



IgG4-Related Disease of the Liver and Kidney: Diagnostic Integration for Emergency Medicine

Antoine J. Zgheib¹, Antoine T. Aoun²

ABSTRACT

IgG4-related disease (IgG4-RD) is a chronic fibro-inflammatory condition triggered by autoimmunity that can affect multiple organ systems, with the hepatobiliary tract and kidneys being two of the most commonly involved. Given that the clinical and imaging presentation of IgG4-RD is similar to that seen in cases of malignancy, infections, and other autoimmune conditions, diagnosis is difficult, especially in the setting of acute care when delayed diagnosis could result in the performance of unnecessary invasive tests and improper treatment. This paper reviews the recent advances in diagnosis and management of the disease, specifically classification, imaging, pathology, biomarkers, and treatment modalities for IgG4 related disease affecting the biliary tree and kidney. A structured review of the literature in PubMed/MEDLINE, Embase, and Cochrane Library was performed for the period up until June 2026, including mainly the literature from 2012 to 2026 and landmark earlier papers, updated to reflect the April 2025 FDA approval of inebilizumab for IgG4-RD. IgG4-RD is shown to primarily involve men above 50 years of age, typically manifesting itself as IgG4-related sclerosing cholangitis in the hepatobiliary system and as tubulointerstitial nephritis in the kidneys; however, glomerulonephritis and inflammatory pseudotumors can occur. The diagnosis of IgG4-RD is achieved by using the combination of clinical findings with distinct radiologic findings, high levels of serologic parameters, and histopathological evidence of lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and the increased number of plasma cells positive for IgG4. Recently, circulating plasmablasts have been shown to be a better biomarker than serum IgG4 in certain patients. Induction therapy is based on glucocorticoids, while rituximab is used as an efficient steroid-sparing alternative in case of recurrences or refractoriness to corticosteroids, and the B-cell depleting agent inebilizumab was approved by the FDA in 2025 as an additional steroid-sparing option. The importance of early diagnosis of IgG4-RD in order to differentiate this condition from malignancies and inflammatory diseases and achieve successful treatment cannot be underestimated.

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SUBMITTED: 12 JULY 2026

REVISED: 15 AUGUST 2026

ACCEPTED: 18 AUGUST 2026

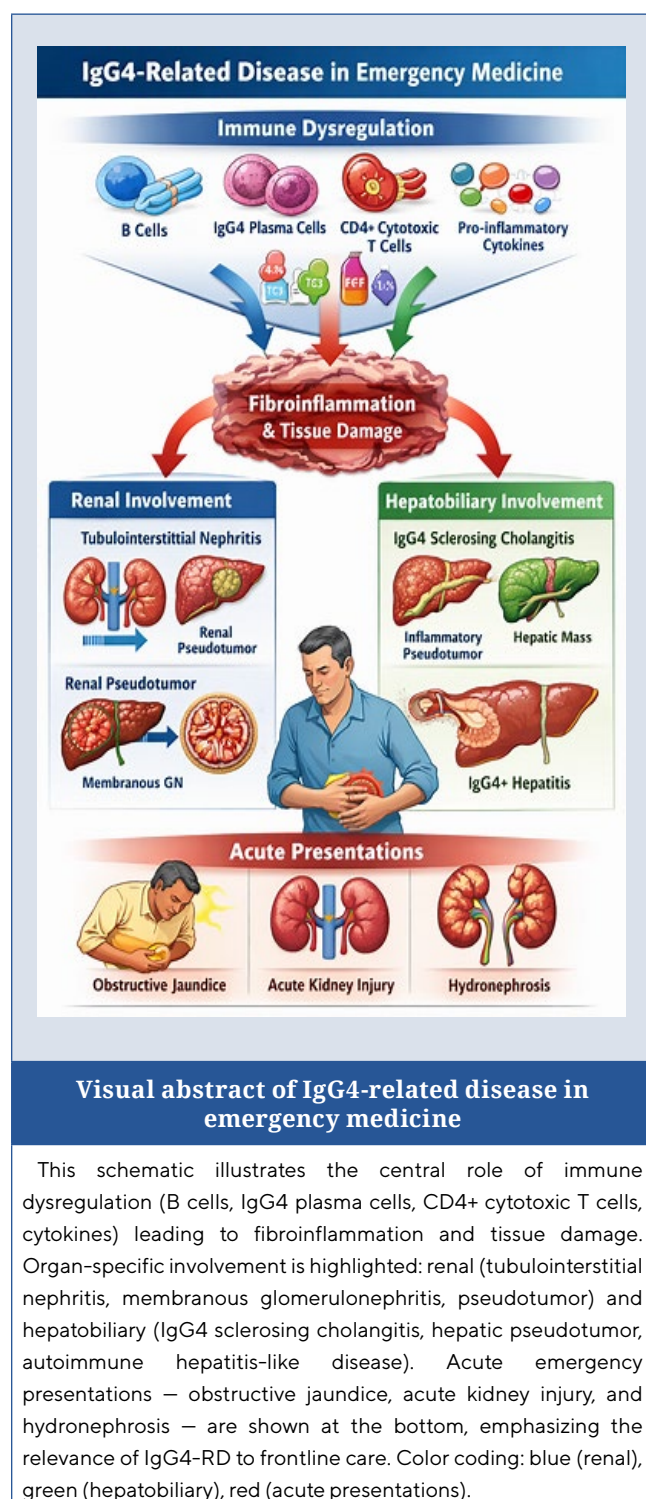
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How to cite this paper? J. Zgheib A, T. Aoun A. IgG4-Related Disease of the Liver and Kidney: Diagnostic Integration for Emergency Medicine. *Panorama of Emergency Medicine*. 2026,4(1) <https://doi.org/10.26738/poem.v4i1.24>



