# IgG4-Related Disease as Mimicker of Malignancy

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## Abstract

*Background:* IgG4-related disease is an immune-mediated disease that may present as a tumefactive lesion in nearly any organ. These mass lesions often resemble malignancy both clinically and radiologically, and some patients undergo unnecessary surgical resection. We performed a retrospective single center study examining how many patients with IgG4-RD were initially believed to havemalignancy,with particular attention to those who underwent potentially avoidable surgical procedures.

*Methods:* 63 patients with biopsy confirmed IgG4-Related Disease based on International Consensus Criteria were included. Clinical, laboratory, radiological and histological data were collected and analyzed.

*Results:* Over 60% of patients (38/63) were initially thought to have a malignancywhen they initially presented with symptomatic IgG4-RD. The most common types of malignancy suspected were lymphoma (18/38) and pancreatic cancer (11/38). Of the 38 patients with suspected malignancy, 14 underwent an invasive intervention either to alleviate the severity of their symptoms or as treatment for their presumed malignancy.These included Whipple resection/attempted Whipple (3), nephrectomy (3), bile duct resection and reconstruction (1), removal of other abdominal/retroperitoneal masses (3), and stenting of obstructed organs (4).

*Conclusion:* IgG4-RD should be on the differential diagnosis of patients with mass lesions, in particular those with pancreatic masses and obstructive jaundice, extensive lymphadenopathy, or retroperitoneal masses. Oncologists and other physicians involved in cancer care should be aware of the various manifestations and diagnostic approach to IgG4-RD in order to provide accurate diagnosis and minimize unnecessary invasive procedures.


## Novelty Statement

This is the largest case review in literature highlighting the similarity in presentation between IgG4-RD and malignancy. In several of our cases, patients believed to have a malignancy underwent invasive intervention, even prior to histopathological confirmation of the diagnosis, only to have a retrospective revision of their diagnosis to IgG4-RD, a medically responsive disease. Some patients suffer lifelong morbidity from their surgical procedure. Oncologists and clinicians involved in cancer care should be aware of the various manifestations and diagnostic approach to IgG4-RD.

## Introduction

IgG4-Related Disease is an immune-mediated disease characterized by tumefactive lesions, typically in glandular tissue(1). The disease can affect nearly any organ except synovial tissue, with a median age of diagnosis of 60–70 in most large studies and a 2:1 male: female ratio(2). The standard treatment of IgG4-RD is corticosteroids and/or rituximab, and a good response within 2–4 weeks is characteristic of the disease(1, 2).

With the exception of classic autoimmune pancreatitis (3), traditionally all presentations of IgG4-RD require histologic confirmation of diagnosis. Tissue diagnosis is crucial to distinguish the disease from potential mimickers such as multicentric Castleman disease, and to exclude malignant neoplasms(4, 5). The International Consensus Criteria for diagnosis of IgG4-related includes(2):

i. A dense polyclonal lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells
ii. Storiform fibrosis, and
iii. Obliterative phlebitis

The number of IgG4 positive plasma cells per high powered field varies according to the tissue, from > 10/high power field (hpf) in meninges to > 100/hpf in skin; but in all sites, the IgG4/IgG ratio is typically > 40%.

Recently, the American College of Rheumatology/European League Against Rheumatism published a new set of classification criteria for the diagnosis of IgG4-Related Disease(6). These new criteria are based on a set of clinical, serological, radiological, and pathological characteristics. Each item in the clinical, serological, radiological, and pathological categories are scored based on the strength of their association with IgG4-RD. The ACR/EULAR group used a diagnosis threshold of 20 points or above, using these criteria, with a specificity of 97.8% and a sensitivity of 82%. One of the benefits of this new classification criteria is that patients may be diagnosed with IgG4-RD without the need for a biopsy – which, up until recently, has been the gold standard of diagnosing the disease(6).

Since the discovery of IgG4-RD in the early 2000's, its differentiation from malignant causes of tumefactive lesions has been a difficult problem for clinicians and radiologists. There are numerous case reports of IgG4-RD presenting as mass lesions and being mistaken for malignancy in organs such as pancreas, lung, mediastinum, and gallbladder(7–9). The discovery of IgG4-related pancreatitis was driven largely by the fact that many patients were undergoing potentially unnecessary Whipple's resections only to find that they had autoimmune pancreatitis, which is treatable with medical therapy, rather than pancreatic cancer(5). When Japanese investigators looked for biomarkers to distinguish autoimmune pancreatitis from pancreatic cancer, they discovered that patients with autoimmune pancreatitis had a polyclonal hypergammaglobulinemia with beta-gamma bridging which was in fact elevated serum IgG4(5). Subsequently, IgG4-plasma cell enriched infiltrates were discovered in numerous organs, and the term "IgG4-related disease" was coined(4). Conversely, elevated serum IgG4 and IgG4-positive plasma cells can also be a reactive finding in other conditions(10), and some patients initially thought to have IgG4-RD may in fact have clonal neoplasms such as lymphoma and chronic myelomonocytic leukemia(11–13).

