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IgG4-related disease presenting with renal injury and obstructive nephropathy discovered incidentally: a case report with literature review

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ABSTRACT

IgG-4 related disease (IgG4-RD) is a chronic inflammatory condition characterized by tissues infiltration with lymphocytes and IgG4 secreting plasma cells, significant fibrosis and response well to steroids. It is typically a systemic disease that involves various organs. We are presenting a 57-year-old female who was found to have elevated serum creatinine, Proteinuria. An ultrasound scan revealed bilateral hydronephrosis and an abdominal computed tomography (CT) scan illustrated a large retroperitoneal mass. Further evaluation of the mass with whole-body positron emission tomography (PET CT) scan was suggestive of retroperitoneal fibrosis or lymphoma. A CT guided biopsy was done, and results were consistent with fibrosis in the context of IgG-4 related disease. IgG-4 serum levels were elevated. The patient was treated with oral steroids. Azathioprine and Rituximab. Renal function improved significantly and was stable upon 3 months follow up with a decrease in IgG-4 levels and with a significant reduction in the mass lesion.

Keywords: IgG-4 related diseases (IgG-4 RD), Retroperitoneal fibrosis (RPF), Obstructive nephropathy.

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Introduction:

IgG-4 related disease (IgG-4 RD) is a new spectrum of diseases emerging in Medicine. It is characterized by a mass lesion and an underlying autoimmune and chronic inflammatory process that can affect single or multiple organs [1,2]. It commonly affects the pancreas (as autoimmune pancreatitis), slivery glands, orbit, or biliary system. Rarely, IgG4 can involve the kidneys leading to IgG4 nephropathy [1,4]. IgG-4 related retroperitoneal fibrosis occurs frequently in the larger context of chronic peri aortitis that can affect the ureters causing hydronephrosis and kidney injury. IgG-4 related Renal involvement with retroperitoneal fibrosis was described before [3]. However, this association is still a rare entity that need further studying to outline characteristics and traits. Herein we present a case of obstructive nephropathy caused by IgG-4 retroperitoneal fibrosis extending into the posterior mediastinum.

Case Presentation:

A 57-year-old female with no significant past medical history is a part of Hypothyroidism. She was at her usual state of health when she went to a local clinic for a routine checkup, her laboratory workup revealed an elevated kidney function with creatinine above 400umol/L. Then her abdominal ultrasound showed severe bilateral hydronephrosis. She was referred to our hospital for further workup and management. Upon arrival she was vitally stable: temperature 37.1^{O} C, Blood Pressure BP 153/86 mmHg, Heart Rate 76 bpm, Saturation 98%, she stated that she recently felt dizzy on a few occasions, no other symptoms, or complaints.

Physical examination was unremarkable except for marked pallor, basic labs were sent showing: Creatinine (Cr) 465 umol/L, Urea (Ur) 22.4 mmol/L, urine protein creatinine ratio was 33.7 mg/mmol (normal high <22.6). White blood cells (WBC) 8.2 x10^3/uL, Hemoglobin (HGB) 7.8 g/dL, platelets 325 x10^3/uL, Na 134 mmol/L, K 4.8 mmol/L, bicarbonate 15 mmol/L. The initial urine protein creatinine ratio was 33.7 mg/mmol (normal high <22.6). An urgent abdominal computed tomography (CT) without contrast confirmed the presence of bilateral hydronephrosis and hydroureter with perinephric fat stranding and a large irregular abdominal mass obstructing both ureters measuring 15X7.5X3 cm engulfing abdominal Aorta and Vena Cava suggestive of Lymphoma or retroperitoneal fibrosis.

