IMMUNOGLOBULIN G4-RELATED DISEASE (IGG4-RD)

DIAGNOSIS AND TREATMENT APPROACH

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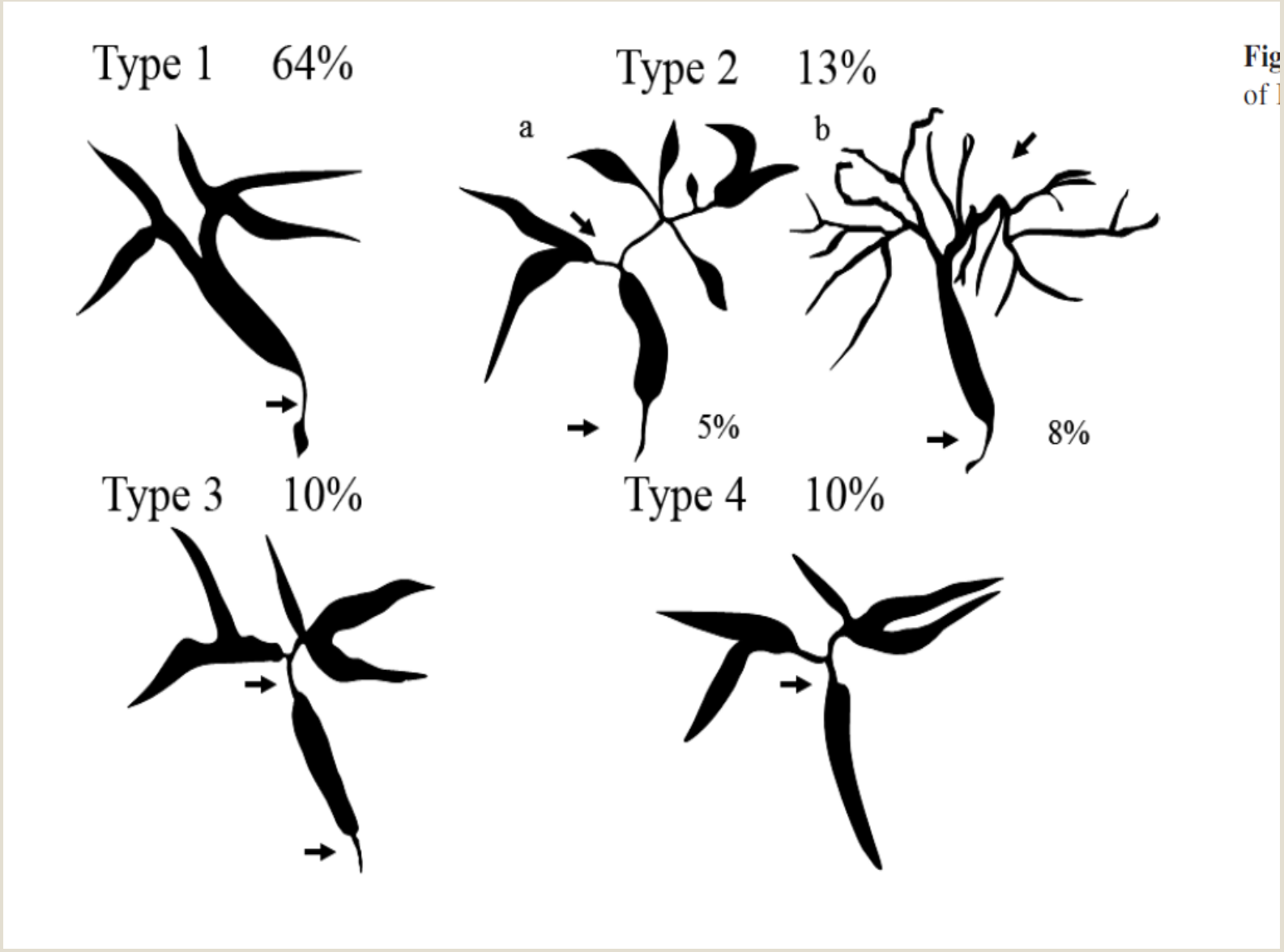
INTRODUCTION

- Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory condition that can affect multiple organs

- Diagnosis of IgG4-RD relies on a blend of characteristic histopathologic, clinical, serologic, and radiologic findings.
- Key features include organ swelling resembling tumors, lymphoplasmacytic infiltrate with IgG4-positive plasma cells, and distinctive "storiform" fibrosis.
- Elevated IgG4 levels are detected in 60-70% of IgG4-RD patients.

The major examples of patients at high risk for having IgG4-RD are those with any of the following:

- Pancreatitis of unknown origin
- Sclerosing cholangitis
- Bilateral salivary and/or lacrimal gland enlargement
- Retroperitoneal fibrosis (RPF)
- Orbital pseudotumor or proptosis
- Development of a mass lesion in any of the following organs: pancreas, biliary tree, orbits, lungs, kidneys, major salivary gland, or lacrimal gland
- Finding of a serum IgG4 concentration greater than five times the upper limit of normal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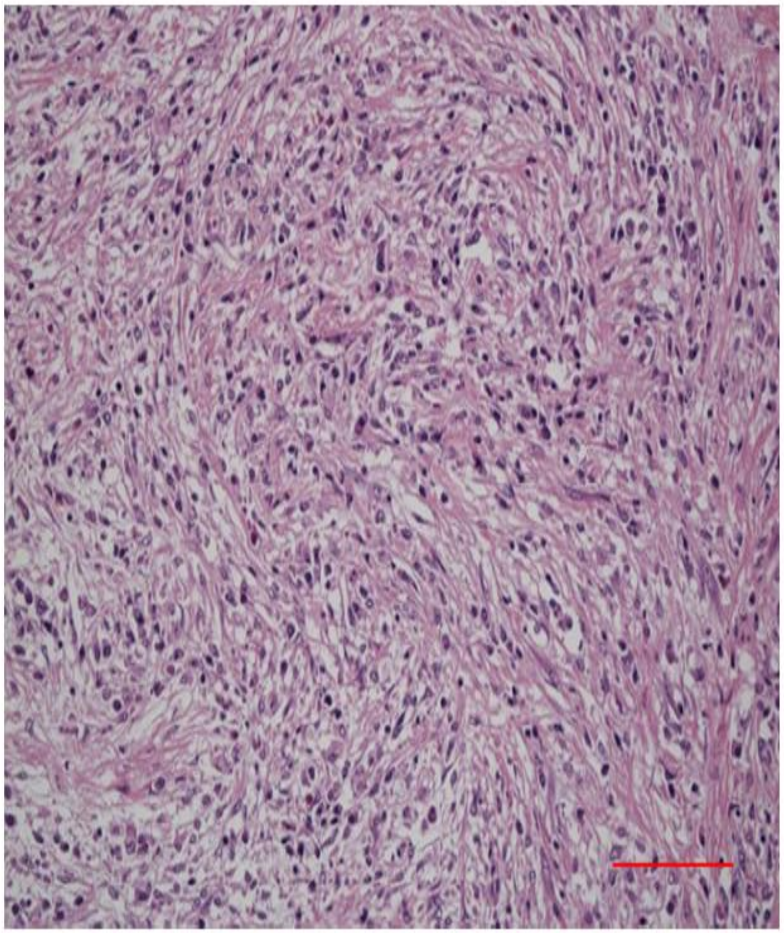

Fig. 3 Histological findings of storiform fibrosis in the bile duct of IgG4-SC. (Scale: 100 μm)

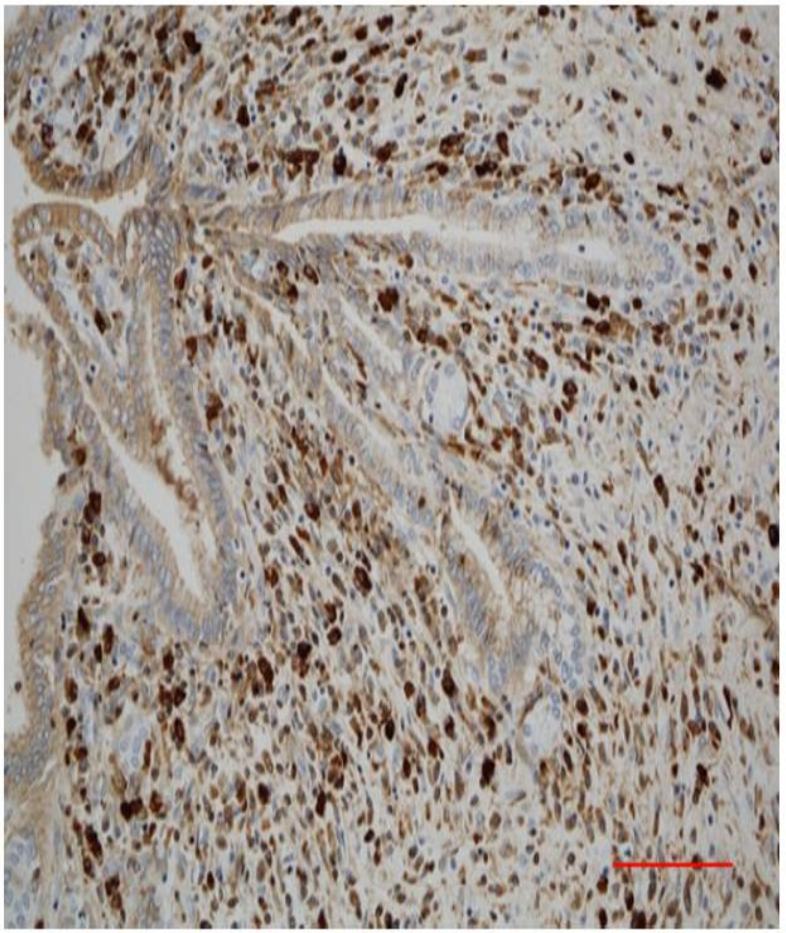

Fig. 5 Immunohistochemical findings of infiltration of numerous IgG4-positive cells in the bile duct of IgG4-SC. IgG4-immunostaining. (Scale: 100 μm)