INTRODUCTION

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder first recognized in the early 2000s in association with autoimmune pancreatitis, and subsequently defined as a multi-organ condition with a unifying histopathological signature: dense lymphoplasmacytic infiltration enriched with IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis [1–3]. These features recur across diverse

anatomical sites, conferring a distinct identity despite the disease's heterogeneity.

For emergency physicians, the hepatobiliary system and kidneys represent two of the most clinically significant domains of involvement. IgG4 related sclerosing cholangitis (IgG4-SC) or hepatic inflammatory pseudotumors may mimic cholangiocarcinoma, primary sclerosing cholangitis (PSC), or hepatocellular carcinoma and may clinically feature obstructive jaundice or mass formation [4,5]. In a similar fashion, IgG4-associated kidney disease (IgG4-RKD) primarily involves the tubulointerstitium of the kidney, resulting in tubulointerstitial nephritis (TIN) which frequently presents itself in the form of acute renal injury, proteinuria, or even pseudotumors [6]. Delayed diagnosis in these cases is associated with permanent scarring or chronic kidney disease.

The diagnostic dilemma is due to several overlapping factors; elevation of IgG4 in the serum does not have enough specificity, positive IgG4 plasma cells are not exclusive to this disorder, and imaging findings overlap with the malignant and inflammatory diseases. Biopsy is considered one of the main tools in the diagnosis of this disease but may suffer from sampling errors and preponderance of fibrosis [7,8]. This dilemma becomes even more relevant in emergency settings where it is crucial to distinguish between malignancy, infection, and immune-related causes of the disease.

In the last 10 years, remarkable achievements in imaging, histology, and biomarkers' identification have taken place. The aim of this review is to discuss recent advances in diagnostics of IgG4-RD, specifically involving liver and kidneys, with a special attention to the emergency setting.

The literature search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Library using combinations of the keywords "IgG4-related disease," "IgG4-related sclerosing cholangitis," "IgG4-related kidney disease," "tubulointerstitial nephritis," "diagnosis," "biomarkers," "imaging," "treatment," and "emergency medicine." Eligible sources included English-language peer-reviewed original studies, systematic reviews, meta-analyses, and society guidelines addressing the diagnosis, imaging, histopathology, or management of hepatobiliary and renal IgG4-RD; case reports were included only when they illustrated a diagnostic pitfall or landmark clinical observation not otherwise represented in larger series. Non-English sources, conference abstracts without full-text availability, and articles unrelated to hepatobiliary or renal involvement were excluded. Titles and abstracts were screened for relevance, followed by full-text review of potentially eligible articles, and reference lists of key papers were hand-searched to identify additional relevant studies; given the narrative rather than systematic design of this review, formal dual-reviewer screening and PRISMA reporting were not applied.

EPIDEMIOLOGY

Although IgG4-RD is increasingly recognized worldwide, most epidemiological data remain derived from Asian cohorts, particularly Japan, where systematic screening for autoimmune pancreatitis first illuminated the condition [9]. Population-based studies now confirm IgG4-RD as rare but clinically significant (Table 1).

A landmark U.S. administrative claims-based study estimated the prevalence of IgG4-RD at approximately 5.3 cases per 100,000 persons, while the estimated annual incidence ranged from 0.28 to 1.39 cases per 100,000 person-years, depending on the case-identification algorithm applied in the claims database rather than representing a statistical confidence interval. Likewise, a recent population-based study from Slovenia reported an annual incidence of 1.39 per 100,000 person-years, supporting the upper end of the

U.S. estimate. Together, these findings indicate regional and methodological variability in reported incidence rather than true temporal trends. Because prevalence estimates are derived from administrative data and vary according to the diagnostic algorithm used, they should be interpreted as approximate population estimates rather than precise population parameters [5, 10]. The disease predominantly strikes men above 50 years of age, with a male-to-female ratio ranging up to 3:1 in the Asian populations but with reduced discrepancy in the Western countries [9, 10].

Involvement of the kidney ranges between 10% to 27%, which makes it one of the commonest extraskelatal lesions [6, 11]. The occurrence of hepatobiliary manifestations, such as IgG4-SC, autoimmune pancreatitis type 1, and hepatic pseudotumors, represents about 25% to 35% of cases, especially in those presented with biliary tract tumors [4].