Malignancy may also occur contemporaneously with IgG4-RD(14). Lymphoma is one of the common cancer occurrence reported in literature in IgG4-RD patients, however, the physiological mechanisms are not well understood(13). Most of these reports come from East Asian countries and consist of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue and non-Hodgkin lymphoma(15).There have also been case reports of pancreatic cancer in IgG4-RD patients(16). In addition, there was one case report of simultaneous occurrence of IgG4-related tubulointerstitial nephritis and colon adenocarcinoma with hepatic metastasis(17). These case reports highlights that although IgG4-RD and malignancies may be mimickers of each other, the two are not mutually exclusive, and it may be prudent to screen for co-existing malignancy in the right circumstances.

We therefore reviewed our experience with IgG4-RD at a single institution with a focus on ruling malignancy in or out. We wish to highlight the features of IgG4-RD pertinent to clinical oncologists in order that patients with IgG4-RD may avoid unnecessary surgical resections and biopsies.

## Materials And Methods

Institutional review board approval was obtained. We performed a single-center retrospective chart review of 63 patients with biopsy-confirmed IgG4-related disease at Vancouver General Hospital in Vancouver, British Columbia, from 2015–2019. All patients underwent pathology review by an expert pathologist (DFS, GWS, BFS) according to the International Consensus Criteria(2). Serum IgG4 was measured by immunonephelometry, with pre-emptive precautions against hook effect error, prior to October 2016, and by liquid chromatography tandem mass spectrometry thereafter(18).

Demographic information from all patients, including their age at presentation, age at diagnosis, gender, ethnicity, and any history of malignancies into a de-identified database. Disease characterizing information, including site of organ involvement, initial IgG4, CRP, CBC, and tumour marker were recorded, if available. We examined whether patients were suspected of having a malignancy, all surgical intervention and procedures undertaken, and complications related to these procedures.

## Results

63 patients with IgG4-related disease were included in this study. Patient demographics, year of correct diagnosis, and organ site involvement of IgG4-RD were summarized in Fig. 1. The earliest diagnosed case in our center dates back to 2012 with 3 cases. The cases remained low until 2015, averaging 2–4 cases per year. The diagnosis rate went up significantly starting in 2016 to 2019. The most common sites of IgG4-RD involvement included the salivary glands (n = 35/63), pancreas (n = 17/63), and lymph nodes (18/63). We also report rarer sites such as coronary artery, pericardium, hard palate.

Table 2 summarized the most common malignancy to mimic IgG4-RD in our patients, and the types of invasive interventions patients with an original diagnosis of malignancy underwent. Lymphoma and pancreatic cancer comprised of 29 out of 38 cases. Along those lines, the most common invasive interventions included Whipple procedure (3/14), and IR stent insertion (4/14).

Table 1
Patient Demographics

| **Gender** | |
|---|---|
| M | 40 |
| F | 23 |
| Age (years) | 64.9 |
| Median | 67 |
| Range | 33–89 |
| Ethnicity | |
| Asian | 38 |
| White | 15 |
| South Asian | 7 |
| Hispanic | 2 |
| Arab | 1 |
| African American | 0 |
| Year of Diagnosis | |
| 2012 | 3 |
| 2013 | 4 |
| 2014 | 4 |
| 2015 | 2 |
| 2016 | 17 |
| 2017 | 16 |
| 2018 | 12 |
| 2019 | 5 |
| Organ Involvement | |
| Salivary gland | 35 |
| Lymph node | 18 |
| Pancreas | 17 |
| Lacrimal gland | 16 |
| Kidney | 9 |
| Lung | 6 |
| Biliary | 4 |
| Liver | 4 |
| Retroperitoneum | 4 |
| Sinus | 3 |
| Aorta | 2 |
| Adrenal gland | 1 |

| Gender | |
|---|---|
| Cecum | 1 |
| Coronary Artery | 1 |
| Splenic Vein | 1 |
| Pericardium | 1 |
| Peri-urethra | 1 |
| Prostate gland | 1 |
| Hard Palate | 1 |