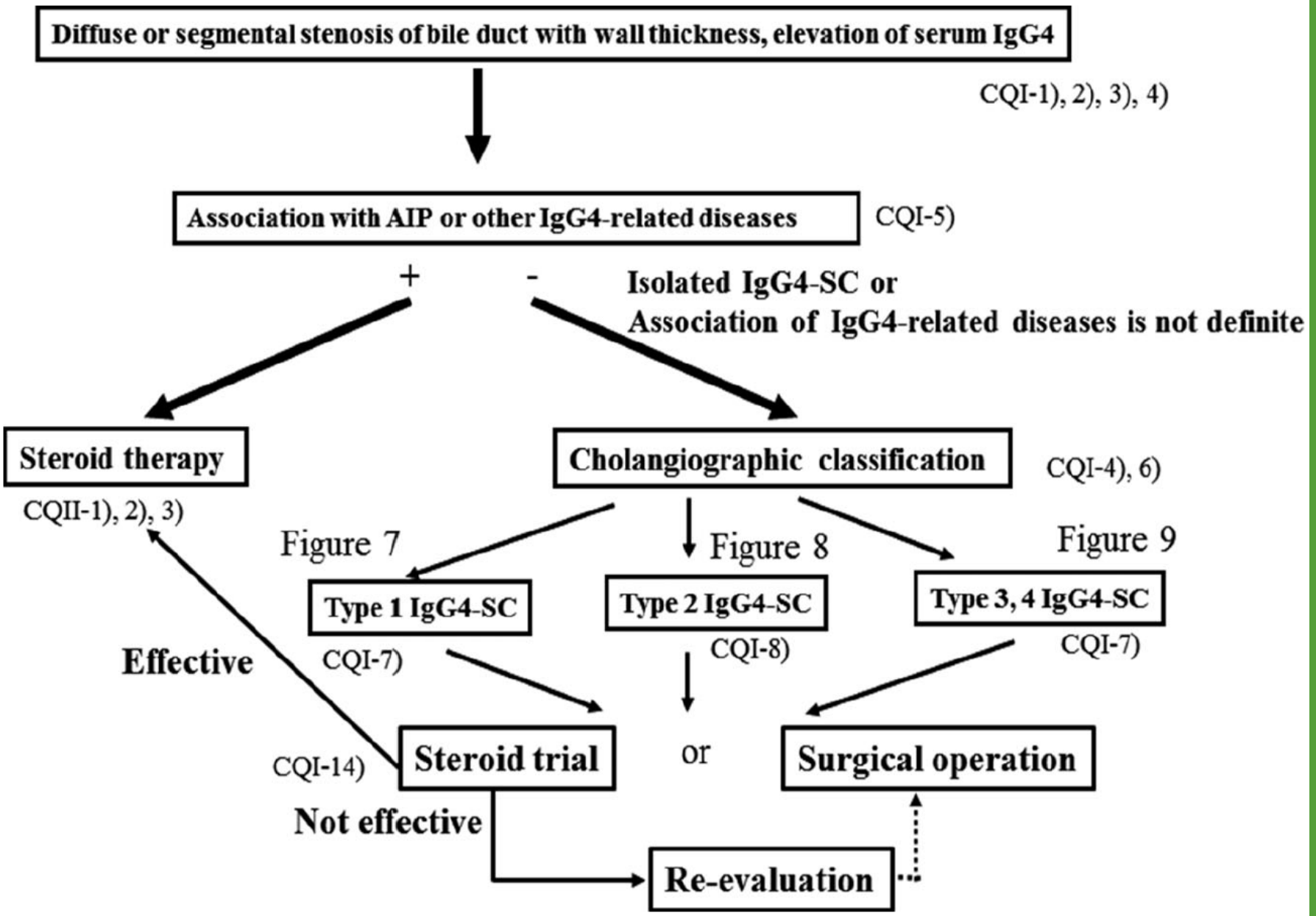

Fig. 6 Algorithm for diagnosis and treatment of IgG4-SC referred from Reference 18

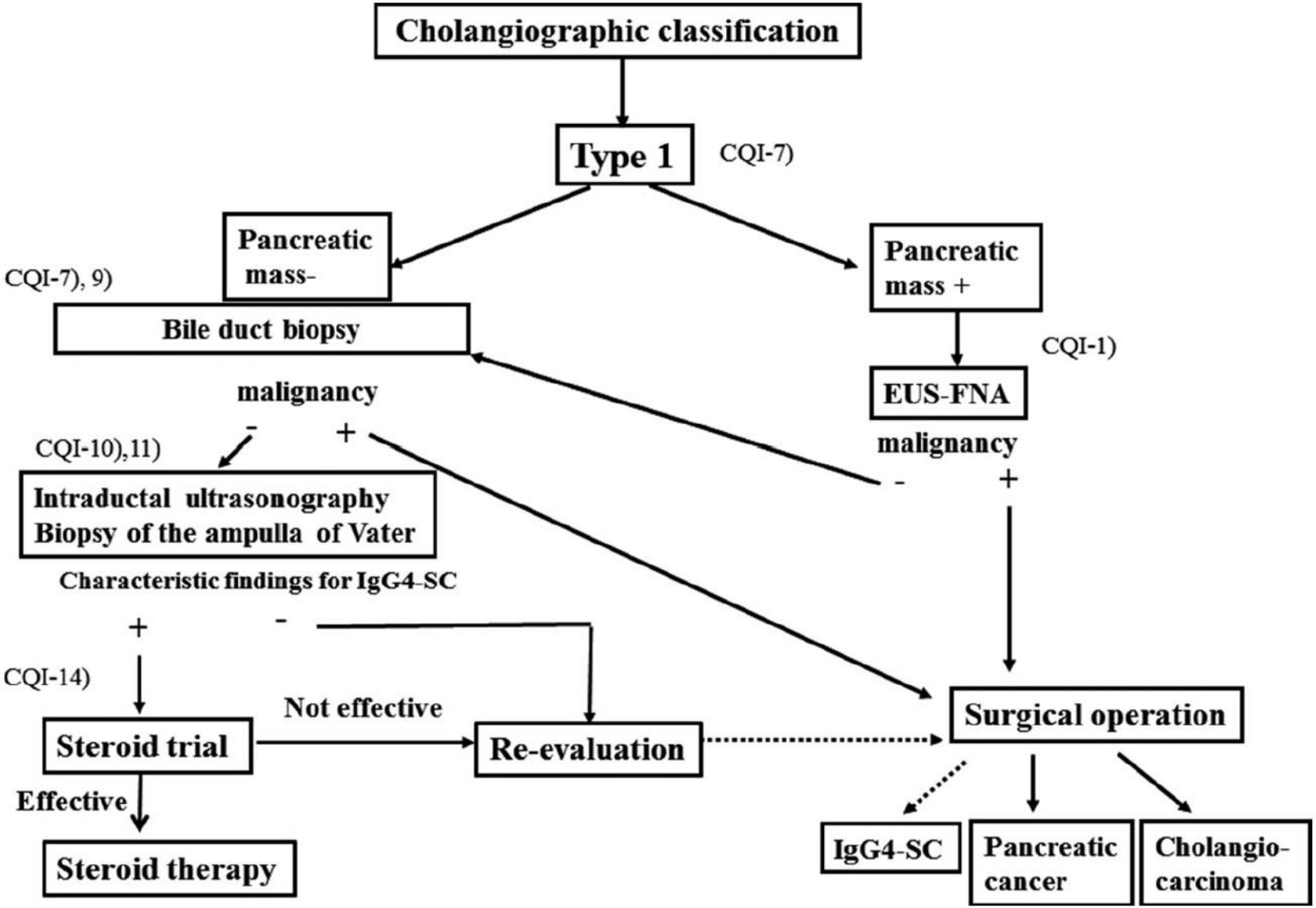

Fig. 7 Algorithm for diagnosis and treatment of IgG4-SC referred from Reference 18

