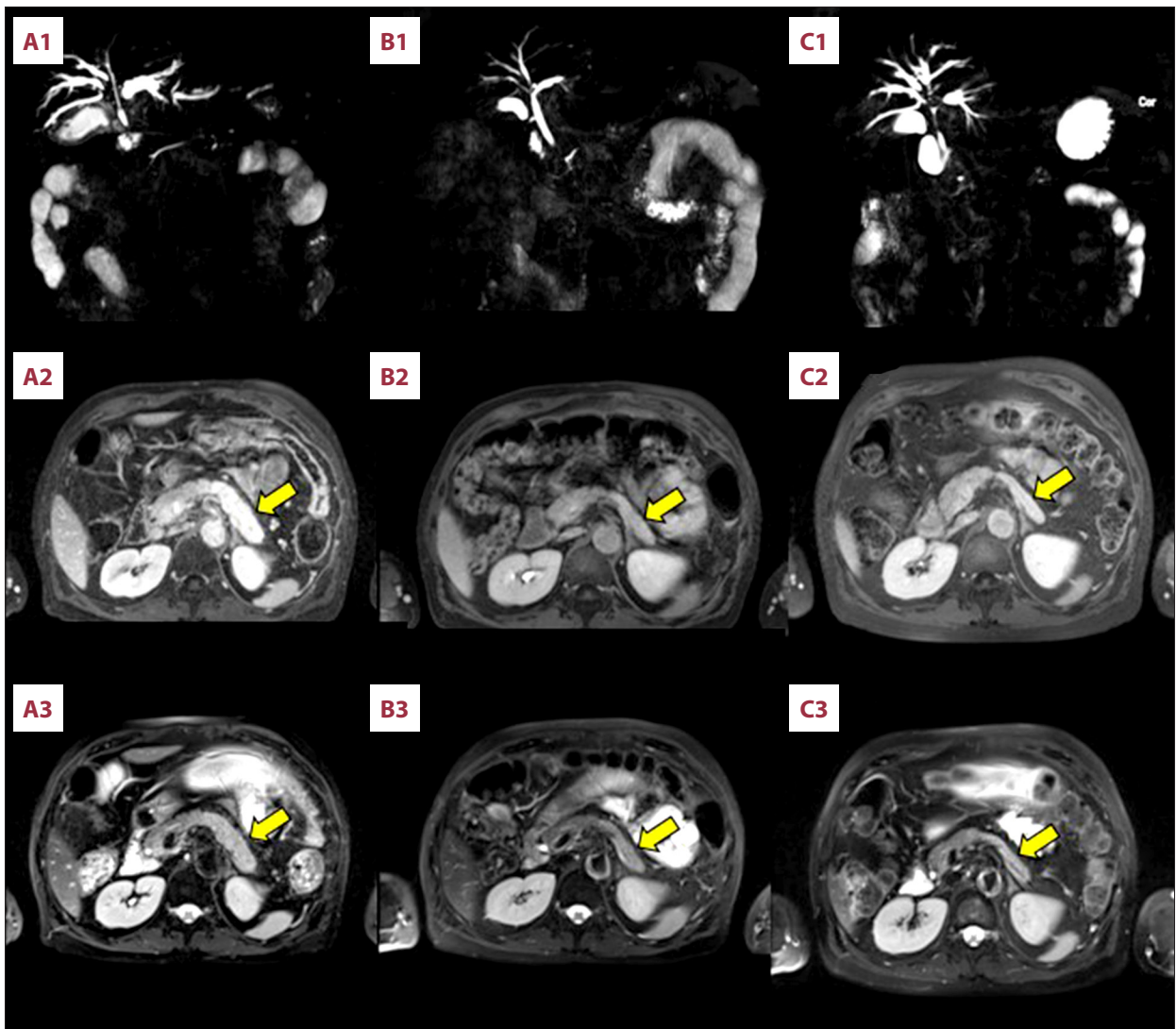


Figure 2. Magnetic resonance cholangiopancreatography (MRCP) and magnetic resonance imaging (MRI) studies at different times during treatment of immunoglobulin G4-related disease. (**A1-A3**: on admission, **B1-B3**: after 6 weeks, **C1-C3**: after 5 months of treatment). **A1** MRCP shows initial intrahepatic and extrahepatic biliary tree dilatation on admission (before treatment) (also see **Figure 1A**). **B1** After 6 weeks of the steroid therapy, MRI reveals total resolution of the subhepatic common bile duct (CBD) stenosis. **C1** shows a progressive CBD stenosis with dilated intrahepatic bile ducts after short discontinuation of prednisolone, about 5 months after the start of treatment. **A2, B2, C2** (axial T1-weighted) and **A3, B3, C3** (axial T2-weighted): In the follow-up examinations after 6 weeks (**B2, B3**) and 5 months later after steroid therapy (**C2, C3**), the pancreas appears normal-size, with resolution of the previously seen low-attenuation halo, although a high T2 signal and delayed enhancement of the parenchyma were still detectable on MRI.