Table 2
Malignancy Mimickers & invasive procedures

| **Presumed Malignancy (n = 38)** | |
|---|---|
| Lymphoma | 18 |
| Pancreatic | 11 |
| Cholangiocarcinoma | 2 |
| Gastric | 1 |
| Cecum | 1 |
| Renal | 1 |
| Sarcoid | 1 |
| Mesothelioma | 1 |
| Prostate | 1 |
| **Invasive intervention (n = 14)** | |
| IR Stent insertion | 4 |
| Whipple Procedure | 3 |
| Nephrectomy | 3 |
| Laparotomy mass resection | 2 |
| Hemicolectomy | 1 |
| Biliary reconstruction 1 | |

A comparison of the patient/disease characteristics between the patients who were initially diagnosed with a malignancy, and the patients who were initially diagnosed with IgG4-RD are presented in Table 3. We calculated the Student T score and p value for comparison of laboratory characteristics between the two groups. There were no significant difference between the two groups in terms of their age of presentation/diagnosis, serum IgG4 level, CBC or eosinophil counts at presentation. Reassuringly, there are no significant differences between the two groups in terms of overall clinical outcomes, with the majority of patients in surveillance or remission.

Table 3
Comparison of patients with IgG4-RD where malignancy was suspected (yes) or not (no)

| Presumed Malignancy | Yes | Standard Deviation | No | Standard Deviation | Student T score | P Value |
|---|---|---|---|---|---|---|
| **Average Age (Presentation)** | 59.1 | 13.58 | 55.7 | 12.29 | 0.99733 | 0.1613 |
| **Average Age (Diagnosis)** | 62.9 | 13.17 | 60.6 | 12.57 | 0.67826 | 0.5002 |
| **Gender** | | | | | | |
| F | 14 | | 9 | | | |
| M | 24 | | 16 | | | |
| **Previous Malignancy** | 3 | | 3 | | | |
| **IgG** | 16.36 | 6.76 | 11.95 | 8.62 | 0.46272 | 0.3251 |
| **IgG4** | 6.83 | 7.55 | 8.77 | 11.06 | -0.81268 | 0.21 |
| **Eosinophil** | 0.7988 | 1.92 | 0.5913 | 0.978 | 0.47803 | 0.3172 |
| **Hb** | 124.3 | 20.31 | 126.8 | 17.16 | 1.04463 | 0.6064 |
| **Platelets** | 298.5 | 141.7 | 243.6 | 35.87 | 1.9234 | 0.03 |
| **WBC** | 7.88 | 3.7 | 6.99 | 2.11 | -0.5181 | 0.1503 |
| **Lymph node involvement** | | | | | | |
| Yes | 13 | | 5 | | | |
| No | 25 | | 20 | | | |
| **Outcome** | | | | | | |
| Surveillance | 13 | | 10 | | | |
| Remission | 8 | | 3 | | | |
| Maintenance treatment | 10 | | 8 | | | |
| Treatment | 5 | | 1 | | | |
| Deceased | 1 | | 1 | | | |
| Lost to follow up | 1 | | 2 | | | |

Table 4 contains synopses of each case where the patient underwent an invasive procedure intended as treatment for their presumed malignancy. Common symptoms included pain, painless jaundice, obstructive symptoms, constitutional symptoms, which are often considered severe and warranted urgent treatment. All 14 patients had radiographic findings highly suspicious for malignancy such as discrete masses in the affected organs. In some cases, the mass was exerting downstream effects such as intestinal/biliary obstruction, IVC compression. A great number of cases that resulted in invasive intervention were done prior to 2015 (n = 6/14). Another 7 cases were done between 2016–2018. Only one case of surgical resection as a result of malignancy mimicker was done in 2019. Interestingly, one patient (patient #14) had an elevated CA 19 – 9 marker of > 800 u/mL.

Table 4
Cases of surgical intervention for presumed malignancy prior to diagnosis of IgG4-related disease