In the light of these findings, the patient underwent a bilateral double J – stent placement to relieve the obstruction, unfortunately, the patient Cr continued to rise. At this point it was not clear if the kidney impairment is chronic or acute, a renal scintigraphy was organized showing: the split function is 28% left - 72% right. The right kidney upper moiety shows a split function of 42% and the lower one is 58% from the overall right kidney function. The findings are characteristic of total obstruction. With these results, a decision was made to insert bilateral percutaneous nephrostomies (PCN), following the Cr and other metabolic parameters started trending down. An underlying malignancy was of concern, accordingly, we proceeded with whole-body positron emission tomography (PET CT), which revealed Intensely FDG-avid infiltrative mass in the retroperitoneal region and the posterior mediastinum (retro-crural area) with more intense uptake in the mediastinal part. The image is most suggestive of active retroperitoneal fibrosis extending to the retro-crural regions (fibrosing mediastinitis). Following that a CT guided biopsy was performed, waiting for biopsy result from an autoimmune, complement and work up were done and all came back negative, however, IgG4 level was elevated to 916 mg/L (reference range 39-864). The patient was discharged with stable Cr 217 umol/L.

Biopsy results issued 7 days after the procedure showed extensive fibrosis with thick hyalinized collagen bundles associated with lymphoplasmacytic infiltrate and lymphoid

aggregates. With Numerous plasma cells and few areas of back-to-back proliferating blood vessels entrapped by the fibrosis, no evidence of granulomas or obvious malignancy (Figure 3). IgG: Positive in plasma cells, IgG-4: Positive in plasma cells with IgG4/IgG ratio of >40% (Figure 4). Other stains (S100, SOX-10, CKAE1/AE3, MDM2, CDK4, HMB 45, ALK, Stat 6) done to exclude other diseases were negative. The findings are suggestive of IgG4 diseases.

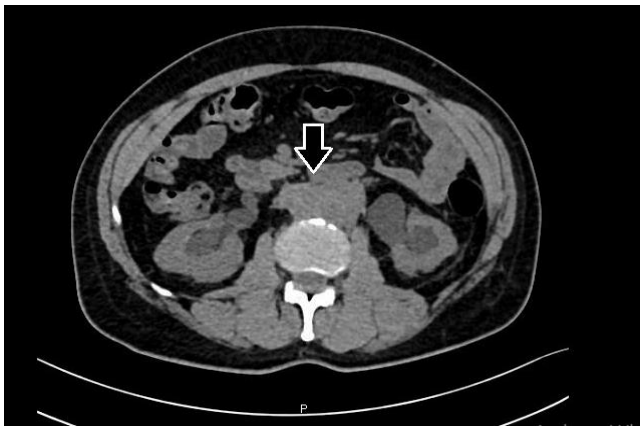

Figure (1): abdominal CT without contrast showing irregular retroperitoneal mass (arrow) with adjacent bilateral hydronephrosis.