To our surprise, all of the specimens showed increased IgG4-positive plasma-cell infiltration and an IgG4/IgG rate >40%, leading to the diagnosis of systemic IgG4-RD. Thus, this disease was already present in the patient's neck lymph nodes and submandibular and parotid glands several years before and had manifested in his hepatobiliary system as IgG4-SC, masquerading as cholangiocarcinoma. Furthermore, there was probably an additional manifestation of this disease as AIP type 1 in the pancreatic tail (MRCP, **Figures 1C, 1D and 2A2, 2A3**). However, histology of the pancreas was not performed; thus,

AIP was not identified, because no signs of clinically apparent pancreatitis were present.

The resected NSCLC of the right upper lung also showed positive immunoreactivity for IgG4. Histologically, the IgG4-positive plasma cells were arranged in peritumoral follicular lymphocyte aggregates but overall, they were not in direct contact with the carcinoma cells (data not shown).

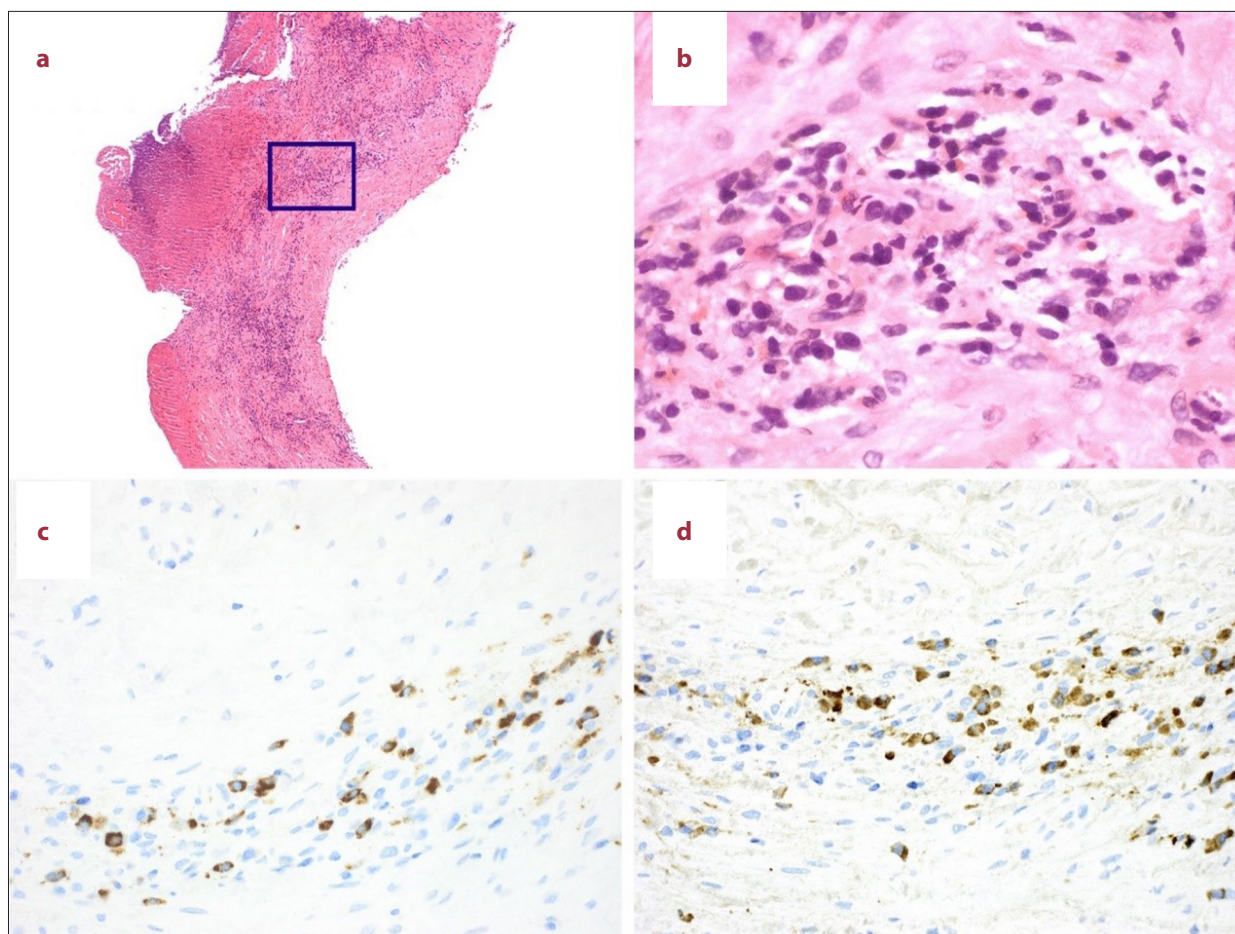


Figure 3A. Histological and immunohistochemical findings from the common bile duct (CBD) biopsy on admission. (a) Bile duct biopsy of the CBD with hematoxylin and eosin (HE) staining shows marked chronic inflammation with low-power magnification ($\times 10$) and increased numbers of plasma cells (b) at higher magnification ($\times 400$). Immunohistochemistry reveals increased numbers of immunoglobulin (Ig) G4-positive plasma cells (c) relative to IgG-positive forms (d) (immunoperoxidase, $\times 200$).

Administration of high-dose oral prednisolone (60 mg) resulted in a marked decrease in the patient's total bilirubin within about 3 weeks (Figure 4). His levels of AP, γ GT, aspartate transaminase (AST), and alanine aminotransferase (ALT) also decreased to nearly normal values during that time (data not shown).