TABLE 1 - Epidemiological Features of IgG4-Related Disease

Parameter	Findings	References
Annual incidence	0.28-1.39 per 100,000 person-years	[5,10]
Prevalence	Approximately 5.3 per 100,000 persons	[10]
Mean age at diagnosis	~56 years	[10]
Sex ratio	Male predominance (M:F up to 3:1 in Asia)	[9]
Kidney involvement	10-27% of cases	[6, 11]
Hepatobiliary involvement	~25-35% of cases	[4]
Pancreatic involvement	Most common single-organ involvement (AIP type 1)	[9]

PATHOPHYSIOLOGY

However, there have been some advancements in the immunopathogenesis of IgG4 related disease in the last decade although several aspects still need clarification. According to the present theories, IgG4-RD develops due to aberrant immune responses in individuals predisposed genetically, with the stimulation from certain environmental antigens resulting in B cell and plasmablast proliferation, accumulation of CD4+ CTLs, and abnormal cytokine secretion [12].

CD4+SLAMF7+ CTLs play an important role in fibrosis formation by secreting IL 1 β TGF β and IFN β to cause activation of fibroblasts and accumulation of collagen in a storiform manner [13]. In addition, the influence of Th2 and regulatory T-cell cytokines (IL 4, IL 10, IL 13, IL 35) on the immune response and class switching to IgG4 in plasma cells causes high levels of IgG4 in the serum of affected patients [12,14].

However, it should be noted that IgG4 itself does not cause any damage to the body; IgG4 is a non-complement fixing immunoglobulin subclass which

has weak Fc receptor binding and can serve more as an indicator of the chronic antigenic stimulation [15]. Galectin 3 and annexin A11 have been found to be promising candidate autoantigens through proteomic analysis [16].

In terms of emergency medicine, this knowledge helps us to understand why the patients suffer from acute obstructive jaundice, renal dysfunction or pseudotumors, because fibro-inflammatory process leads to the impairment of organs' functioning, and the process of dysregulation leads to the development of signs of inflammation.

CLINICAL MANIFESTATIONS

The IgG4-RD is a fibroinflammatory disease which has a wide range of clinical features which differ based on the affected organs. The most clinically relevant manifestations include hepatobiliary and renal involvement because they often masquerade as cancers, infections or other autoimmune diseases

which can pose difficulties in diagnosis, especially when the patient is admitted to an emergency department. The patients may have symptoms such as obstruction jaundice, abdominal pain, acute kidney failure, proteinuria or mass formation which can be misdiagnosed as malignancy or severe infection. The principal hepatobiliary and renal manifestations of IgG4-RD are summarized in **Table 2** and discussed below.

HEPATOBIILIARY INVOLVEMENT

IgG4-related hepatobiliary disease encompasses a spectrum of presentations. The most clinically significant is IgG4-related sclerosing cholangitis (IgG4-SC), which affects intrahepatic and/or extrahepatic bile ducts, producing wall thickening, stricture formation, and obstructive jaundice [4]. Radiologically, four types of IgG4-SC are recognized (Hirano classification), with hilar involvement (Types 3 and 4) most often misdiagnosed as cholangiocarcinoma [17].

Other hepatobiliary manifestations include hepatic inflammatory pseudotumors, which mimic hepatocellular carcinoma or metastasis, and less common entities such as IgG4-related cholecystitis and autoimmune hepatitis-like presentations [18]. In

the emergency setting, these conditions frequently present as obstructive jaundice, abdominal pain, or mass lesions requiring urgent differentiation from malignancy.

RENAL INVOLVEMENT (IGG4-RKD)

The kidney is the most common extra-pancreatic organ involved in the pathology of IgG4-RD [6]. Almost 80 percent of all cases of nephritic presentations present as TIN characterized by marked infiltration of IgG4+ plasma cells, tubular injury, and fibrosis [11]. This can be either acute or chronic presentation.

Membranous glomerulonephritis (MGN) is found in 5-10% of cases and commonly accompanies TIN; its clinical presentation includes proteinuria or nephrotic syndrome [19]. The phenomenon of renal pseudotumors (solitary or multiple cortical lesions) is identified in up to 30% of IgG4-TIN patients and often prompts an oncologic workup [20]. Retroperitoneal fibrosis causes bilateral hydronephrosis as a result of encasement of ureters by inflammatory tissue [6].

In terms of emergency medicine, this condition is especially important due to possible presentation as unexplained acute kidney injury, proteinuria, or renal tumors similar to carcinoma.

TABLE 2 - Clinical Manifestations of IgG4-RD in the Liver and Kidney

Organ/Site	Manifestation	Key Clinical Feature	References
Bile duct	IgG4-related sclerosing cholangitis	Obstructive jaundice; mimics PSC/CCA	[4, 17]
Liver parenchyma	Inflammatory pseudotumor	Mass lesion; mimics HCC/ metastasis	[18]
Gallbladder	IgG4-related cholecystitis	Wall thickening; mimics cholangiocarcinoma	[18]
Liver	Autoimmune hepatitis-like disease	Elevated transaminases; IgG4+ hepatitis	[18]
Kidney (tubulointerstitium)	Tubulointerstitial nephritis (TIN)	AKI/CKD; cortical lesions on CT	[6, 11]
Kidney (glomerulus)	Membranous glomerulonephritis (MGN)	Proteinuria, nephrotic syndrome	[19]
Kidney (parenchyma)	Renal pseudotumor	Cortical nodules; mimics RCC	[20]
Retroperitoneum	Retroperitoneal fibrosis	Bilateral hydronephrosis	[6]

DIAGNOSIS APPROACHES

DIAGNOSTIC TOOLS

The successful diagnosis of IgG4-RD is dependent on the combination of the clinical, serologic, radiologic, and histologic findings. The 2019 ACR/ EULAR Classification Criteria continue to be the most established tool for diagnosis that uses a four-step approach consisting of entry criteria, exclusion criteria, inclusion criteria, and a classification score [21]. The

sensitivity and specificity of these criteria are 85.5% and 99.2%, respectively, in research settings; however, their use in emergency setting has yet to be evaluated [22].