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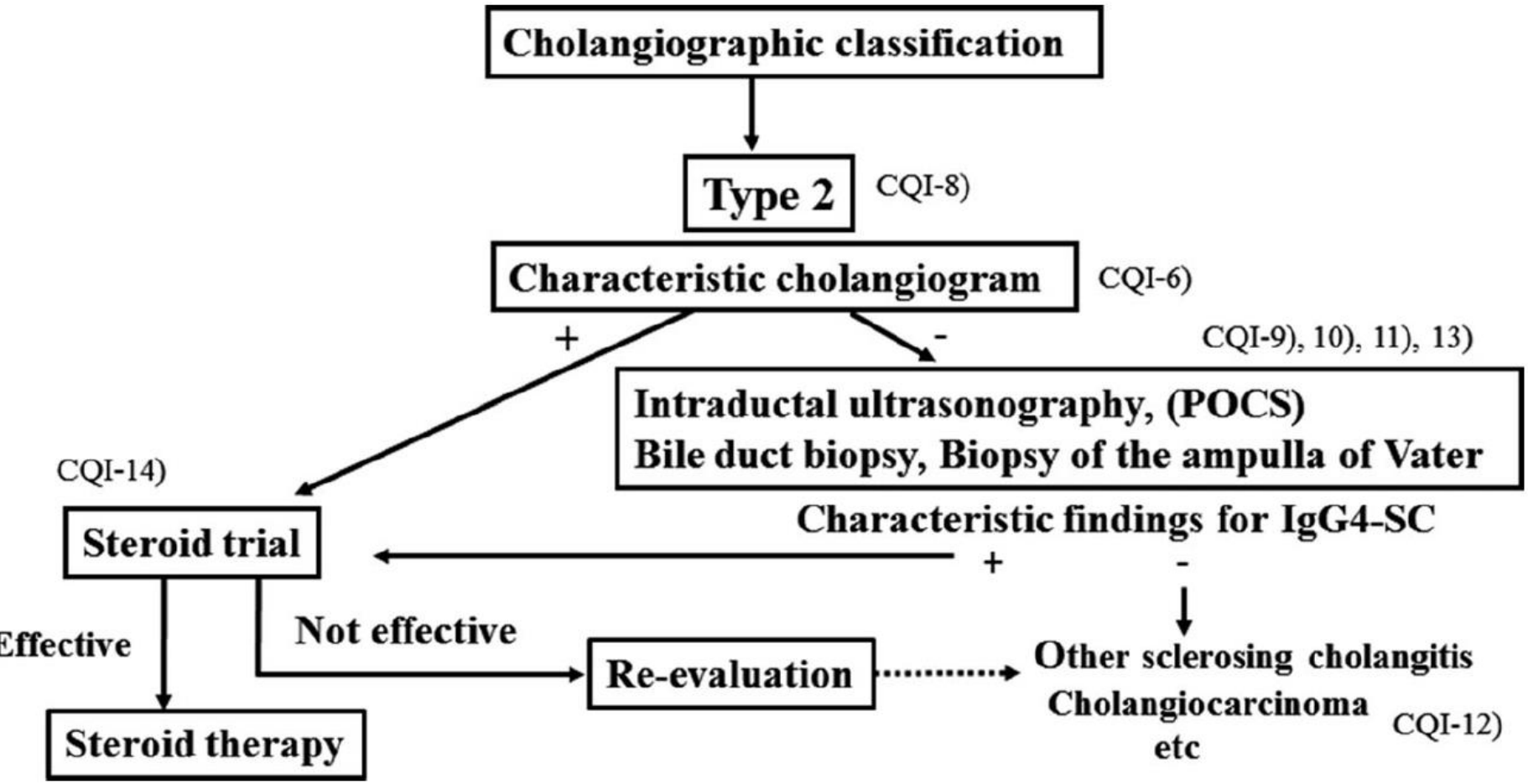
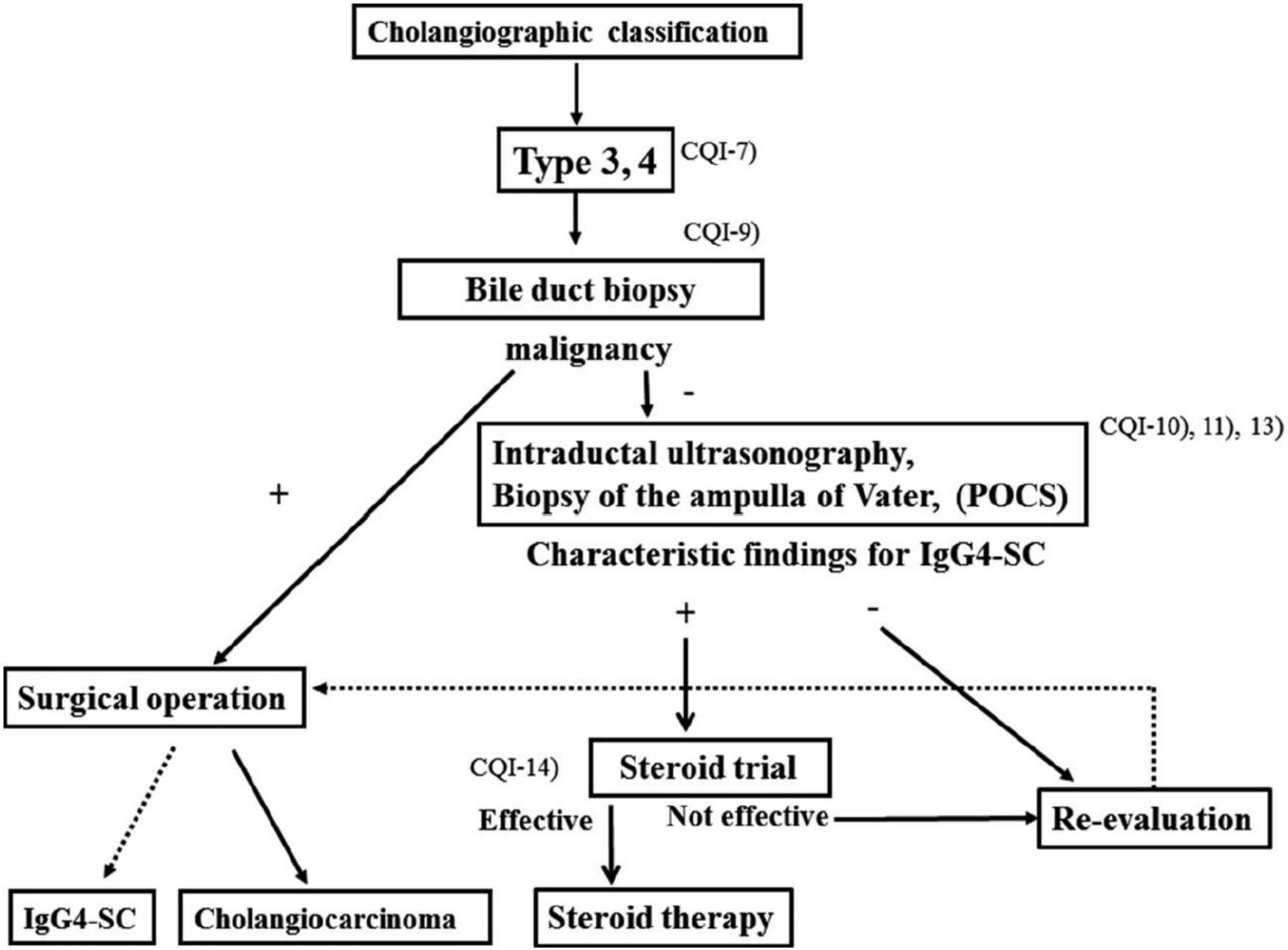