Unfortunately, the patient developed increased blood glucose concentrations while taking prednisolone, which had to be controlled with long- and short-acting insulin (Levemir, Actrapid). Apart from the hyperglycemia, he tolerated the prednisolone well.

For prevention of osteoporosis and a peptic ulcer during glucocorticoid treatment, vitamin D (1000 IE/d), calcium (1250 mg/d), and pantoprazole (40 mg/d) were administered orally.

During the treatment that followed, prednisolone was tapered gradually to a maintenance dose of 10 mg/d under control of cholestatic serum parameters (Figure 4). With this treatment, the

patient was in clinical and biochemical remission. Follow-up MRI and MRCP, which were performed about 6 weeks after the start of the steroid therapy, showed total resolution of the sub-hilar CBD stenosis with no signs of cholestasis, as well as a reduction in the focal AIP in the tail of the pancreas (Figure 2B1-2B3).

In addition to radiological remission, follow-up blood tests showed a nearly normal total bilirubin level (Figure 4). Furthermore, the patient's cholestatic parameters, transaminases, hypergammaglobulinemia, and hypoalbuminemia also normalized (data not shown).

After about 5 months of prednisolone treatment, without consultation, the patient tapered his dosage from 10 mg/d to 5 mg/d for 2 days, which resulted in a distinct increase in total bilirubin ($191.52 \mu\text{mol/L}$) (Figure 4). Furthermore, his γ GT (1211 U/L), AP (313 U/L), ALT (143 U/L), and AST (143 U/L) were increased. Parameters of liver synthesis (international normalized ratio, Quick, albumin) remained in normal.