Emergency physicians have to keep in mind that malignancy and infection have to be ruled out before any other condition, including IgG4-RD, especially for patients with obstructive jaundice or renal mass.

In practice, the emergency physician's diagnostic role is generally limited to initiating the supportive work-up needed to raise or lower suspicion for IgG4-

RD: cross-sectional imaging (CT, MRI/MRCP, or ultrasonography), serum IgG4 and complement levels, and routine liver and renal chemistries. Formal application of the 2019 ACR/EULAR classification score, coordination of image-guided or endoscopic biopsy, and interpretation of specialist serologic panels are generally deferred to the admitting medicine service or to gastroenterology, nephrology, or rheumatology once malignancy and infection have been reasonably excluded.

HISTOPATHOLOGICAL DEVELOPMENTS

Histopathological evaluation continues to be the mainstay for the diagnosis of IgG4-related disease. As stated by the 2012 international consensus document, the hallmarks of the histopathological triad include the dense infiltrate of IgG4-positive plasma cells (exceeding 10 cells per high-power field [HPF] on needle biopsies or 50 cells per HPF on resections), storiform fibrosis, and obliterative phlebitis [3].

The latest developments in the field of molecular pathology, such as gene expression profiles and single-cell RNA sequencing, allowed gaining more insights into the involvement of CD4+ cytotoxic T lymphocytes and activated fibroblasts in the pathogenesis of IgG4-RD [13,23]. Furthermore, new techniques of digital pathology, as well as image analysis assisted by artificial intelligence, provided a more accurate estimation of IgG4-positive plasma cells, minimizing interobserver variability [24]. Nevertheless, the presence of elevated levels of IgG4-positive plasma cells is not pathognomonic for IgG4-RD and could be encountered in other diseases, such as inflammatory

bowel disease, Castleman disease, and some cancers [7].

Emergency setting is characterized by a lack of histopathological confirmation at the early stages of IgG4-related disease; thus, clinical, imaging, and serologic findings have to be used by the physician.

IMAGING ADVANCES

HEPATOBIILIARY IMAGING

Hepatobiliary scintigraphy is an important component in the diagnostic assessment of IgG4-SC. Nevertheless, substantial overlap with imaging findings of cholangiocarcinoma and PSC makes the use of a multimodal diagnostic strategy imperative (Figure 1).

Long and smooth biliary strictures accompanied by concentric wall thickening are usually seen on MRCP in IgG4-SC cases, rather than short and irregular strictures that are typical of cholangiocarcinoma [25]. Delayed homogeneous enhancement and "tram-track" sign are additional supportive features on contrast enhanced MRI for the diagnosis of IgG4-SC [26-28]. High-intensity fluorodeoxyglucose uptake in IgG4-SC tumors is often observed in PET-CT studies. However, in contrast to malignancies, the uptake decreases dramatically after corticosteroid treatment [29,30]. EUS and IDUS can assist in the diagnostic process since intact bile ducts' wall structures with symmetrical thickening are associated with IgG4-SC, while disruption of the normal structure is indicative of cholangiocarcinoma [31-33].

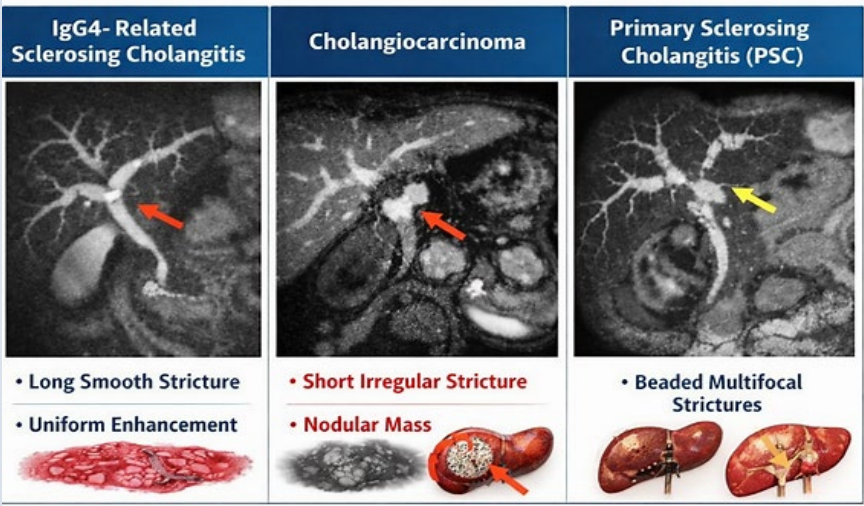


FIGURE 1 - Imaging differentiation of IgG4-related sclerosing cholangitis (IgG4-SC), cholangiocarcinoma, and primary sclerosing cholangitis (PSC).

