Review

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The role of imaging in immunoglobulin G4-related disease of the upper urinary tract

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Abstract

Background: Immunoglobulin G4-related disease remains a modern, relatively unknown field in the urological world. An increasing number of cases require urological input, often with invasive diagnostics and aggressive medical treatment first-line. Given this, we sought to evaluate modern radiological options of disease affecting the upper urinary tract, to provide clarity and reduce diagnostic burden and delay in this poorly understood yet potentially debilitating disease process.

Summary: We conducted a systematic literature search including PubMed and Medline, focusing on immunoglobulin G4-related disease affecting the upper urinary tract, before reviewing articles assessing different radiological modalities in diagnosis. Consistent computed tomography findings have been demonstrated in the literature and contributed to recent breakthroughs in classification criteria, however invasive biopsy remains a mainstay in work-up, given the difficulties in comparing against malignancy. Early work in positron-emission tomography and magnetic resonance imaging has shown promise in radiologically distinguishing from other differentials, especially diffusion-weighted imaging showing high sensitivity levels, but not yet enough to formulate protocols and cause histological investigation to be redundant.

Key messages: Our article has highlighted repeated findings in the literature of computed tomography appearances of IgG4-RD in the upper urinary tract, however invasive work-up remains a mainstay given the overlap with malignancy. Prospective, comparative studies into magnetic resonance imaging and positron-emission tomography are now required, given their early results, to improve consistency in reporting and reduce patient burden when investigating this benign, yet debilitating disease process.

Keywords: Imaging; Immunoglobulin-G4; Kidney; Urinary tract

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an autoimmune disorder that has grown in recognition over the past two decades.[1] The authors described raised serum IgG4 concentrations in a select group of patients suffering from a sclerosing form of pancreatitis, and subsequently, demonstrated extrapancreatic manifestations of a morphologically identical disease process.[2] These findings included lymphoplasmacytic infiltration, storiform-pattern fibrosis and obliterative phlebitis, and if collaboratively described alongside high concentrations of $IgG4^+$ plasma cells, a diagnosis of IgG4-RD was strongly considered. Currently, due to the recent recognition of IgG4-RD, its epidemiology remains poorly described, although a substantial male preponderance for abdominal organ involvement exists in the literature, of around 4:1, with patients often presenting in their fifth decade and above.[3] In 2019, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) devised the first classification criteria for the condition, aiming to aid diagnosis, trigger clinical trials and further epidemiological study.[4] More recently, focusing on the pathology alone, often from resected surgical specimens, has been met with caution, with the aim of collating clinical correlation, biochemical markers and radiological findings prior to reaching diagnosis. Given this, the aim of this study is to review the current literature and evaluate the role of imaging in diagnosing and managing a disease process that frequently mimics malignancy, rendering urological interest paramount to prevent potentially unnecessary surgical morbidity.

2. Materials and methods

A literature search was carried out in June 2021 via PubMed and Medline, with respective bibliographic lists, using keywords "immunoglobulin G4-related disease", "IgG4-RD", "immunoglobulin G4-related kidney disease and IgG4-RKD", alongside "kidney", "renal", "retroperitoneum", "retroperitoneal", and "ureter" (Supplementary Fig. 1, http://links.lww.com/CURRUROL/A9).

Exclusion criteria consisted of article not in English and nonhuman model studies, with only articles from the past 10 years included, rendering 299 abstracts found for analysis. A further 261 were excluded as they were not original research

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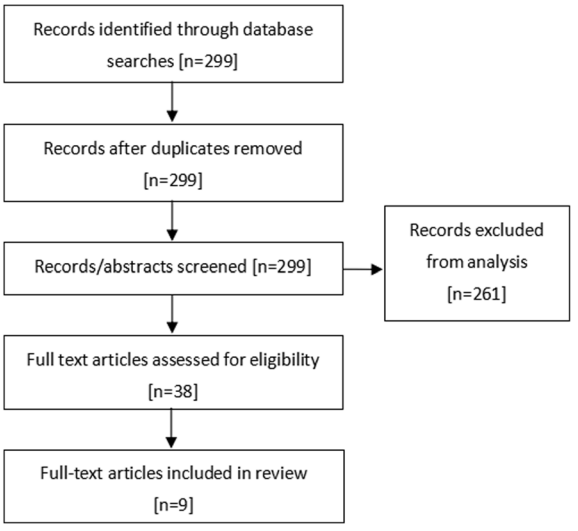

Figure 1. PRISMA diagram.

articles, did not study upper urinary tract IgG4-RD, or did not focus on imaging findings. Two articles had inaccessible full-text and as such could not be analyzed, as shown in the PRISMA diagram (Fig. 1). Nine studies were included in this review article (Table 1).