| Patient | Symptoms | Imaging | Serum IgG4 (g/L; normal < 1.25) | Suspected malignancy | Surgery | Surgical complications |
|---|---|---|---|---|---|---|
| 67 South Asian female | Abdominal pain, chronic pancreatitis | High-grade mid to distal small bowel obstruction, pancreatic mass<br><br>Mediastinal and hilar LAD | 25.7 | Pancreatic | Whipple resection 1980 | None recorded |
| 55 White male | epigastric discomfort | concerning pancreatic lesion | 2.39 | Pancreatic | Whipple resection, 2016 | None recorded |
| 65 Asian male | painless jaundice<br><br>salivary gland swelling | 1.7 cm mass at head of pancreas | 4.1 | Pancreatic | Whipple resection attempt (aborted intra-operatively), 2010 | None recorded |
| 60 Asian female | Painless jaundice, biliary obstruction | Stricture of common bile duct | 2.9 | Cholangiocarcinoma | Extensive bile duct reconstruction and resection of stricture, 2019 | Surgical site infections with drains requiring multiple admissions and long course of antibiotics |
| 68 South Asian male | right renal mass with adenopathy | Right renal mass (3.3 × 1.8 × 1.7 cm); lymphadenopathy along the aortocaval chains, up to 2.7 × 1.1 cm | 6.49 | Lymphoma | Right nephrectomy and renal transplant, 2014 | Marginal perfusion to graft kidney |
| 37 Asian male | Intestinal obstruction, salivary gland swelling, hepatic duct dilation and CBD stenosis | Multiple lung nodules; intra-thoracic lymphadenopathy; right kidney mass | 11.6 | Lymphoma | Right nephrectomy, 2001 | Chronic kidney disease |
| 71 Caucasian male | epigastric pain | Pancreatic mass (1.9 × 1.2 cm);<br><br>Pre-aortic mass (3.5 × 1.4 cm) at level of IMA takeoff<br><br>retroperitoneal and iliac lymphadenopathy | 9.75 | Lymphoma vs. Metastatic Pancreatic Cancer | laparotomy with removal of pre-aortic mass, 2014 | Injury to inferior mesenteric artery |
| 63 Asian male | Nightsweats, weight loss | Suprarenal right kidney mass (7.2 × 6.8 × 5.4 cm) and splenomegaly (15 cm) | 1.36 | MALT lymphoma | Para-adrenal mass resection, 2018 | Non recorded |
| 67 South Asian male | Nausea, vomiting, bloating | cecal mass at ileocecal region with adjacent lymphadenopathy | 1.9 | Cecal adenocarcinoma vs lymphoma | Right hemicolectomy, 2016 | None recorded |

| Patient | Symptoms | Imaging | Serum IgG4 (g/L; normal < 1.25) | Suspected malignancy | Surgery | Surgical complications |
|---|---|---|---|---|---|---|
| 68 Asian male | acute urinary retention, jaundice | Bile duct dilatation, abnormal prostate gland (irregular enhancement, peripheral wedge shaped enhancing regions) | 6.22 | Prostate vs. pancreatic | stent insertion for distal common bile duct stricture, 2017 | None recorded |
| 41 White female | malaise, nausea | moderate left renal atrophy,<br><br>distal abdominal aorta, inferior vena cava and iliac vessels surrounded by<br><br>confluent soft tissue | N/A | Lymphoma | R kidney nephrostomy, 2016 | None recorded |
| 73 White male | Painless jaundice | Intrahepatic duct dilatation with intraductal sludge/debris;<br><br>Pancreatic atrophy, scattered calcifications and duct dilatation | 14.1 | Pancreatic | Metal biliary stent insertion, 2012 | None recorded |
| 73 Asian male | Abdominal fullness, jaundice, nightsweats | Changes within the pancreatic body and tail suggestive of autoimmune pancreatitis | 4.5 | Pancreatic | 2x double-pigtail stents, 2018 | None recorded |
| 64 Asian male | Painless biliary obstruction/jaundice | Extensive hilar mass (8.3 × 3 cm); para esophageal, porta hepatis and paraaortic lymphadenopathy; bulky pancreas | 2.24 | Cholangiocarcinoma (Klatskin tumor)<br><br>CA 19 – 9: >800 u/mL<br><br>(reference) 2.24 | Recurrent stents, 2017 | None recorded |

Figure 1–3 illustrates radiographical findings of three patients with urogenital/gastrointestinal involvement of their IgG4-RD. They highlight the resemblance between the tumefactive lesions in IgG4-RD and malignant masses.

The patient illustrated in Fig. 1 presented with acute urinary retention and jaundice, and MRI results showed heterogeneity of prostate gland, irregular enhancement, and multiple peripheral wedge shaped non-enhancing regions.

The patient illustrated in Fig. 2 was found on CT to have a well demarcated splenic mass. He also had a borderline elevated serum IgG4 level on presentation. A core biopsy of the perirenal mass revealed increased expression of IgG4 positive plasma cells on immunohistochemistry.

Figure 3 represents a patient who presented with lymphadenopathy and urinary symptoms. MRI of the pelvis revealed periurethral mass displacing the vagina posteriorly. She had an initial IgG4 of 5.42. The excisional biopsy of her cervical lymph node revealed reactive follicular hyperplasia, and it was eventual biopsy of the periurethral mass that showed "fibromuscular stroma infiltrated by chronic inflammatory cells, increased IgG4 positive plasma cells."