MRCP and contrast-enhanced MRI panels demonstrate the distinct morphologic patterns of biliary stricture: IgG4-SC: long, smooth, concentric stricture with uniform enhancement. Cholangiocarcinoma: short, irregular stricture with nodular mass and heterogeneous enhancement. PSC: multifocal beaded strictures with alternating dilatation and narrowing.

These imaging hallmarks assist emergency physicians in differentiating IgG4-SC from malignant or inflammatory mimics, guiding early immunosuppressive therapy and avoiding unnecessary surgical intervention (Table 3).

TABLE 3 - Imaging Differentiation of IgG4-SC vs Cholangiocarcinoma vs PSC				
Imaging Feature	IgG4-SC	Cholangiocarcinoma (pCCA)	PSC	References
Stricture length	Long (>1 cm), diffuse	Short, abrupt	Short, multifocal	[25]
Morphology	Smooth, symmetric	Irregular, asymmetric	Beaded, irregular	[25, 26]
Wall thickness	>2 mm, concentric	Nodular, eccentric	Minimal	[26]
CE-MRI enhancement	Delayed, uniform	Early, heterogeneous	Minimal	[26-28]
PET-CT uptake	Diffuse, steroid-responsive	Focal, persistent	Minimal	[29, 30]
IDUS findings	Symmetric hypoechoic layer ≥0.8mm	Disrupted layers	Absent	[33]

RENAL IMAGING

Imaging is critical to the diagnosis of IgG4-RKD, being useful for characterization of kidney involvement and distinction of inflammatory mass lesions from renal neoplasms (Figure 2).

Compared to other imaging modalities, CT imaging normally depicts bilateral renal enlargement, numerous small peripheral nodules, and the characteristic halo

sign surrounding the kidneys, all suggesting IgG4-RKD [20]. The use of magnetic resonance imaging (MRI) helps with diagnosis because of the low T2 weighted signals and delayed enhancement of the lesions, which help differentiate between IgG4-RKD and renal cell carcinoma [34]. Also, positron emission tomography-computed tomography (PET-CT) often shows diffuse bilateral renal fluorodeoxyglucose uptake, which is quickly normalized on corticosteroids [29,35].

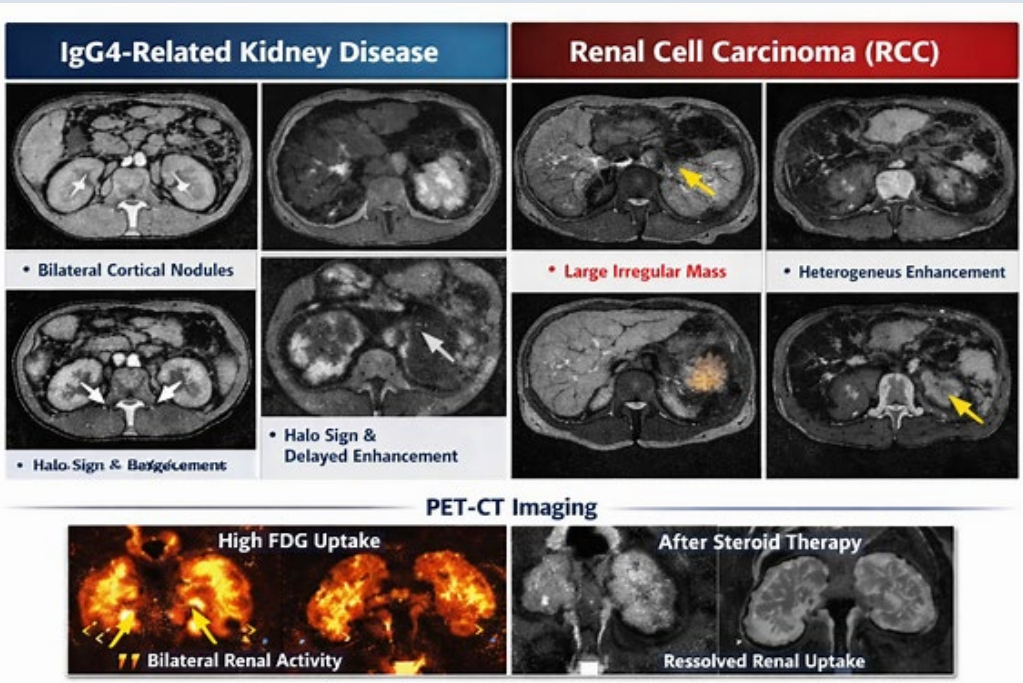


FIGURE 2 - Radiographic characteristics of IgG4-related kidney disease (IgG4-RKD)

In this case, contrast-enhanced CT and MRI depict the classic radiologic manifestations of IgG4-RKD such as bilateral renal cortex nodules, the peri-renal halo sign, and delayed homogeneous enhancement, which serve to differentiate IgG4-RKD from other processes including renal cell carcinoma (RCC). The PET-CT images below illustrate the diffuse bilateral FDG activity seen in IgG4-RKD with complete response following steroid therapy. As shown, PET/CT does not serve to compare with RCC but serves as the classic manifestation of inflammatory disease that responds to steroids.