3. Results

As previously stated, the ACR/EULAR 2019 classification criteria are the first of its kind for IgG4-RD. This compromises a stepwise progression commencing with inclusion criteria and exclusion criteria, before systemic scores (all shown in Fig. 2) are merged with organ-specific scores, including kidney and retroperitoneum.[4] Without meeting the inclusion criteria, a patient is unable to be considered as having IgG4-RD, and similarly should any of the exclusion criteria be appropriate. A score of ≥ 20 on the domain scoring system gives a diagnosis of IgG4-RD.

As we can see from scrutinizing the new classification, inclusion criteria can be dependent upon appropriate radiological involvement, and an exclusion criterion differentiating between IgG4-RD and infection or malignancy is stated. Given this, it is imperative that new literature is evaluated in order to understand the key radiological findings to aid diagnosis in the upper urinary tract, where cancer and infective processes are commonly seen.

The kidney is the most frequently reported involved genitourinary organ. Patients may present with systemic symptoms such as fever, edema, and anorexia, but as with malignancy, cases can be found incidentally through imaging or deteriorating serum renal function. Similarly, glomerular disease can be signified through the presence of hematuria or proteinuria.[3] The ACR/ EULAR organ-specific scores, to be added to the classification, for kidney are as follows:

- Low serum levels of C3 and/or C4 + 6
- Uni- or bilateral renal pelvic thickening or soft tissue + 8
- Bilateral patchy or round low-density lesions seen on renal cortex on contrast-enhanced computed tomography (CECT) + 10

We can see here the importance of imaging findings to aid a diagnosis of immunoglobulin G4-related kidney disease (IgG4-RKD). CT appearances of IgG4-RKD can often be nonspecific, and thus patient harm can occur due to diagnostic delay, given their cohort had a median delay to treatment of 64 months, as well as a requirement for more invasive investigation, such as kidney biopsy.[5] The use of positron-emission tomography (PET) is postulated by the authors, however no further information is given.

Martin-Nares et al.[6] described how CECT was used to evaluate renal patients and demonstrated these nonspecific findings; 10/13 (77%) had low-density lesions, with the remaining 3 showing nephromegaly. These renal lesions are described as multiple, small, low-attenuation, peripheral nodules, and show clear difference from malignant lesions, given the lack of contrast uptake and often synchronous appearance of the lesions. Only 5 patients went on to have a biopsy as confirmation, which were positive in all, however 92.9% of patients, where tested, had high serum IgG4 levels and as such treated accordingly.

Interestingly, Teng et al.[7] describe three consistent CECT findings across their cohort:

- Cortical low-density lesions
- Parenchymal mass or nodule(s)
- Nephromegaly including thickened capsule

The authors here also discussed how ^{18}F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) was utilised in a small cohort of patients, rendering diagnostic

Table 1

Included studies with observations.

Author, yr	Study type	Country	Patients, n	Sub-group focus	Imaging utilized
Martan-Nares et al. (2020)	Retrospective case series	Mexico	69	Kidney and retroperitoneum	CT
Pucar et al. (2019)	Retrospective case series	Australia	5	Kidney and retroperitoneum	CT and/or 18F-FDG PET
Teng et al. (2020)	Retrospective case series	China	65	Kidney, retroperitoneum, and ureter	US, CT, MRI and/or 18F-FDG PET
Kim et al. (2014)	Retrospective cohort study	Republic of Korea	31	Kidney	MRI
Lin et al. (2015)	Prospective cohort study	China	60	Kidney and retroperitoneum	US, CT, MRI, and/or 18F-FDG PET
Zhang et al. (2014)	Prospective cohort study	China	9	Kidney and retroperitoneum	CT and/or 18F-FDG PET
He et al. (2015)	Retrospective cohort study	China	40	Kidney and retroperitoneum	CT
Ebbo et al. (2014)	Retrospective cohort study	France	12	Kidney and retroperitoneum	CT and/or 18F-FDG PET
Lee et al. (2016)	Retrospective case series	Republic of Korea	4	Kidney and retroperitoneum	CT and/or 18F-FDG PET

18F-FDG PET = ^{18}F-fluorodeoxyglucose positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; US = ultrasonography.

value due to the increased uptake in the renal cortex ofaffected patients, although no further information is given. A disadvantage is that imaging of this kind cannot be utilized in patients with significantly deteriorated renal function. Diffuse renal enlargement and peripheral nodules on CT is also described by Lin et al. in their Chinese cohort of IgG4-RD patients, without information on other imaging techniques.[8] He et al. evaluated 26 IgG4-RKD patients retrospectively over

Figure 2. Adapted from the 2019 American College of Rheumatology/European League against Rheumatism classification criteria for IgG4-RD. IgG4-RD = immunoglobulin G4-related disease; hpf = high-powered field.