## Discussion

One of the most common manifestations of IgG4-related disease is the development of a mass, or tumefactive lesion, which can involve virtually any organ in the body. Both the original International Consensus Criteria(2) and the recent 2019 EULAR/ACR criteria (6) are designed to help exclude mimickers of IgG4-RD such as cancer, vasculitis, and rare conditions such as multi-centric Castleman disease. The importance of timely diagnosis of IgG4-RD has been amply highlighted in literature with numerous case studies and reviews, whereby the initial malignancy diagnosis can lead to delayed initiation of medical treatment, and in some cases, major surgical resections(3, 5, 7–9). Due to the tumefactive nature of the disease, it can share striking similar presentations and characteristics to malignancy, resulting in the differentiation of the two complicated in many patients.

Of the 63 patients in our study, 38 were diagnosed with a malignancy initially, requiring a retrospective revision to IgG4-Related Disease. 14 of these patients underwent an invasive intervention due to their initial malignancy diagnosis. 13 of the interventions occurred prior to 2018, likely corresponding to an increase in recognition of IgG4-RD, leading to more patients with the condition correctly diagnosed.

There were no significant difference in laboratory results between the group initially thought to have a malignancy, and the group diagnosed with IgG4-RD initially. While elevated serum IgG4 is often the laboratory marker associated with IgG4-RD, it is not specific to IgG4-RD, as it can often be elevated in conditions such as multicentric Castleman disease, hypereosinophilic syndrome, and vasculitis(1, 10). The serum IgG4 level in both our group of patients were elevated above the upper limit of normal (6.83 g/L in the “yes malignancy” group, and 8.77 g/L in “no malignancy” group). This is not surprising given both groups ultimately ended up being diagnosed with IgG4-RD. Although interestingly, in our patient group, a serum IgG4 level of > 1.35 g/L was in retrospect 100% sensitive for IgG4-RD in our 14 patients who underwent invasive procedures. This emphasizes the importance of consideration of IgG4-RD when the serum IgG4 levels are elevated. It has been reported about 70% of patients with IgG4-RD will have an elevation in serum IgG4 levels, and this percentage can vary depending on ethnicity(1, 19, 20).

To further add to the diagnostic dilemma, there are in general no imaging-specific findings for IgG4-RD. As seen in Fig. 1, 2, and 3, IgG4-RD may often present as tumefactive lesion in affected organs – making a difficult distinction from a malignant mass. On CT imaging, it can present as a homogenous soft tissue mass. On MRI, it can show homogenous or irregular enhancing soft tissue mass in the affected organ. None of our patients had PET scans performed, however, case studies report IgG4-RD lesions showing as hypermetabolic soft tissue lesions(21). In some cases of diffuse pancreatic involvement of IgG4-RD, however, there has been a specific feature reported; this is a diffuse enlargement with loss of the lobules, resembling a “sausage” with surrounding halo. This is felt to represent infiltration and edema. When this is seen on imaging, it can raise high suspicion for IgG4-related pancreatitis.(22) There is currently no specific features for other organ involvements of IgG4-RD. Further studies are needed to investigate differentiating features of IgG4-RD from malignancy on radiographic imaging modalities.

The most common sites of IgG4-RD involvement in our patients included salivary/lacrimal glands (51/63), lymph nodes (18/64), and the pancreas (17/63). These correspond to their malignant mimicker - exocrine gland/lymph node swelling can often be seen with lymphoma; pancreas and biliary masses raise alarm bells for pancreatic cancer and cholangiocarcinoma.

The most common malignant mimicker of IgG4-RD in our patients was lymphoma. 18 of the 38 individuals initially thought to have a malignancy were believed to have lymphoma. IgG4-related lymphadenopathy is an immune-mediated process characterized by lymphoplasmacytic infiltrates with abundant IgG4-positive plasma cells and fibrosis(23), the morphologic features resembling reactive lymphoid hyperplasia. This finding is not surprising given that lymph node involvement is a common manifestation of IgG4-RD(12, 24). There are 5 reported subtypes of IgG4-lymphadenopathy, including multicentric Castleman disease-like changes, follicular hyperplasia, interfollicular lymphoplasmacytic proliferation, progressive transformation of germinal centers, and formation of inflammatory pseudotumour-like lesions(24). Current studies suggest IgG4-related lymphadenopathy is more common in Asian patients (30–65% of those with IgG4-RD), compared with patients in the US and Italy(25). To further add to the diagnostic challenge, lymph node biopsies often show reactive lymphoid hyperplasia without characteristic histopathologic features of IgG4-RD as it is unusual for lymph nodes to undergo the same degree of fibrosis observed in solid organs(13). Some clinical differentiators that may be used to favour a diagnosis of IgG4-RD over lymphoma includes the age and gender, whereby IgG4-RD tends to affect middle aged population, and has a male predominance, whereby lymphoma does not typically discriminate in age or gender(13, 26). In addition, the response to treatment, if it responds to steroids, would highly suggest IgG4-RD over lymphoma(27).