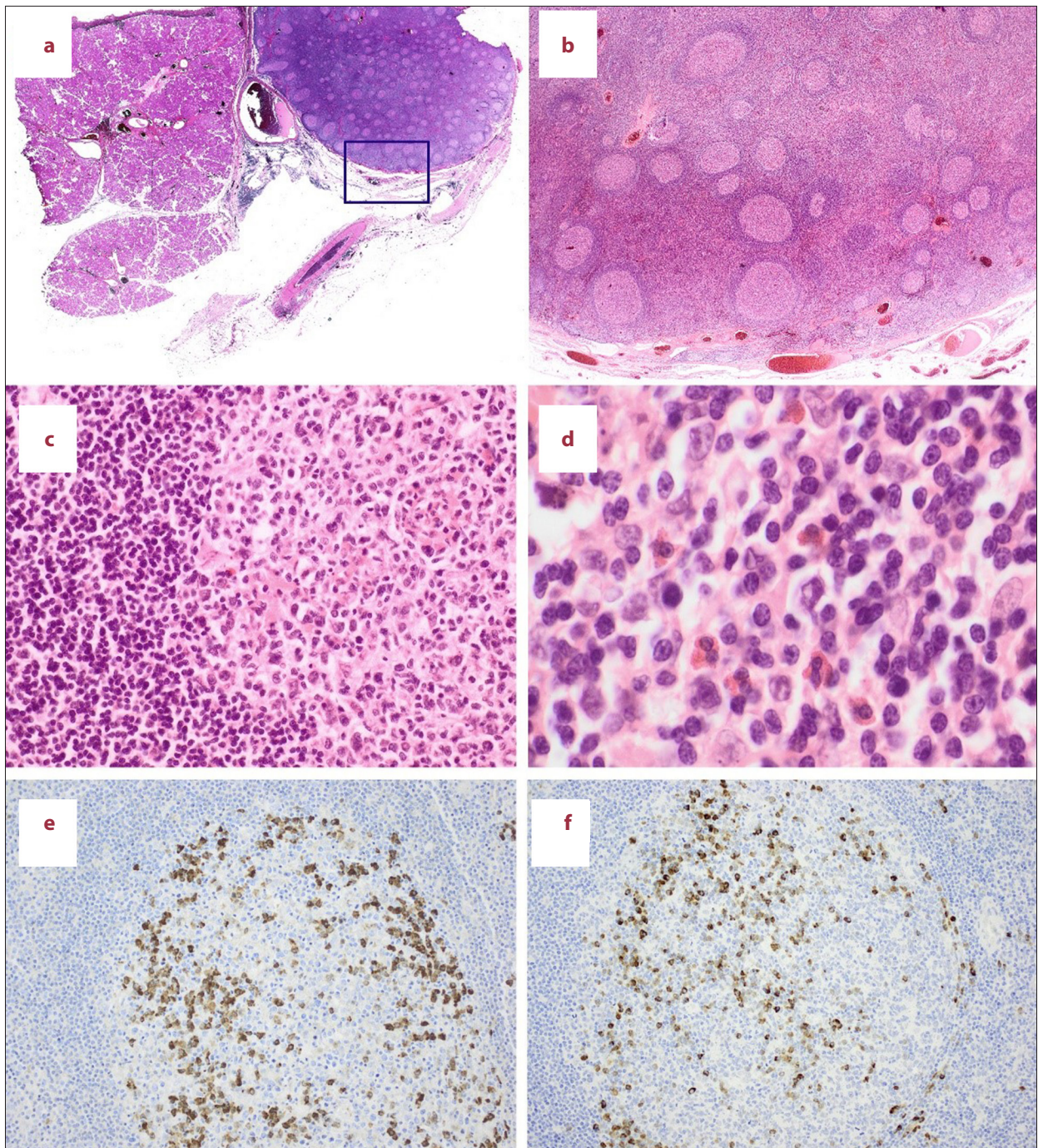


Figure 3B. Retrospectively analyzed immunoglobulin (Ig) G4 preparations in chronological order: Submandibular gland (**left**) with lymph nodes (**right**) 7 years before the diagnosis of IgG4-RD. (**a**) Low-power magnification (HE, $\times 10$) of the submandibular gland (left side) and enlarged cervical lymph node (right side) with (**b**) increased number of lymphoid follicles (HE, $\times 100$). At higher magnification (**c**), the germinal centers have a monotonous appearance with loss of proliferation areas (HE, $\times 200$) and (**d**) increased numbers of plasma cells and eosinophilic granulocytes (HE, $\times 400$). Immunohistochemistry shows significantly increased numbers of IgG4-positive plasma cells (**e**) relative to IgG-positive forms (**f**) (immunoperoxidase, $\times 200$).