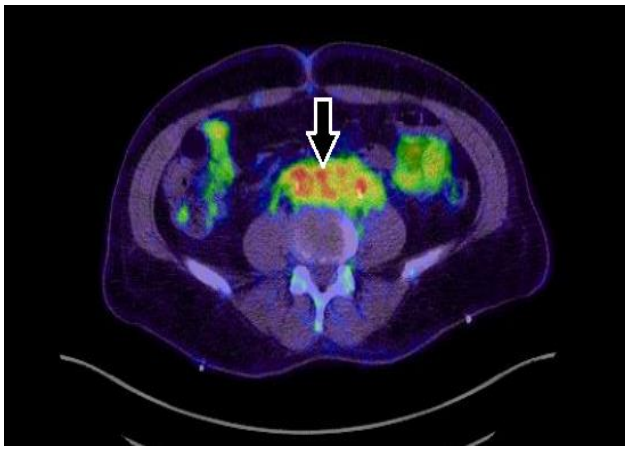

Figure (2): PET CT scan showing retroperitoneal mass with intense FDP uptake

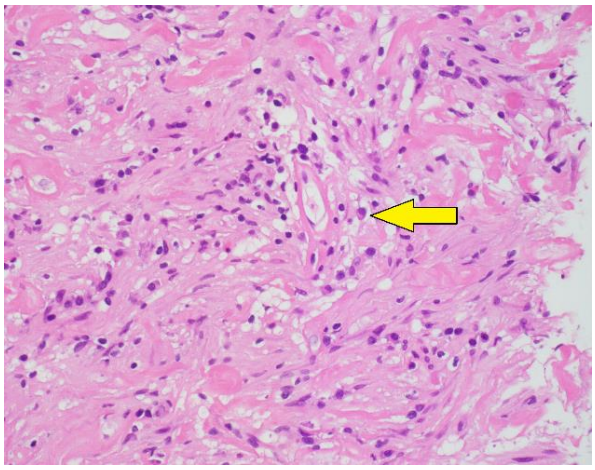

Figure (3): Histology, H&E slide showing fibrous tissue rich in plasma cells (arrow) (magnification X400

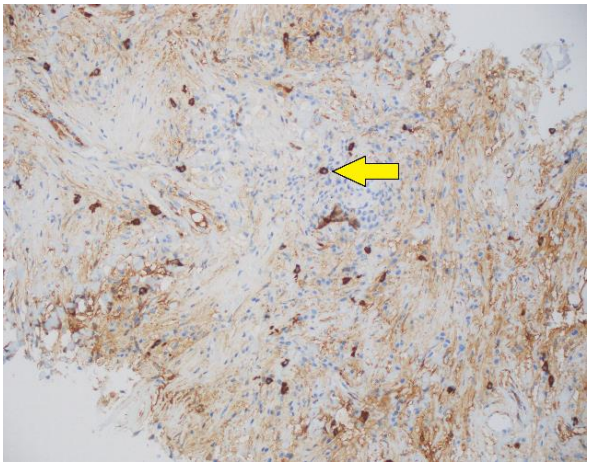

Figure (4): Histology, IgG4 immunohistochemistry stain positive in plasma cells (arrow) (magnification X400).

Based on the above, a diagnosis of IgG4 related disease was made, including IgG4 nephropathy and retroperitoneal fibrosis. A kidney biopsy was not performed as the patient still has bilateral PCN, moreover, we felt that we have enough evidence of nephropathy. Our patient fulfilled the 2019 ACR/EULAR Classification Criteria for IgG4-RD, and as per the above criteria our patient scored 32, and we need >20 for the classification of the IgG4-RD [4].

The patient was started on Prednisolone 80 mg for 2 weeks then tapered to 60 mg for 4 weeks with Azathioprine 50 mg daily and Rituximab 1 g (2 doses, 2 weeks apart). at 3 months follow up the patient was clinically asymptomatic with Cr between 180 – 200 umol/L and IgG-4 serum level dropped to 256 mg/L. At 6 month follow up IgG-4 serum level was 218 mg/L, Urine protein/creatinine ratio was < 10.68 mg/mmol and repeated PET CT showed significantly regressing uptake in the retroperitoneal component. The posterior mediastinal (retro-crural) component of the disease is almost completely resolved, these findings suggesting a 60% interval decrease in metabolic activity of the disease (Figure 5). The patient response to immunosuppression and marked improvement in kidney function and protein/creatinine ratio support diagnosis of IgG-4 nephropathy. The patient is planned to receive another Rituximab course in 6 months, the duration of treatment will be decided upon the clinical and radiological follow up.

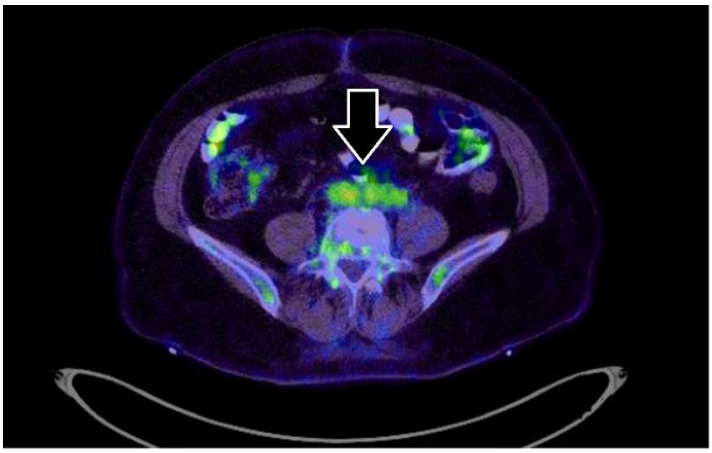

Figure (5): retroperitoneal soft tissue fibrosis (arrow) with markedly decreased FDP uptake compared to a previous study (Figure 2).