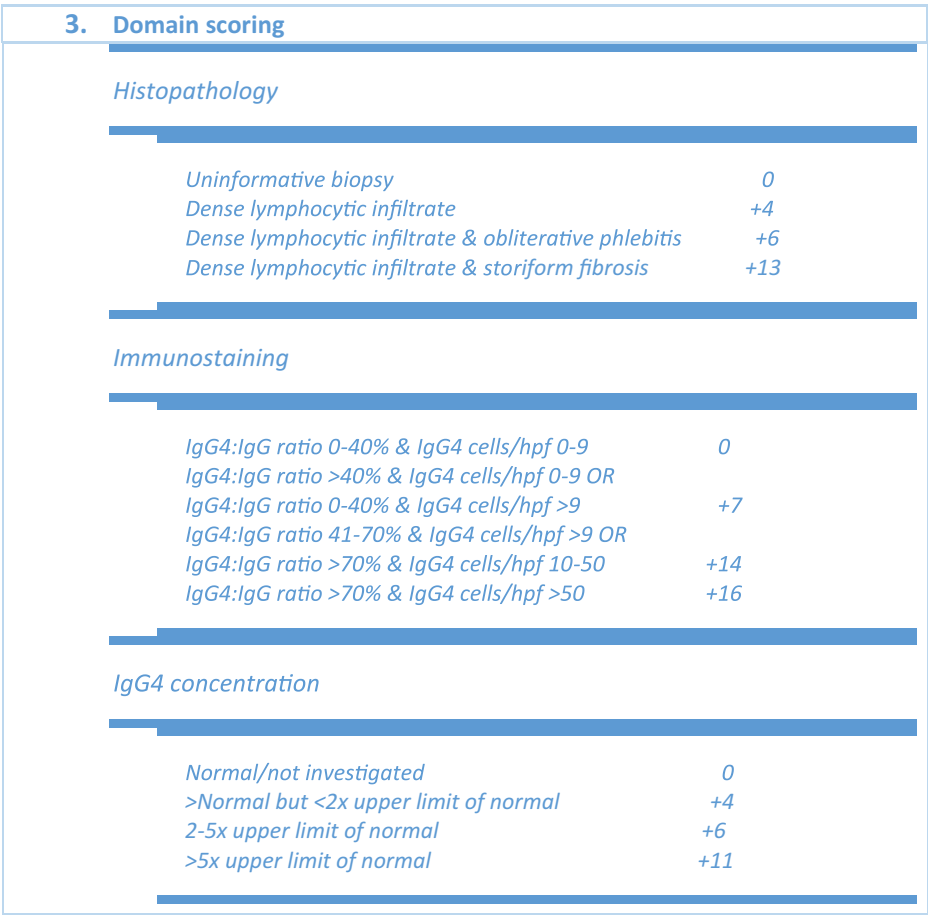

Figure 2. (Continued).

5 years, reaching similar conclu-sions, and it is clear from the literature that findings on CT are consistent in IgG4-RKD, and patients with these findings should undergo serum evaluation of IgG4 levels.[9]

A prospective cohort study by Zhang et al. aimed to address the use of PET for evaluating IgG4-RD, given the nonspecific and limited findings discussed regarding conventional CT scanning in this disease process.[10] It is described how ^{18}F-FDG demonstrates glucose metabolism in organ sites across the whole body, and as such can offer information on disease activity where infiltration of IgG4 is postulated, and synchronous activity can be found. In this cohort, patchy lesions in enlarged or irregular kidneys were again noted, with atleast moderate ^{18}F-FDG uptake in affected patients. Interestingly, ^{18}F-FDG PET additionally detected 40.5% (53/131) organ involvement in 71.4% (25/35) patients. Overall, 4 patients had kidney involvement, however utilizing PET found another 3 patients with renal involvement, and as such renal function monitoring and treatment regimens were able to be instigated sooner. Furthermore, Zhang et al. explained how given the complex nature of the disease process and its diagnostics, PET offered increased selection options and accessibility for biopsy through demonstrating areas of high uptake rate, and as mentioned earlier, including patients with previous negative findings on conventional CT imaging.[10] Unfortunately, this study only included patients with a known diagnosis of IgG4-RD, and as such, selection bias is inferred given reporting radiologists are already aware of the patient's diagnosis and information or signs to report on. A keen area of interest to develop is utilizing PET in the initial work-up of this disease and evaluating its diagnostic accuracy, and how it compares at delineating against malignancy or infection.

