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Case Report

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Beyond the Surface: Two Cases of IgA Nephropathy Mimicking Nutcracker Syndrome

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Abstract

Aims: Intermittent gross hematuria associated with persistent microscopic hematuria can be a common presentation of glomerular and nonglomerular pathologies. Sometimes we have a combination of both so it is difficult to find the primary cause of these clinical manifestations.

Methods: we report the cases of two 13 year old boys with stories of persistent microhematuria, some episodes of gross hematuria and non-orthostatic proteinuria.

Results: In both cases the preliminary examinations showed normal renal function, no hypocomplementemia, normal ANA-titer, negative stone screening test and non-glomerular hematuria. We suspected in both a Nutcracker Syndrome (NS), so we performed doppler ultrasound (US) in the first case, which was inconclusive due to borderline measures, and an angio-CT in both cases which revealed a Nutcracker Phenomenon. Both patients, months after, developed more episodes of gross hematuria, both associated with impaired renal function, so we performed renal biopsies which revealed IgA Nephropathy.

Conclusions: Although all symptoms were likely attributed to IgA nephropathy, the initial presentation strongly suggested NS. Our cases underscore the importance of maintaining a high index of suspicion for glomerulopathy in patients with recurrent macrohematuria, even when NS is the leading diagnosis. Despite inconclusive findings, the association between IgA nephropathy and NS is documented in the literature, though the underlying pathophysiology remains unclear.

Keywords: Hematuria, IgA nephropathy, Nutcracker syndrome

Background

IgA nephropathy is the most common cause of glomerulonephritis in resource-abundant countries, with a peak diagnosis in East Asian individuals and in white individuals. About 75% of children and young adults come to attention for an episode of hematuria following an upper respiratory or gastrointestinal infection.[1] The real prevalence of the disease is not known because of the need of a renal biopsy to make the diagnosis, and probably the amount of clinically silent IgA nephropathy is high.

Nutcracker Syndrome (NS) is defined as the effect of the compression of the left renal vein (LRV) by the superior mesenteric artery (SMA). The prevalence of NS is not known since there is a lack of univocal diagnostic criteria, and the diagnosis remains a diagnosis of exclusion. We know that there is a higher female prevalence,[2] and that symptoms can vary from flank pain, to ematuria and proteinuria.

LRV entrapment has been reported to coexist with some idiopathic glomerular disease in some case reports, among which coexistence with IgAN were the most commonly reported ones.[3,4]

The combination increases the difficulty of differentiating the primary cause of renal manifestations and influences the choice of therapy.

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Cases

We report the cases of two young boys who came to our attention with symptoms mimicking NS, but finally had a coexisting IgA nephropathy.

Case 1

A 13-year-old boy with a history of treated left varicocele came to our attention following an incidental finding of microhematuria detected during a sports medical examination. The patient had a long-limbed habitus: weight 45.9kg (25th-50th percentile), height 164cm (50th percentile), and a body mass index (BMI) of 18.22 kg/m^2. His blood pressure was at the 90th percentile for sex and height, and his physical examination was unremarkable.

Urine dipstick confirmed microhematuria and mild proteinuria. Laboratory tests revealed normal blood cell counts, normal renal function, normal complement levels, and low-titer ANA positivity. Two urinary erythrocyte morphology (UEM) evaluations indicated non-glomerular hematuria (30% dysmorphic erythrocytes and 1% acanthocytes). Multiple urine analyses confirmed persistent microhematuria and mild non-orthostatic proteinuria, while a comprehensive urinary stone screen yielded negative results. An initial abdominal ultrasound was performed and appeared normal.

Almost 17 months after the first visit, the patient experienced two separate episodes of gross hematuria following mild viral infections, both of which resolved spontaneously after a few days. Additionally, he had a recurrence of the left varicocele.