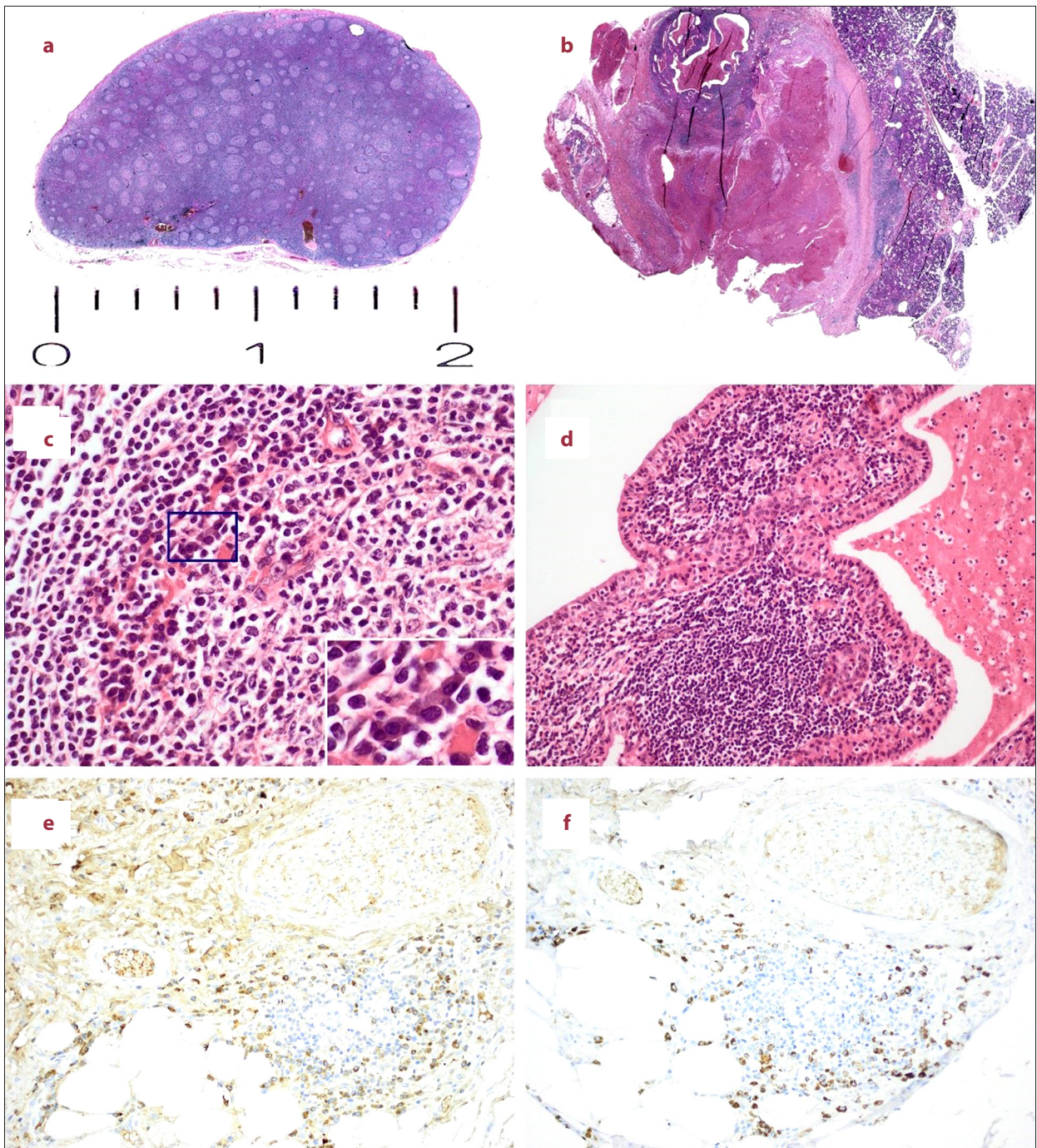


Figure 3C. Parotid tumor and enlarged lymph nodes 13 months before the diagnosis of immunoglobulin (Ig) G4-related disease. Low-power magnification shows (a) an enlarged lymph node with increased numbers of lymphoid follicles and (b) the parotid gland with an encapsulated cystic tumor (HE, $\times 10$). The lymphoid follicles (c) in the lymph node show increased numbers of plasma cells (inset), especially at the border between the germinal center and mantle zone (HE, $\times 200$). (d) The parotid tumor was a so-called cystadenolymphoma (Warthin tumor), also with increased numbers of plasma cells (not shown) (HE, $\times 200$). Immunohistochemistry again shows significantly increased numbers of IgG4-positive plasma cells (e) relative to IgG-positive forms (f) (immunoperoxidase, $\times 200$).