It should be noted that, however, there have been reports of association between IgG4 production and lymphoma(28, 29). The relationship between IgG4-RD and the subsequent development of hematologic malignancies have not been clearly described or

evaluated. If the clinical index of suspicion for malignancy is high, then this should be ruled out prior to the diagnosis of IgG4-RD.

In this study, IgG4-RD was initially thought to be pancreatic cancer in 11 patients and cholangiocarcinoma two patients. Patients with IgG4-related pancreatitis and/or IgG4-related cholecystitis often present with painless jaundice and obstructive biliary symptoms and imaging often shows diffuse pancreatic enlargement (“sausage-like swelling”) or a pancreatic mass, all of which may be difficult to distinguish from pancreatic cancer(3–5). In. In our patient group, there were 17 patients with pancreatic involvement, and 11 were initially thought to have pancreatic cancer. Those with diffuse enlargement of pancreas on imaging were less likely to be misinterpreted as having pancreatic cancer. Typical radiographic findings of autoimmune pancreatitis involve diffusely enlarged pancreatic duct and parenchyma with delayed enhancement caused by fibroinflammatory change of the peripancreatic adipose tissue, which is not commonly seen in malignancies of the pancreas(3). Of the 17 patients with pancreatic involvement, only 5 had solitary pancreatic involvement, and the remaining 11 patients had concomitant organ involvement, most commonly with salivary/lacrimal glands, kidneys, and liver. Multi-organ involvement should prompt one to entertain alternative diagnoses.

The dilemma with cholangiocarcinoma is that some of the cases are surgically difficult to resect. In these cases, patients may be considered for orthotopic liver transplant for curative intent. Many surgeons consider liver biopsy to be a contraindication for liver transplantation, hence the decision to pursue tissue diagnosis prior to surgery poses a predicament. In these cases, patients may be taken to the operating room without formal tissue diagnosis. Currently, there are no imaging findings specific enough to differentiate lesions from cholangiocarcinoma or IgG4-RD.

Interestingly, we had one patient (case # 14, Table 4) with IgG4-related lymphadenopathy and pancreatitis, who was initially believed to have cholangiocarcinoma as he presented with obstructive symptoms, and had a tumor marker CA19-9 significantly elevated at > 800 u/mL. Current case studies in literature suggest an elevated CA19-9 would favor a diagnosis of pancreatic cancer over IgG4-RD. This calls into question the specificity of tumor markers in distinguishing benign from malignant conditions. CA 19 − 9 can be elevated in pancreatitis or biliary obstruction. Certainly the concurrence of a mass and elevated CA 19 − 9 should raise concern for malignancy over all other conditions. More studies are needed to further elucidate on the incidence of elevated tumor markers in benign conditions.

14 patients in our study underwent invasive intervention tailored to the treatment of their malignant diagnosis. All but one case occurred prior to 2018, likely due to an increasing recognition for the condition. The interventions included Whipple resection (3/14), Interventional-Guided biliary stent insertion (4/14), nephrectomy (3/14), mass resection (2/14), hemicolectomy (1/14), and biliary reconstruction (1/14). Some procedures, such as stenting of biliary and ureteric obstruction, are likely unavoidable in patients who present with late stage disease. However, early recognition and appropriate systemic treatment with rituximab and/or corticosteroids may limit the need for procedural intervention in many of these patients. Four of these patients unfortunately suffered long-term complications from their surgery (recurrent surgical site infections, marginal perfusion to graft kidney, chronic kidney disease, injury to inferior mesenteric artery).

## Conclusion

This is the largest study to date to examine IgG4-RD as a mimic of various malignancies. IgG4-RD is commonly mistaken for cancer, particularly lymphoma and pancreatic cancer, and patients are at risk of delayed diagnosis and necessary surgical procedures. As histopathologic diagnosis is the gold standard for IgG4-RD, an adequate tissue sample is preferred for all patients with the working diagnosis of malignancy vs. IgG4-RD in order to avoid unnecessary invasive interventions. IgG4-RD is readily responsive to steroids and rituximab, and in cases where a biopsy is implausible or contraindicated, a trial of therapy can be pursued to aid in diagnosis.

IgG4-RD should be on the differential diagnosis of patients with mass lesions, in particular those with pancreatic masses and obstructive jaundice, extensive lymphadenopathy, or retroperitoneal masses. Oncologists and other physicians involved in cancer care should be aware of the various manifestations and diagnostic approach to IgG4-RD in order to provide accurate diagnosis and minimize unnecessary invasive procedures.