DIAGNOSTIC PITFALLS

Although there have been advances in imaging, histopathology, and markers, misdiagnosis is one of the main issues in IgG4-RD. In up to 40% of cases of IgG4-SC, initial diagnosis is inaccurate, being misdiagnosed as PSC or cholangiocarcinoma, resulting in inappropriate surgical treatment or delayed immunosuppression [36]. In particular for the emergency physicians, it is important to know the potential pitfalls in patients with obstructive jaundice, renal masses, or acute kidney injury.

There are several diagnostic pitfalls that should be considered while diagnosing IgG4-RD. Raised serum levels of IgG4 lack specificity and can also be found in cholangiocarcinoma, PSC, and other inflammatory diseases [7]. Increased number of IgG4-positive plasma cells is non-specific and is seen in inflammatory bowel disease, Castleman disease, and

some cancers as well [7]. Histopathological diagnosis may be hampered by biopsy sample errors, as patchy involvement or superficial tissue biopsy may miss the presence of typical storiform fibrosis and/or obliterative phlebitis [3]. Though a positive response to steroids helps establish the diagnosis, it cannot be considered definitive as certain types of lymphomas and small-cell tumors may show an improvement in the clinical picture, making it difficult to distinguish from IgG4-RD [36]. In addition, up to 40% of IgG4-RD patients will have a normal level of IgG4 antibodies, meaning that normal serology is not indicative of absence of this condition [37]. Diagnostic challenges may be faced due to overlap syndromes, including granulomatosis with polyangiitis and Castleman disease, which often mimic IgG4-RD in its orbital and renal presentations (Table 4) [36]. Lastly, renal inflammatory pseudotumors may appear radiologically identical to renal cell carcinoma, posing a threat of nephrectomy [20].

TABLE 4 - Diagnostic Pitfalls in IgG4-RD of the Liver and Kidney

Pitfall	Clinical Context	Mitigation Strategy	References
Elevated serum IgG4 (low specificity)	IgG4 >135 mg/dL in PSC/CCA patients	Use twofold threshold (>270 mg/dL); combine with imaging/histology	[7, 37]
IgG4+ plasma cells alone	Seen in IBD, Castleman disease, carcinoma stroma	Require storiform fibrosis and/or obliterative phlebitis	[3, 7]
Biopsy sampling error	Patchy disease; superficial biopsy misses fibrosis	Core needle biopsy; multiple passes	[3]
Steroid response misinterpretation	Lymphomas/small-cell tumors transiently improve	Exclude malignancy before empirical steroid trial	[36]
IgG4-negative IgG4-RD	30-40% of confirmed cases have normal IgG4	Do not exclude based on serology alone	[37]
Overlap with GPA/Castleman	Orbital/renal disease mimics IgG4-RD	ANCA testing; lymph node biopsy; molecular assays	[36]
Renal pseudotumor vs RCC	Cortical mass indistinguishable on CT	MRI kinetics, PET-CT, cautious steroid trial	[20]

MANAGEMENT AND TREATMENT

FIRST-LINE THERAPY: GLUCOCORTICOIDS

Glucocorticoids still constitute the mainstay of IgG4-RD treatment. Induction protocols include administration of prednisone orally at 0.6 mg/kg/day (usually 30-40 mg/day) for 2-4 weeks, followed by a tapering regimen over 3-6 months [1]. The early commencement of therapy is important in IgG4-RKD because patients who receive treatment within the first three months after the onset of symptoms have markedly superior renal outcomes than those receiving treatment after that period [38].

For emergency doctors, fast commencement of steroid treatment is particularly important in cases of obstructive jaundice and kidney injury.

MAINTENANCE AND STEROID-SPARING DRUGS

Relapse is seen in 30-60% of patients after the discontinuation of corticosteroids, and therefore, maintenance drugs or steroid-sparing drugs may be needed in order to prevent recurrences and limit the duration of corticosteroid therapy [39].

The options for maintenance therapy consist of low-dose corticosteroids (2.5-5 mg/day), azathioprine (1.5-2 mg/kg/day), mycophenolate mofetil (1.5-2 g/day), and in some cases, 6-mercaptopurine, based on the extent and severity of the disease.

They are especially helpful for those patients with recurrent biliary strictures or progressive renal fibrosis.

BIOLOGIC THERAPY

Rituximab, a specific CD20 monoclonal antibody, has proven its efficacy in the treatment of refractory or recurrent cases of IgG4-RD. In research, rapid

remissions, reduction in plasmablasts, and steroid sparing effects have been observed [39]. Rituximab is especially beneficial to patients that are steroid intolerant or those with an aggressive course of the disease.

In April 2025, the U.S. Food and Drug Administration approved inebilizumab, a humanized monoclonal antibody that depletes CD19+ B cells and plasmablasts, as the first agent specifically indicated for IgG4-RD. Approval was based on the phase 3 MITIGATE trial, in which inebilizumab reduced the risk of disease flare by 87% compared with placebo over 52 weeks and achieved higher rates of flare-free, glucocorticoid-free complete remission [40]. For emergency physicians, awareness of this expanding class of steroid-sparing biologics is clinically relevant, since patients with IgG4-RD are increasingly likely to present to the emergency department while receiving inebilizumab or rituximab. Such patients warrant heightened vigilance for infusion-related reactions and for infections related to B-cell depletion and hypogammaglobulinemia, and acute flares or suspected infections in these patients should be managed in coordination with the treating specialist given the potential for atypical or blunted inflammatory responses.