Discussion:

Retroperitoneal fibrosis is relatively a rare disease, characterized by a chronic inflammatory process involving the soft tissues and organs of the retroperitoneum, this inflammation later progresses to fibrosis. The condition is usually asymptomatic, it can be classified based on aetiology to secondary due to drugs, tumours, and radiation or idiopathic which is estimated to represent 2/3 of retroperitoneal fibrosis cases [2]. IgG4 related diseases were first described in 2003, since then many case reports were published showing a diverse array of organ involvements and manifestations [1]. IgG 4 related retroperitoneal fibrosis is one of these manifestations, it tends to affect older men (mean age 66) with a prevalence rate of 0.1/100 000 to 0.8/100 000 [2]. the majority of the cases are asymptomatic and usually involve multiple organs. However, isolated IgG4 retroperitoneal fibrosis is extremely rare [5]. It is worth noting that these estimates and statistics are based on small populations and may not represent the whole spectrum of the disease, that's why reporting these cases is essential to create data for future reviews and meta-analysis.

The diagnostic approach of IgG-4 related retroperitoneal fibrosis is based on clinical, radiological and biopsy assessment [1,6]. The American College of Rheumatology with association with the European League Against Rheumatism published criteria for the classification of IgG-4 related disease using a scoring system with a cutoff of 20 points [1], upon applying these criteria; our patient's characteristics scored 32 with the entry criteria are met and no exclusion criteria. It is vitally important for accurate recognition of this disease and to rule out other possibilities like malignancy. In such cases biopsy is the cornerstone, the histopathology findings demonstrate a plasma cells rich infiltrate with extensive fibrosis. In our case pathology report showed the typical findings of plasma cell infiltrates, fibrosis and IgG4/IgG ratio of >40%. IgG-4 serum levels are usually elevated. However, up to 30% of cases have normal IgG-4 levels [7]. it appears that IgG-4 levels correlate with the number of organs affected, the activity of the disease as it decreases with successful management [3,7], in our case, the initial IgG-4 serum levels were moderately elevated but they were markedly lower upon follow up.

Imaging studies are of great importance as they help localize the lesion and its connection to adjust organs, discover other foci and secure access for biopsy. Ultrasound will reveal hydronephrosis if present due to fibrosis, but it may fail in providing further information on the mass. Computed Tomography (CT) scanning with contrast or Magnetic Resonance Imaging (MRI) may be needed to visualize the mass and its extent and can hint the diagnosis depending on fibrosis extent such in our patient but contrast-induced kidney impairment can limit their use if harm outweighs the benefit. In such a scenario PET CT scan is an alternative. PET CT scan is often used to search for other organ involvement, and it has a major role in diagnosis due to distinctive patterns of fibrosis, inflammation, and activity of the disease [2,8]. In our case malignancy was the primary suspicion but after PET CT scan findings, retroperitoneal fibrosis became our priority.

Steroids are considered the first line in remission induction, a dose of 0.6 mg to 1 mg per kilogram was proposed and showed to be effective, this need to be tapered down over weeks to months [1]. However, due to the high relapse rate and the need for a long duration of therapy; steroids sparing agents are often needed such as Azathioprine or Mycophenolate mofetil. Rituximab was found to be successful in a few cases [2,9]. Our patient received initially prednisolone for 4 weeks then was started on Azathioprine and Rituximab. We used the Rituximab as a recent study that was very promising for the role of Rituximab in such a case [10]. In this study, it has been found that 77% of the patients with IgG-Rd has a good response and 23% has an incomplete response, but no

one has had no response or relapses. Kidney function tests improved comparing admission parameters, they plateaued around 180 umol/L, that's partially due to subacute obstructive nephropathy and partially due to possible contrast-induced nephropathy as the patient received contrast media when the CT guided biopsy was done.