## Abbreviations

IgG4-RD
Immunoglobulin G4-related disease

ACR
American College of Rheumatology
EULAR
European League Against Rheumatism
CA19-9
Carbohydrate antigen 19 – 9

## Declarations

Ethics approval and consent to participate: Ethics approval obtained through the clinical research ethics board (H17-02765).

Consent for publication: consent of publication obtained from patients for figures included in this manuscript.

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Author contributions:WZ collected data, synthesized results, and formulated the manuscript. TM and SC provided radiographical images. LC aided in data collection. HL, DS, GS, BS, EL, RI, SC, AM provided expert opinion on patient cases. MC and LC supervised and oversaw the project. All authors reviewed, edited, and approved the manuscript.

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## Figures

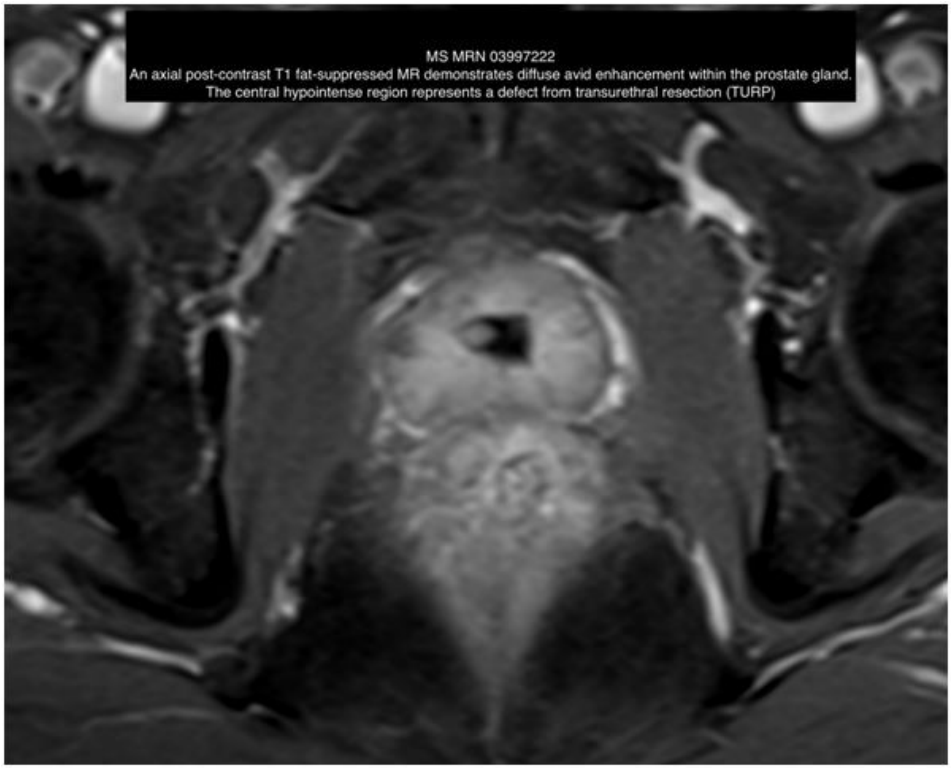


**Figure 1**

MRI of IgG4-related prostatitis

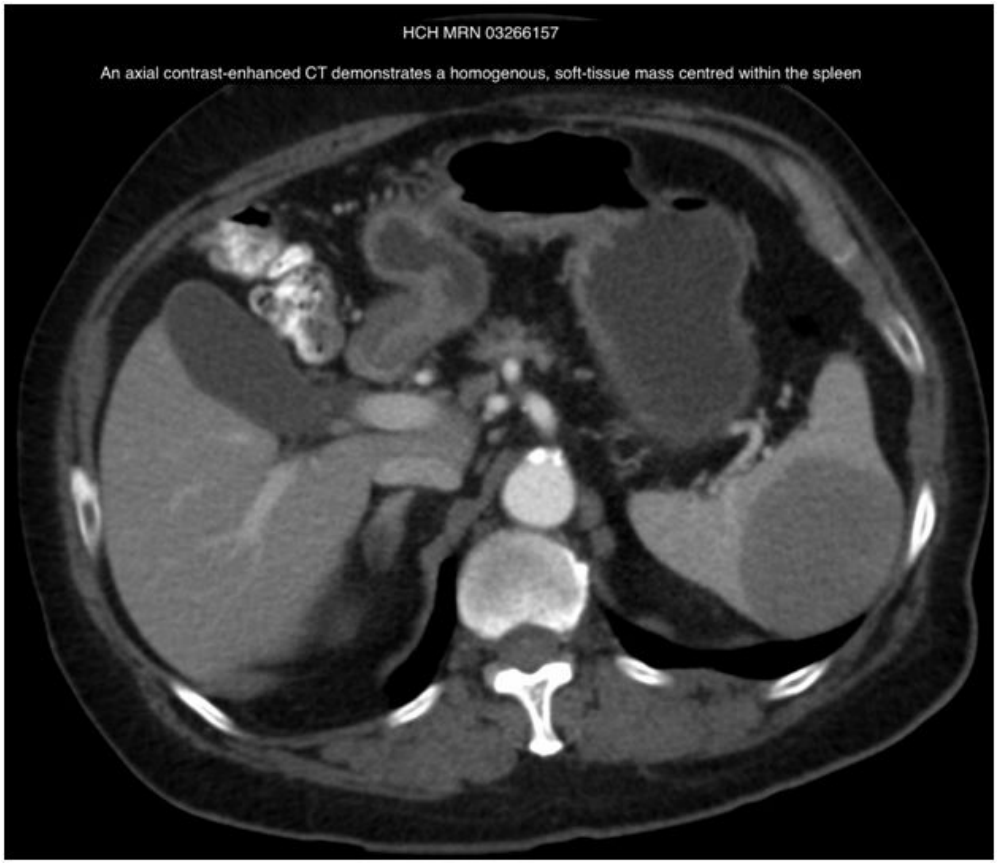


**Figure 2**

CT abdomen of spleen involvement in IgG4-RD

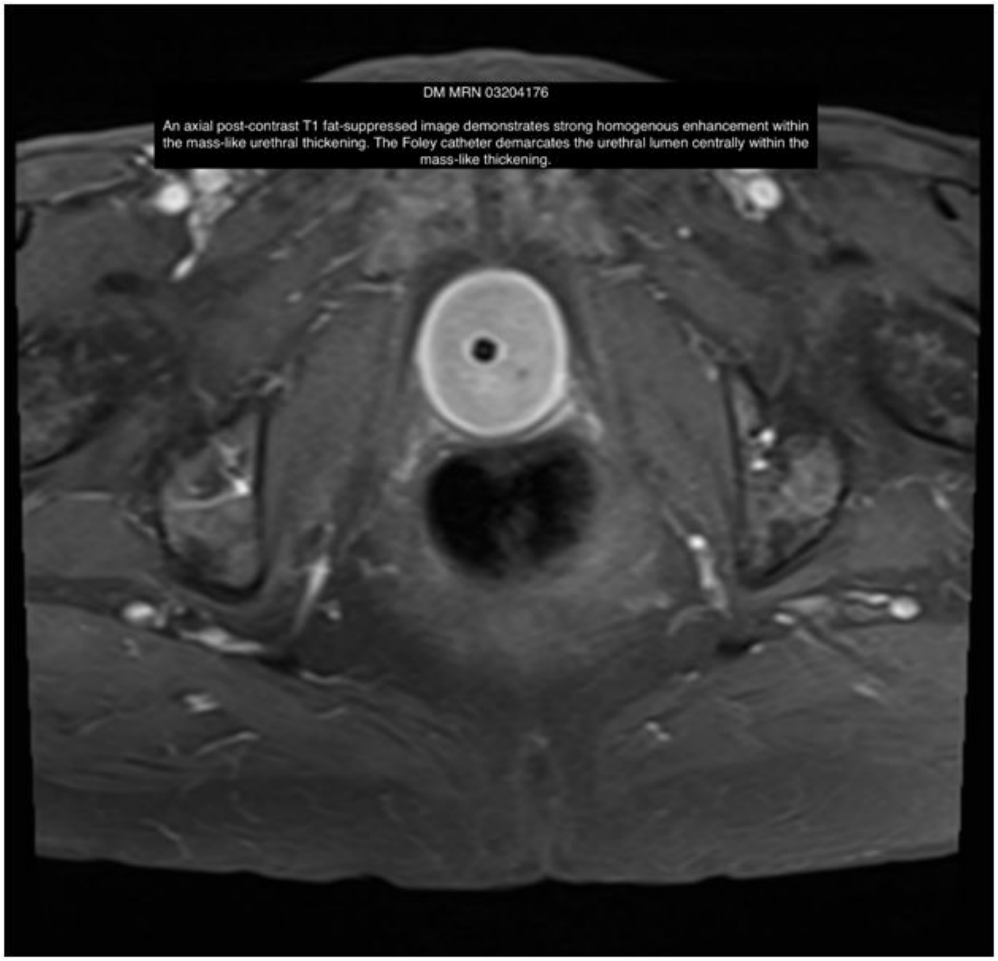


**Figure 3**

MRI of urothelial involvement of IgG4-RD