ig. 8 Algorithm for diagnosis and treatment of IgG4-SC referred from Reference 18

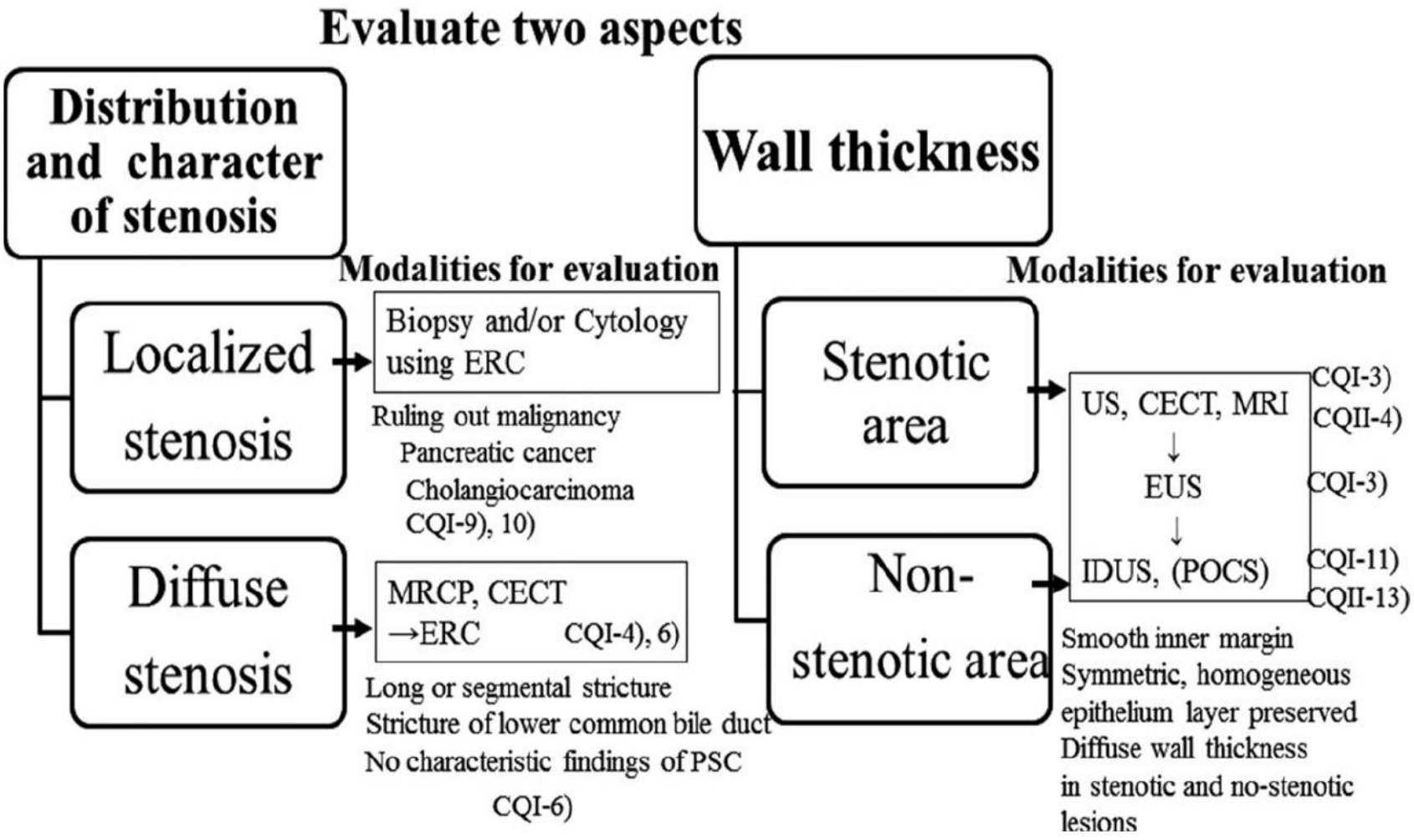

Cholangiographic classification
Type 3, 4
CQI-7)
CQI-9)
Bile duct biopsy
malignancy
-
+
Intraductal ultrasonography,
Biopsy of the ampulla of Vater, (POCS)
CQI-10), 11), 13)
Characteristic findings for IgG4-SC
+
-
Surgical operation
CQI-14)
Steroid trial
Effective
Not effective
Re-evaluation
IgG4-SC
Cholangiocarcinoma
Steroid therapy

1. Imaging reflect characteristic pathological findings

1) Submucosal inflammation with little change of epithelium

2) Wall thickness diffusely spreading to no-stenotic bile duct in cholangiogram

2. Dramatic improvement by steroid therapy



1. Diagnostic items

(1) Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall.

(2) Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl).

(3) Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis.

(4) Histopathological examination shows:

a. Marked lymphocytic and plasmacyte infiltration and fibrosis

b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF

c. Storiform fibrosis

d. Obliterative phlebitis

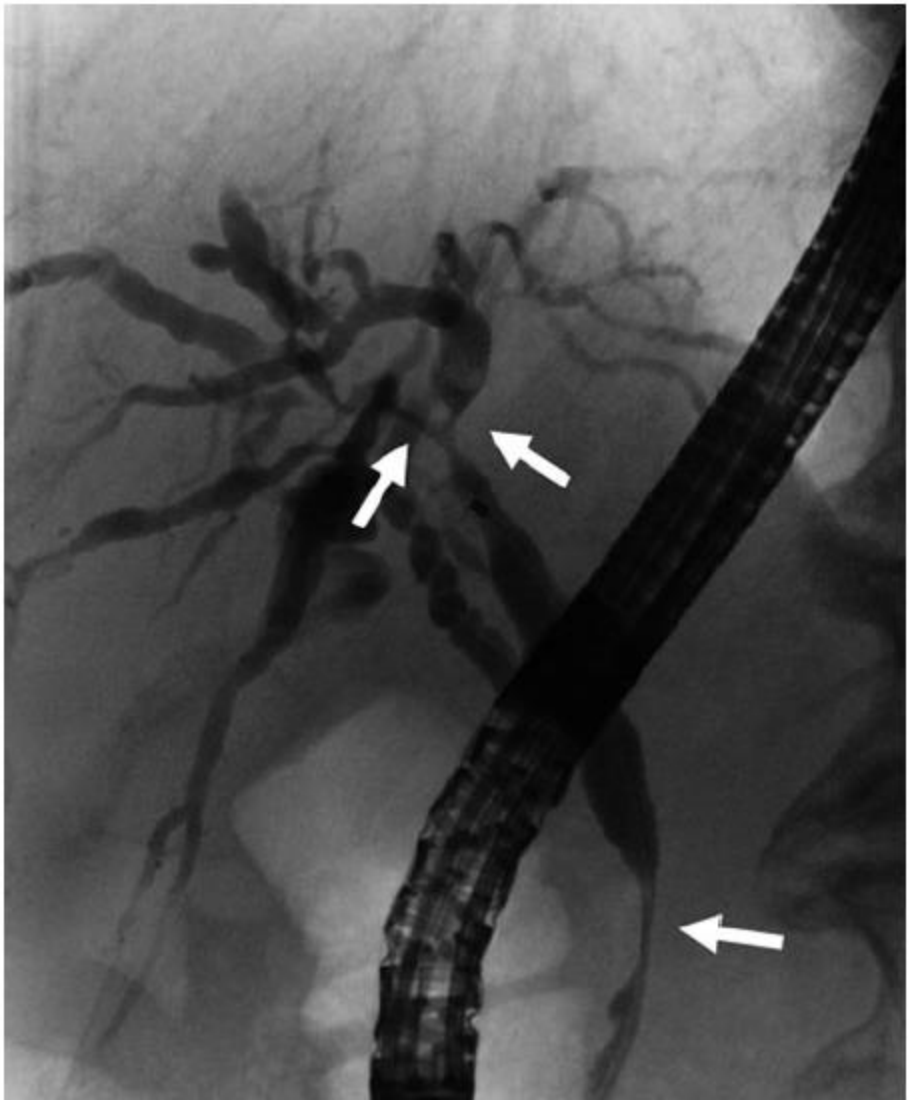
Option: Effectiveness of steroid therapy

A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administrated, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out.

2. Diagnosis

Definite diagnosis:	(1) + (3)
	(1) + (2) + (4) a, b
	(4) a, b, c
	(4) a, b, d
Probable diagnosis:	(1) + (2) + Option
Possible diagnosis:	(1) + (2)

IDUS is useful for differential diagnosis in conjunction with ERCP. Wall thickening in the non-stricture areas is characteristic of IgG4-SC, and a sensitivity of 95–100%, specificity of 91%, and accuracy of 94% were reported



Simultaneous performance and bile fluid cytology w improving the diagnostic ut

Elevation in bile fluid Ig cases of IgG4-SC but not with sensitivity and specific

Table 4 Differential characteris

	IgG4-related cholangitis (I
Age of onset	Elderly
Serum IgG4 level	Elevated
Coexisting diseases	IgG4-related
Image of biliary trees	Long strictur bile duct st
Inflammatory site of bile duct wall	Inflammation rare epithel
Liver histology	Abundant Ig plasma cell

SC?

- We suggest IDUS for the differential diagnosis from cholangiocarcinoma or PSC (Recommendation 2, level D).