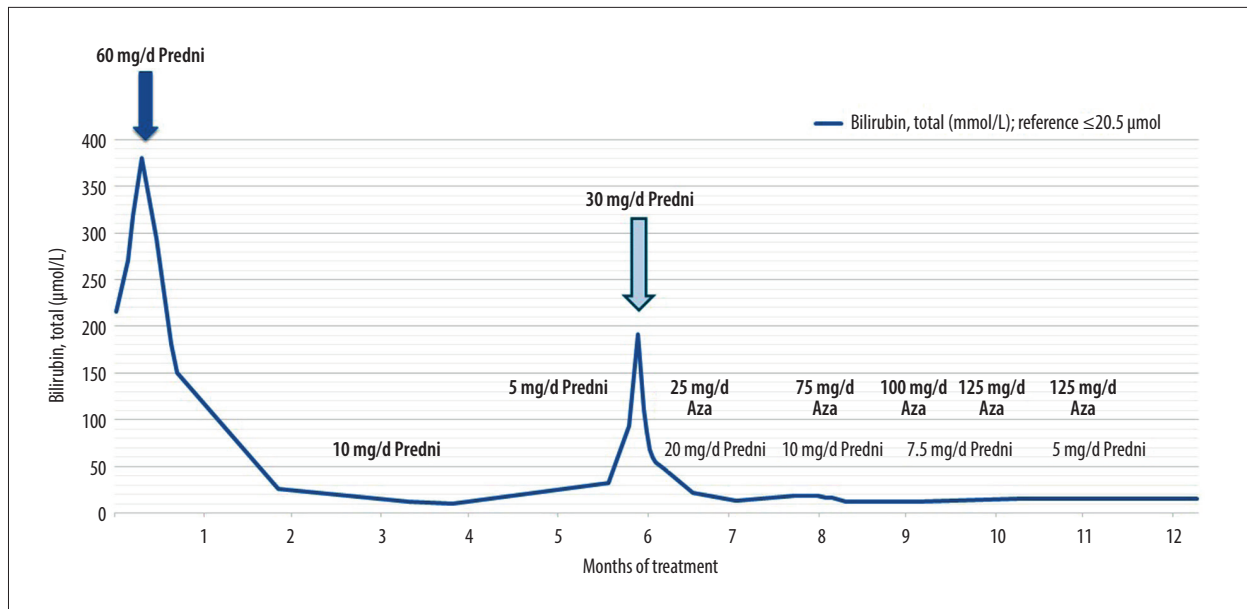


Figure 4. Total bilirubin during the patient's clinical course while being treated with prednisolone (Predni) and azathioprine (Aza).

Because of suspected cholangitis (CRP 99.3 mg/L; normal value <5 mg/L), blood cultures were taken and treatment was started with a broad-spectrum antibiotic, meropenem. With this therapy, the patient's CRP normalized; the results of the blood cultures were negative.

Abdominal ultrasound showed signs of intrahepatic and extrahepatic cholestasis, again with no evidence of a clear bile-flow obstruction. MRI (Figure 2C1-2C3) showed progressive CBD stenosis with dilated intrahepatic bile ducts. An ERCP confirmed the presence of multiple bile duct strictures, which were compatible with IgG4-SC (data not shown).

The patient's oral prednisolone was increased to 30 mg/d for 1 week and tapered gradually to 20 mg/d, resulting in near normalization of his total bilirubin (Figure 4) as well as of AP, γ GT, AST, and ALT after about 3 weeks of treatment.

The patient's lipids remained elevated (total cholesterol 303 mg/dL, triglycerides 352 mg/dL, LDL 191 mg/dL), whereas his HDL concentrations were slightly reduced (32 mg/dL). Statin therapy was not started because of possible hepatic adverse effects and the patient's aversion to the drug.

Prednisolone was further tapered slowly to 5 mg and azathioprine was started as an additional immunosuppressive agent (Figure 4).

Subsequently, the patient remained free of symptoms and his blood tests showed normal values for total bilirubin, cholestatic parameters, and transaminases after 1 year of immunosuppressive treatment. The xanthelasmas on his eyelids did

not change in their appearance and staging examinations using computed tomography of the neck, chest, and abdomen excluded a recurrence of the NSCLC and showed no signs of cholestasis in his liver.

Discussion

Our patient presented to the clinic with obstructive painless jaundice due to a suspected sub-hilar CBD stenosis, which was associated with intrahepatic and extrahepatic cholestasis on imaging. His history of cervical lymphadenopathy and benign salivary gland enlargement combined with radiological signs of a focal AIP in the tail of the pancreas was suggestive of systemic IgG4-RD.

Serologically, the patient's IgG4 plasma levels were increased and immunohistochemical analysis of a sample from a CBD biopsy revealed IgG4-SC. Treatment with high-dose oral prednisolone resulted in normalization of bilirubin, cholestatic parameters (AP, γ GT), and transaminases (AST, ALT).