A co-existing kidney involvement with retroperitoneal fibrosis in the context of IgG-4 was reported by Kim et al [3]. in our case we cannot rule out the possibility of co-existing kidney involvement as biopsy was obtained from retroperitoneum only, but urine protein creatinine ratio was 33.7 mg/mmol (normal high <22.6) that was normalized upon follow up to < 10.68 mg/mmol suggesting a co-existing involvement. management would not differ in such case of involvement.

Conclusion:

IgG-4-RD can present as Kidney injury due to concomitant IgG4 nephropathy and Retroperitoneal fibrosis. A high index of suspicion is essential for early diagnosis and treatment to prevent fibrosis and irreversible damage.

Conflict of Interest:

The authors declare no conflict of interest

Authors Contribution:

Dr. Mouhammad Jassem Alawad performed the literature review and wrote the manuscript, Dr. Saffa Elawad provided mentorship, performed literature review, and edited the manuscript, Dr. Bara Wazwaz provided us with pathological slides and interpretation. Dr. Abdul Wahab Al Allaf reviewed, and edited the manuscript from a scientific and English language point of view.

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Ethical Approval:

This case was approved by the Medical Research Center of Hamad Medical Corporation MRC-04-21-905, and the patient consented to the publication of his case.

Data Availability Statement:

Data and materials are available upon request.

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References:

[1] Stone JH, Zen Y, Deshpande V. IgG4-Related Disease. *New England Journal of Medicine*. 2012;366(6):539-551. doi:10.1056/nejmra1104650.

[2] Lian L, Wang C, Tian J. IgG4-related retroperitoneal fibrosis: a newly characterized disease. *International Journal of Rheumatic Diseases*. 2016;19(11):1049-1055. doi:10.1111/1756-185x.12863.

[3] Kim YJ, Kim G-E, Ma SK, Kim SW, Bae EH. Case report: IgG4-related renal disease co-existing with retroperitoneal fibrosis. *Translational Andrology and Urology*. 2020;9(2):794-799. doi:10.21037/tau.2020.02.06.

[4] Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Annals of the Rheumatic Diseases*. 2019;79(1):77-87. doi:10.1136/annrheumdis-2019-216561

[5] Razok A, Malik R, Cackamvalli P, Zahid M. IgG4 related disease as a cause of isolated retroperitoneal fibrosis with no other organ involvement; Case report. *Annals of Medicine and Surgery*. 2021;61:69-72. doi:10.1016/j.amsu.2020.12.028.

[6] Umehara H, Okazaki K, Kawa S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. *Modern Rheumatology*. 2021;31(3):529-533. doi:10.1080/14397595.2020.1859710.

[7] Niaz A, Ahmad AH, Khaleeq-ur-Rahman, Saeed MA, Sabir O, Tarif N. IgG4-related retroperitoneal fibrosis: A case report and review of literature. *J Pak Med Assoc*. 2016;66(2):220-222.

[8] Yamada K, Kawano M. IgG4-Related Kidney Disease and IgG4-Related Retroperitoneal Fibrosis. *Seminars in Liver Disease*. 2016;36(03):283-290. doi:10.1055/s-0036-1584316.

[9] Inoue S, Takahashi C, Hikita K. A Case of IgG4-Related Retroperitoneal Fibrosis from the Renal Pelvis Mimicking Bilateral Hydronephrosis. *Urologia Internationalis*. 2014;97(1):118-122. doi:10.1159/000354765.

[10] Nasonov E, Beketova T, Ananyeva LP, et al. SAT0171 RITUXIMAB IN SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES: ONE CENTER EXPERIENCE OF TREATMENT 515 PATIENTS. *Annals of the Rheumatic Diseases*. 2020;79(Suppl 1):1027.1-1027. doi:10.1136/annrheumdis-2020-eular.2142.