Comment: Endoscopic transpapillary IDUS is a reliable procedure to obtain high-resolution images of the bile duct wall after ERCP. IDUS is performed by inserting a small-caliber ultrasonic probe into the bile duct. IDUS is widely used for evaluation of bile duct stones, differential diagnosis of indeterminate biliary strictures, and superficial spread of cholangiocarcinoma. IDUS should be performed before biliary drainage, as such drainage often

cholangiocarcinoma, accord
acteristic curve analysis
cholangiocarcinoma cases
thickness greater than 1 m
cut-off can be used to com
noma from IgG4-SC diag
finding for differentiating
giocarcinoma is that wall
from the lower bile duct
IgG4-SC cases.

Most cases of IgG4-SC
strictures exhibit bile duc

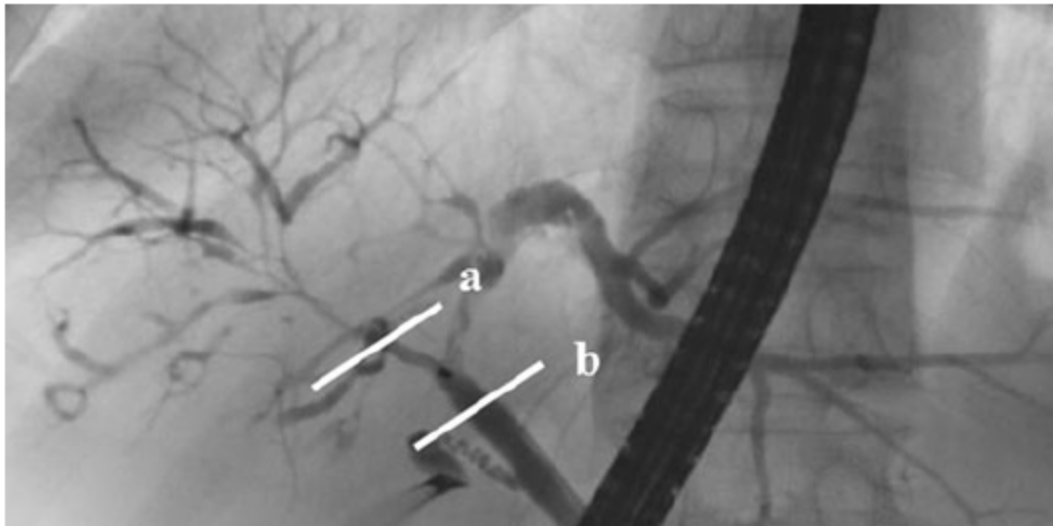


Fig. 27 IDUS image of (**a**) biliary stricture and (**b**) non-biliary stricture in a patient with IgG4-SC

DIAGNOSIS APPROACH

- Diagnosing IgG4-RD involves identifying specific features through tissue biopsy.
- Additional organ involvement can be suspected by evaluating the patient's medical history, physical examination, and routine laboratory tests and imaging.
- Diagnosis requires a comprehensive approach combining biopsy findings with clinical and investigative data.

- The specific procedure depends upon which target organ will be biopsied and whether a discrete mass is present. A core needle biopsy is often adequate, but fine-needle aspirates do not provide adequate tissue
- We agree with the expert consensus that confirmation of the diagnosis by biopsy is important for the exclusion of malignancy and other disorders that may mimic IgG4-RD

- Key features for IgG4-RD diagnosis include dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis in biopsied tissue.
- A strong diagnosis indicator is the presence of increased IgG4-positive plasma cells within the affected tissue.
- The required number of IgG4-positive plasma cells per high-power field varies by tissue, typically 30-50 cells/HPF. Some organs, like the kidney, may require as few as 10 IgG4-positive plasma cells/HPF for diagnosis.

- Many conditions can be associated with elevated numbers of IgG4-positive plasma cells in lymph nodes, and the specificity of this finding is poor
- The histopathologic appearance of the tissue is considered more important than the IgG4-positive cell counts or ratios of IgG4- to IgG-positive cells.
- Serum IgG4 concentrations alone are not sensitive or specific enough for diagnosing IgG4-RD.

- The major disorders that should be distinguished from IgG4-RD include pancreatic cancer, cholangiocarcinoma, primary sclerosing cholangitis

TREATMENT APPROACH

- The goals of therapy are to reduce inflammation and induce disease remission, with the aim of preserving organ function while minimizing the adverse effects of therapy with glucocorticoids and other agents

Initial therapy – Initial therapy with glucocorticoids, and sometimes with an additional immunosuppressive or a biologic agent

- **Remission maintenance** – Further therapy to maintain remission and to re-induce remission in patients with recurrent disease activity is often needed

- **Surgery and other interventional procedures** – Surgical interventions, including stenting to relieve mechanical obstruction caused by the disease

BASELINE TESTING

- **Blood testing**:
- Complete blood count with differential white including eosinophil count
- Serum chemistry panels, including, amylase, and lipase
- IgG subclass levels
- IgE concentrations
- Serum protein electrophoresis
- Serum C3 and C4 concentrations
- Glycated hemoglobin (hemoglobin A1c)

OTHER TEST

- **Stool testing** – Fecal elastase, which we obtain in patients with known or suspected pancreatic involvement, is an indication of exocrine pancreatic reserve
- **Urinalysis** – Asymptomatic proteinuria may be an indication of subclinical IgG4-related tubulointerstitial nephritis (TIN). However, many patients with significant IgG4-related kidney disease have a completely normal urinalysis.
- **Imaging**:
- **Computed tomography (CT) scan of the chest, abdomen, and pelvis**
- **Positron emission tomographic (PET) scanning**

TREATMENT INDICATIONS

- All patients with symptomatic, active IgG4-related disease (IgG4-RD) require treatment. Some patients require treatment urgently,
- Particularly subsets of patients with pancreaticobiliary or renal disease.
- Selected patients may benefit from urgent surgical intervention, such as stenting for mechanical obstruction.