Histologically, IgG4-RD often presents with a lymphoplasmic cell infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and obliterating phlebitis. Furthermore, immunohistochemical differentiation between IgG- and IgG4-positive plasma cells with a ratio of IgG4-positive to IgG >40% as well as >10 IgG4-positive plasma cells/hpf is of diagnostic importance. In addition, an eosinophilic granulocyte infiltrate can occur in the histological picture of IgG4-RD [12]. An isolated increase in serum IgG4 increase is not a reliable parameter for diagnosis of IgG4-RD [4].

It is noteworthy that in the present case, the initial manifestation of IgG4-RD was IgG4-related sialadenitis of the submandibular gland (Küttner tumor), which had occurred 7 years before. It also manifested as IgG4-related parotitis in a benign cystadenolymphoma (Whartin tumor), also known as Mikulicz disease, and as cervical IgG4-related lymphadenopathy. The current presentation of the disease was IgG4-SC, probably with an associated focal AIP type 1 seen on the MRI, MRCP, and EUS. It is remarkable that our patient never developed symptoms typical of pancreatitis and his lipase levels were never abnormal. Because signs of malignancy in the pancreas were missed on imaging (MRI, MRCP, EUS), the organ was not biopsied.

According to the HISORt criteria (Histology typical for IgG4-RD, Imaging of the pancreas, Serology (elevated IgG4-levels), Other organ involvement of IgG4-RD and Response to steroid treatment in the imaging studies) [13], the findings in our patient's pancreas are compatible with the diagnosis of AIP type 1, given the typical imaging signs (with a "diffusely enlarged gland with a delayed (rim) enhancement"), increased serum IgG4 levels, other IgG4-related organ involvement (sialadenitis, lymphadenopathy, cholangiopathy), and radiological improvement of the AIP after treatment with steroids. Furthermore, the international consensus guidance statements on the treatment of IgG4-RD suggest that "the most accurate assessment of IgG4-RD is based on a full clinical history, physical examination, selected laboratory investigations, and appropriate radiology studies" [7]. Therefore, a histologic study of the pancreas to confirm the diagnosis of AIP type 1 seemed unnecessary.

Our patient's clinical course, with synchronous or metachronous multiorgan manifestations and good response to steroids, is typical of IgG4-RD [2,3].

About 5 months after the start of immunosuppressive treatment with prednisolone, a relapse of his CBD stricture occurred, which was probably caused by the short period of dose reduction of prednisolone from 10 mg to 5 mg per day. Relapses of IgG4-SC often occur after dose reduction of glucocorticoids [14]. Risk factors for disease relapse in IgG4-RD are high serum IgG4 levels; involvement of the proximal bile duct, pancreas, and multiple organs; a high level of soluble IL-2 receptor; and low levels of IgA and IgM [15,16].

You et al [14] reported that patients with relapsed-IgG4-SC less often develop the full picture of AIP type 1. These findings are in line with our observations in the present case that the patient developed just focal AIP in the tail of the pancreas with organ enlargement and typical (rim) enhancement but with no narrowing of the pancreatic duct. In addition, he had no clinical or laboratory signs of pancreatitis.

Subsequent treatment with azathioprine resulted in a good clinical and biochemical response in the ensuing months, until 1 year after therapy initiation.

Our patient's clinical course underscores the effectiveness of high-dose glucocorticoid treatment for disease remission but also shows that glucocorticoid monotherapy failed during dose reductions, which resulted in relapse of IgG4-SC.

Glucocorticoid monotherapy is known to fail to control IgG4-RD over the long term [7] and it is associated with increased toxicities, such as diabetes, osteoporosis, hyperlipidemia, secondary adrenal insufficiency, thrombosis, and risk of bacterial infections [17-20], particularly in older patients [17].

Our patient was 64 years old, had glucocorticoid-induced diabetes, hyperlipemia, a bacterial infection (cholangitis), multiorgan involvement of IgG4-RD, and relapsed IgG4-RD, which increased his risk for further disease relapses. Therefore, glucocorticoid monotherapy would not be a realistic option for long-term control of his IgG4-RD.