SUPPORTIVE AND EMERGENCY CARE

The acute treatment of IgG4-RD needs to be personalized based on the degree of organ involvement and complications. In those cases where biliary strictures occur, it is necessary to implement an urgent procedure involving biliary stenting; however, definitive treatment will need to begin with the use of immunosuppressive therapy. With substantial involvement of the kidney, nephrology consultation is advisable, and renal replacement therapy might be required for the patients with acute kidney injury until the restoration of renal function occurs through immunosuppressive treatment. Disease assessment is important in terms of using PET-CT and plasmablast assays to evaluate disease activity, detect relapses, and monitor treatment [35,41,42].

FUTURE DIRECTIONS

Further research efforts should be directed toward implementation of recent progress in diagnosing IgG4-RD into practical tools applicable in emergency and acute medicine when quick decisions are necessary. Multicentric studies should be performed to confirm the use of the 2019 ACR/EULAR Classification Criteria in patients with acute obstructive jaundice, renal masses, and acute kidney injury, as these groups were not included in the criteria creation process. On the other hand, the incorporation of novel markers of the disease, such as circulating plasmablasts, complement profiles, and new molecular profiles, into diagnostic

tools should be studied prospectively to find out if these markers enhance the diagnostic accuracy compared to the traditional serum IgG4 measurement [42]. Finally, the new treatment modalities focused on blocking certain cytokine pathways, like IL-4, IL-13, and transforming growth factor- β as well as on fibroblast activation, are being tested [14, 16].

AI-aided analysis of imaging, radiomics, and digital pathology may help in differentiating IgG4-RD from mimicking malignancies and inflammation, in addition to reducing interobserver variability [24]. Further studies are required to assess standardized disease activity measures, treatment response guided by PET-CT scan, and monitoring based on biomarkers for achieving personalized approach to IgG4-RD patients [29, 42]. Lastly, prospective registries and multidisciplinary research, including emergency medicine, gastroenterology, nephrology, radiology, pathology, and rheumatology, are needed for defining evidence-based diagnostic algorithms and achieving better long-term outcomes for patients with IgG4-RD.

EMERGENCY MEDICINE PERSPECTIVE

IgG4-RD poses a significant diagnostic challenge in emergency medicine because its hepatobiliary and renal manifestations frequently mimic malignancy, infection, and other autoimmune disorders. In case there is delay in diagnosis of the disease, unnecessary surgeries may be conducted or the initiation of immunosuppression therapy may be delayed; the condition may develop into irreversible fibrosis. Emergency care physicians should be highly vigilant about IgG4-RD among middle aged and elderly patients who present with symptoms of obstructive jaundice, renal masses, or unexplained acute kidney injury, especially when multisystem disease is suspected [25, 26]. When considering the hepato-biliary system, IgG4-SC is likely in those who have strictures which show long and smooth stenosis as well as concentric wall thickening in magnetic resonance cholangio-pancreatography (MRCP) or contrast-enhanced magnetic resonance imaging. This is suggestive of IgG4-RD rather than cholangiocarcinoma [25, 26]. Likewise, bilateral renal cortical nodules, renal enlargement, or renal dysfunction of an unexplained nature suggests IgG4-RKD, particularly if PET-CT shows diffuse fluorodeoxyglucose uptake which resolves rapidly after being put under corticosteroids [20, 35].

For an initial investigation of suspected IgG4-RD, a well-designed diagnostic process incorporating both clinical evaluation, laboratory studies, imaging, histological analysis, and multidisciplinary input needs to be employed (Figure 3). Laboratory evaluation at first visit may involve testing for serum concentration of IgG4, complements (C3/C4), liver and kidney functions, inflammatory markers, and also tumor

markers like carbohydrate antigen 19-9 for cases of bile duct cancer. Cross-sectional imaging with contrast-enhanced CT, MRI/MRCP, or ultrasonography should be performed to identify characteristic hepatobiliary and renal manifestations while excluding malignant or infectious mimics [25,26]. Because elevated serum IgG4 lacks specificity, imaging and serological findings should always be interpreted together rather than in isolation [7, 37].

When diagnostic uncertainty persists, PET-CT may help define the extent of disease and identify suitable biopsy sites [29, 35]. Whenever clinically feasible, tissue biopsy demonstrating the characteristic histopathological features of IgG4-RD should be obtained before initiating immunosuppressive therapy, as histopathology remains the diagnostic gold standard [3]. However, in patients presenting with

organ-threatening disease, such as rapidly progressive acute kidney injury, severe obstructive jaundice, or impending irreversible fibrosis, emergency physicians must carefully balance the urgency of initiating corticosteroid therapy against the practical delays associated with obtaining and interpreting biopsy specimens. In such circumstances, empirical corticosteroid therapy may be justified only after reasonable exclusion of malignancy and active infection, preferably following multidisciplinary consultation, with tissue confirmation pursued as soon as clinically feasible [31, 32, 36, 41]. Although a rapid clinical and radiological response within 2-4 weeks strongly supports the diagnosis of IgG4-RD, transient steroid responsiveness may also occur in lymphoma and certain other malignancies and therefore should not be considered diagnostic in isolation [36].