TREATMENT...

- Asymptomatic patients with progressive IgG4-RD in vital organs (e.g., aortitis, retroperitoneal fibrosis) based on radiologic or lab findings should initiate therapy.
- Asymptomatic individuals with nonprogressive and limited disease, like lymphadenopathy, submandibular gland enlargement, or incidental lung nodules, can adopt a "watchful waiting" approach.
- Regular monitoring (e.g., every six months) is essential to identify symptom, sign, or lab value changes that may indicate the need for treatment (e.g., pancreatic or renal dysfunction development).

INITIAL THERAPY

- Prednisone monotherapy is recommended for most patients requiring treatment.
- Typically, prednisone is prescribed at a dose of 0.6 mg/kg, usually 30 to 40 mg daily, divided into one or two doses.
- A majority of patients exhibit a response to 40 mg of prednisone daily within two to four weeks, with some responding even sooner.
- Once a noticeable clinical improvement is observed in the affected organ system, glucocorticoid tapering is initiated over a two-month period, with the aim of eventually discontinuing the medication.

- Starting glucocorticoid treatment typically leads to improvements within weeks, such as symptom relief, reduced mass or organ size, better organ function, and lower IgG4 levels.
- Response times may vary; some patients require months to respond, while others may relapse or have an inadequate initial response, especially if their condition is primarily fibrotic at the beginning of glucocorticoid therapy.

- Patients with multiorgan disease or an extremely high serum IgG4 are likely to require an agent other than glucocorticoids alone.
- Patients not adequately responsive to glucocorticoids often flare during initial tapering as the dose is reduced below 10 to 15 mg of prednisone or equivalent daily
- Although evidence is somewhat limited, some findings, including observational data and a small randomized trial, support the view that combination therapy has greater benefit than glucocorticoid monotherapy

- Thus, in a small number of selected patients with multiorgan disease (eg, three or more organs) or an extremely high serum IgG4 concentration (eg, >5 times the upper limit of normal), starting treatment with the combination of glucocorticoids plus a immunomodulators
- his preference is due to stronger evidence supporting the efficacy of rituximab compared to alternative agents like azathioprine or mycophenolate mofetil.
- Disease worsening while on glucocorticoid therapy, however, certainly implies another diagnosis.

RESISTANT TO INITIAL THERAPY AND STEROID DEPENDENCE

- Recommended rituximab dose for specific patients: 1 gram IV every 15 days for two doses.
- Suggested for glucocorticoid-resistant patients or those unable to reduce their dose effectively.
- Also recommended for patients with significant contraindications to glucocorticoid therapy.
- Generally more effective than low-dose glucocorticoids (prednisone <10 mg daily) and other immunosuppressive agents.

- In a meta-analysis examining efficacy and safety of rituximab in IgG4-RD with pancreato-biliary manifestations, it was found that the pooled rate of complete response at six months was 88.9 percent (95% CI 80.5-93.9), while the relapse rate was 21 percent (95% CI 10.5-40.3) .
- Relapses were more frequent in patients who had multiorgan disease

- In patients for whom rituximab is not available, either azathioprine (2mg/kg/day) or mycophenolate mofetil (up to 2.5 g/day as tolerated) are reasonable choices for second-line agents that have potential as glucocorticoid-sparing therapies, especially in studies examining patients with autoimmune pancreatitis (AIP) or with IgG4-related sclerosing cholangitis

- There is limited evidence to guide the treatment of patients who are refractory to rituximab and other immunosuppressive drugs. Reasonable options include retreatment with glucocorticoids, the use of maintenance glucocorticoid therapy, or switching to another immunosuppressive drug (eg, azathioprine to mycophenolate mofetil or to rituximab and vice versa) that has not been previously used for the patient

MAINTENANCE THERAPY

- Whether patients with IgG4-related disease (IgG4-RD) should receive maintenance therapy is still under debate
- It seems that following a successful course of induction therapy, certain patients benefit from maintenance therapy, especially those who are at high risk for disease relapse.
- As reflected in the international consensus guidance statement for IgG4-RD, a glucocorticoid-sparing agent can act as a maintenance therapy; however, there is no evidence addressing the question of how long such agents should be administered.
- Finally, rheumatologists from Asian countries prefer to continue low-dose glucocorticoids (eg, 2.5 to 10 mg/day) for up to three years

MONITORING

We monitor treated patients, as well as those undergoing "watchful waiting," as follows:

- Patients are educated to report any new symptoms
- Clinical and laboratory evaluation should be performed every six months, including a complete blood count, blood chemistries, IgG subclass concentrations, IgE levels (if elevated at baseline), and complement C3 and C4 levels.
- Periodic imaging may be useful in patients whose disease is not easily evaluable through history, physical examination, and laboratory testing.

RECURRENT DISEASE

- Retreatment with glucocorticoids is indicated
- Patients who flare during or after a glucocorticoid taper are likely to require a glucocorticoid-sparing agent, which should be started promptly to prevent excessive glucocorticoid toxicity
- The optimal agent is not established, and treatment should be individualized based in part on comorbidities, patient cost and insurance, and regulatory restrictions

TO SUM UP

- IgG4-related disease (IgG4-RD) should be considered when patients exhibit characteristic organ or tissue involvement patterns.
- Histopathology findings alone are insufficient for IgG4-RD diagnosis; they require interpretation alongside clinical, serologic, and radiologic data.
- Initial treatment for IgG4-RD usually involves glucocorticoids, starting with prednisone (0.6 mg/kg/day) and tapering over two months.
- Response indicators include symptomatic improvement and reduced IgG4 serum levels.
- For patients unresponsive to prednisone (up to 40 mg/day) or those with contraindications to glucocorticoid therapy, rituximab is suggested instead of conventional immunosuppressive agents.

THANKS