The combination of glucocorticoids with immunomodulators has been shown to induce higher remission and lower relapse rates than glucocorticoid monotherapy [23]. In many studies, azathioprine is the immunomodulatory agent commonly used to treat IgG4-RD [7,22-25]. Further, the combination of azathioprine with glucocorticoids is in line with current recommendations and guidelines [7,12,21,22]. However, most of these recommendations are mainly based on retrospective and observational studies rather than on randomized controlled trials, which are needed to prove the efficacy and safety of these regimens [17,23].

Reports about treatment with glucocorticoid monotherapy versus combination therapy with immunomodulators are conflicting [22]. In our patient, however, tapering the dose of prednisolone during treatment with it combined with azathioprine was effective and he had no further relapses of IgG4-RD during follow-up.

Another point of interest is that immunohistochemical analysis of the R0 resected NSCLC (pT1b, pN0 (0/26), L0, V0, G2, R0, KRAS mutation in Exon 2), which presented 17 months before the patient's current admission, showed focal IgG4 plasma cells but no connection with the pulmonary adenocarcinoma. No relationship between malignancy and IgG4-RD has previously been documented, but malignancy has been described as a coincidental finding before or after onset of IgG4-RD [26-30]. The current European Guideline on IgG4-RD describes a relative increased risk of development of malignant diseases such as cancers of the lung, colon, pancreas, and bladder, and lymphoma or leukemia in patients with IgG4-RD [22]. Other

authors have described frequent malignancies in patients with IgG4-RD, mainly extra-pancreatic tumors such as carcinomas of the stomach, prostate, and lung [31].

In this context, a single study also has demonstrated that in patients with AIP, frequency of *KRAS* mutations in the pancreas, CBD, and gallbladder is increased, leading to the suspicion that AIP might be related to *KRAS* mutations, and therefore may be a risk factor for cancer [28].

The NSCLC in our patient had a *KRAS* mutation in Exon 2, which gives rise to the assumption that the disease might have been induced by the pre-existing IgG4-RD. Documentation on more such cases is necessary to determine whether patients with IgG4-RD may be at increased risk of NSCLC with *KRAS* mutation. In our patient, however, follow-up tumor staging with CT of the thorax, abdomen, and head showed no recurrence of the NSCLC after 1 year of treatment.

In the present case, physical examination showed periorbital xanthelasma palpebrarum. Of note, adult-onset asthma and periocular xanthogranuloma, a disease first described by Jakobiec et al in 1993 [32], has recently been linked with IgG4-RD in observational case studies [33,34]. In contrast to the findings described in these reports, the appearance of our patient's xanthelasmas did not change in response to immunosuppressive treatment.

In another retrospective study involving 118 patients with IgG4-related pancreatitis, a high number of them had xanthomatous or xanthogranulomatous findings, including necrobiotic xanthogranuloma [35]. Skin manifestations of IgG4-RD also have been described as livid-papulous formations [36,37].

Xanthelasmas also can be a symptom of primary biliary cholangitis, thyroid dysfunction, or a lipid disorder [38]. In our patient, thyroid dysfunction and primary biliary cholangitis were unlikely because of the normal values for TSH and AMA. He had significantly decreased HDL levels (5 mg/dL), which might have favored the development of xanthelasma palpebrarum as a primary lipid disorder [39]. However, several other lipid disorders were unlikely, given the normal values for apolipoprotein-A1 and B, lipoprotein a, total cholesterol, and LDL. Given these findings, the xanthelasmas seemed to be part of systemic IgG4-RD. Similar findings in a case of histologically-confirmed IgG4-RD that are compatible with those seen in our patient support our clinical observations [40].

Recently, new markers for disease activity in IgG4-RD, such as IgG4-positive plasma blasts (CD19⁺CD27⁺CD20⁻CD38^{hi}), have been described. They correlate with disease activity and may be parameters for monitoring disease and response to treatment, even in patients who have negative serum IgG4 levels [41]. CD4-positive cytotoxic T cells also seem to correlate well with disease activity [42]. In addition, Annexin A11, a calcium-dependent phospholipid-binding protein, has been described as a specific antigen in IgG4-SC and AIP [43].

Conclusions

Manifestation of IgG4-RD is rare and presentations can be local or systemic. Over time, however, the disease affects multiple organs. Taking a thorough medical history and reevaluating surgical specimens are essential for establishing the diagnosis, which involves the presence of IgG4 plasma cells in tissue, according to the HISORT criteria. The present case report underscores the efficacy and safety of azathioprine in combination with prednisolone for treatment. Attention should also be paid to the presence of IgG4-RD and neoplasia in various organs.

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