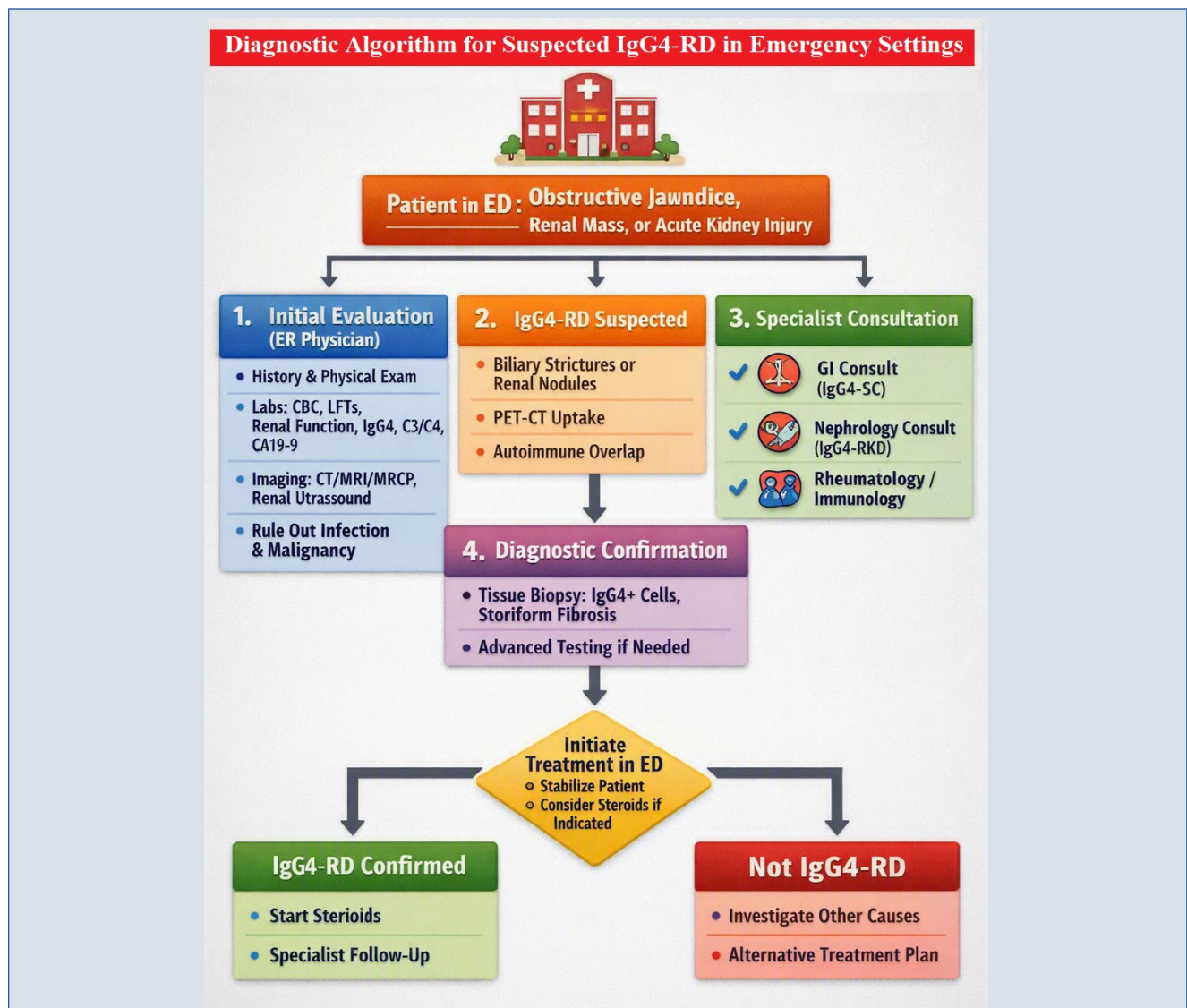


FIGURE 3 - Diagnostic Algorithm for Suspected IgG4 RD in Emergency Settings

This diagnostic flowchart visually organizes the emergency pathway for suspected IgG4-RD, with clear steps for imaging, serology, biopsy, decision points, and therapeutic initiation.

CONCLUSION

Liver and kidney involvement in IgG4-RD presents difficulties for emergency medicine because of its similarity to various diseases including cancers, infections, and other autoimmune diseases. Although a lot of achievements have been made in diagnosing this condition by using imaging techniques, pathological analysis, and biomarkers, yet there are many potential problems that might occur. For emergency medicine, however, the key is keeping high alertness and utilizing everything in an integrated way. Early glucocorticoid therapy can prevent fibrosis and dysfunction in those organs while biologic therapies might help in refractory cases.

KEYWORDS

**IMMUNOGLOBULIN G4-RELATED DISEASE;
CHOLANGITIS, SCLEROSING; TUBULOINTERSTITIAL
NEPHRITIS; DIAGNOSTIC IMAGING; BIOMARKERS;
EMERGENCY MEDICINE**

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AUTHOR CONTRIBUTIONS

All authors contributed equally and validated the final version of record.

DECLARATIONS

CONFLICTS OF INTERESTS

The Authors declare that there is no conflict of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REGISTRATION

No registration applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Ethical approval for this study was not required.

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