Further work on PET and its usefulness in IgG4-RD was performed by Ebbo et al.[11] It is discussed how 2 of their kidney patients did not demonstrate ^{18}F-FDG uptake despite associated organ involvement on CECT, and conversely, 1 patient demonstrated uptake in the kidney alongside other organs, despite no clear renal involvement on CECT. Despite this lack of clarity, an advantage was discussed in that whole-body mapping can be performed by PET in IgG4-RD to address multi-organ involvement. Furthermore, it was noted that 3 of 4 retroperito-neal fibrosis cases demonstrated reduced ^{18}F-FDG uptake on serial scans following steroid treatment, indicating inactive disease, and as such a potential advantage over CECT or magnetic resonance imaging (MRI) with regards to monitoring disease progression, or regression with treatment. Added to this, Lee et al. discussed more detail in their assessment of 28 IgG4-RD patients undergoing PET, alongside ultimately 29 malignant cases and 35 patients

labelled as other inflammatory disease.[12] It is discussed how large organs, including the kidney, demonstrated a more frequent pattern of diffuse, heterogeneous ^{18}F-FDG uptake in comparison to malignant cases. Interestingly, this study conducted binary logistic regression analysis, revealing a unique platform of positive findings for PET to differentiate IgG4-RD from other disease processes. This included mild to moderate ^{18}F-FDG uptake and multi-organ involvement, giving an area under curve of 0.824 (over 0.8 considered excellent discrimination). This is highlighted by the maximum standardised uptake value at PET being greater in non-IgG4-related pathologies (4.6 ± 1.7 vs. 7.1 ± 5.0; $p = 0.065$), including malignancies, although no significance was reached. Clearly, a limitation of this data for our review is the lack of focus on upper urinary tract organs, as well as the study's retrospective design and small sample size. Upon further reading, only 22 of the 94 patients underwent biopsy, potentially leading to diagnostic inaccuracies, albeit interesting conclusions have been mooted comparing PET in IgG4-RD with different disease processes, and scope for larger, prospective studies are required to garner more reliable results.

The evaluation of MRI was a focus of Kim et al. in their retrospective cohort study of 31 IgG4-RKD patients.[13] The consistent finding was described as isosignal intensity on T1-weightedimagingin93.5% ofpatients, with77.4% demonstrating low-signal intensity on T2-weighting. Interestingly, and comparatively to malignancy, 100% of patients had lesions that were iso- or hypo-intense on diffusion-weighted imaging (DWI), compared to normal renal parenchyma. This phase corresponded to 100% sensitivity for diagnosing IgG4-RKD. Dynamic contrast enhancement was hypointense in the arterial phase in 83.3%. The lesion manifestation remained similar to CT findings from other studies. Clearly, an early role is hinted at regarding MRI in IgG4-RKD, specifically the use of DWI to not only detect abnormalities not found on conventional MRI sequence, but to give more valuable information when comparing against other potential differential diagnoses. Recently, MRI protocols have evolved, and a limitation of this study is the sparsity of patients in a short period of time, and consistency in this radiological field given no dedicated protocol. Further to this, all patients already had a diagnosis of IgG4-RKD, and as such, bias is incurred when interpreting scans as no blinding could be performed. As such, given the tentative data, as well as the ability of lymphomas to mildly enhance and distribute similarly, serological information remains a necessity to clinch diagnosis. Clearly however, a potential role in newer MRI diagnostic protocols including DWI may exist, and prospective, blinded data is required to evaluate this further.

4. Conclusions

Our review has demonstrated the difficulties in noninvasive diagnosis of a relatively newly discussed disease process that can affect the upper urinary tract, and as such, present to a urologist. With the ease of access to CT scanners in patients with IgG4-RD, consistent findings have been demonstrated in the literature with regards to the appearances of the kidney, and formulated to contribute to a diagnostic criterion. Early work in newer MRI protocols has demonstrated promise in order to differentiate from more sinister diagnoses and reduce the high biopsy rate, but remains wholly untested in prospective studies. Given this, invasive biopsy remains crucial in not only confirming diagnosis and preventing renal injury, but ruling out malignancy. Despite early progress in radiological patterns and tracer uptake of the disease in ^{18}F-FDG-PET, it is clear that further prospective study is required in evaluating other imaging modalities and their sensitivity and specificity, in order to reduce investigative patient burden and improve diagnostic capacity from other diseases.

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Statement of ethics

Not applicable.

Conflict of interest statement

The authors report no conflicts of interest to declare.

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Author contributions

ST: Conception and design, literature search and study selection, data collection, analysis and interpretation, writing the article;
OE: Literature search and study selection, analysis and interpretation;
All authors contributed to critical revision of the article, final approval of the article.

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