At this point, due to the combination of left varicocele, hematuria, and proteinuria without other potential diagnoses, we suspected NS, so we performed a doppler ultrasound which revealed a finely inhomogeneous and slightly hyperechogenic echostructure with reduced cortico-medullary differentiation (suspicious picture for glomerulonephritis process and its outcomes). The left renal vein at the intersection with the superior mesenteric artery had an AP caliber of 3.5mm in inspiration and 2mm in expiration and an upstream caliber of 9mm in inspiration and 5mm in expiration. Color and power Doppler evaluation showed a patent left renal vein with a velocity of approximately 60cm/s in the juxta-caval region and 28cm/s in the juxtarenal region.

Then we performed an abdominal CT angiogram Figure 1, which revealed a left renal vein compressed by the superior mesenteric artery, despite the normal caliber of the upstream vessel (aorto-mesenteric distance 6mm, aorto-mesenteric angle 22°)", confirming our diagnostic suspect. Therefore, we decided to continue a clinical follow-up.

One and a half years after the beginning of the symptoms the patient developed high fever, gross hematuria, and no respiratory or gastrointestinal symptoms. He was admitted to the emergency department, where elevated blood pressure, fluid retention (1kg over the usual weight), and a twofold increase in creatinine were detected, suggesting acute kidney injury (AKI). Treatment with hydrochlorothiazide was initiated. Subsequent urine and blood tests confirmed stage 3 AKI, persistent gross hematuria with nephrotic-range proteinuria, normal complement levels, and negative anti-ANCA, anti-native DNA, and anti-ANA antibodies. The abdominal ultrasound remained normal.

A kidney biopsy was performed. Light microscopy showed 15 glomeruli, with diffuse segmental mesangial hypercellularity (>4 cells/mesangial area), and focal segmental increased matrix and endocapillary hypercellularity. No crescents were observed, but focal adhesions to Bowman capsule and very mild glomerular basement membrane thickening was present. Tubules showed dilatation, vacuolization, protein droplets and red blood cells casts, but tubular atrophy was mild (<25%). Mild edema and interstitial fibrosis were observed, with few, mainly periglomerular, mononuclear cells inflammation. Vessels were normal. Immunofluorescence demonstrated IgA-dominant staining of mesangium accompanied by C3, and lower IgG, IgM and fibrinogen. Electron microscopy revealed mesangial and paramesangial electron-dense deposits and segmental foot process effacement. The biopsy findings were thus consistent with IgA nephropathy (grading according to the Oxford Classification: M1E1S1T0C0) Figures 2-4. A 6-month corticosteroid regimen according to Pozzi protocol[5] was started, along with ACE inhibitors and Mycophenolate Mofetil. At last follow-up (16 months after treatment initiation) the patient is stable, with normal renal function, persistent microhematuria with rare episodes of gross hematuria associated with respiratory tract infection, and gradually decreasing proteinuria.

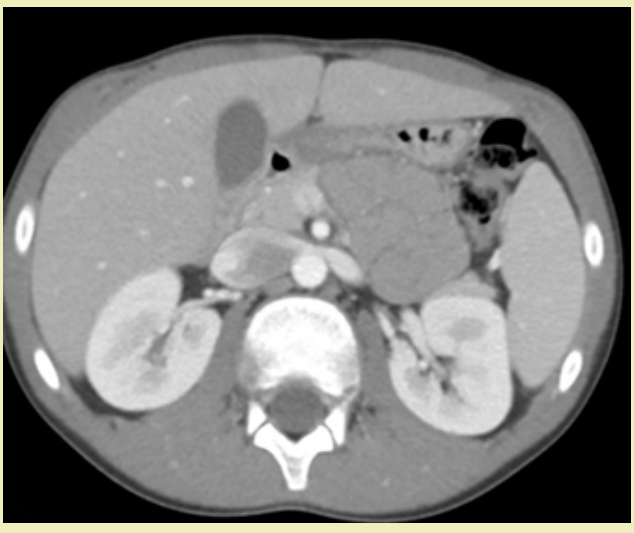
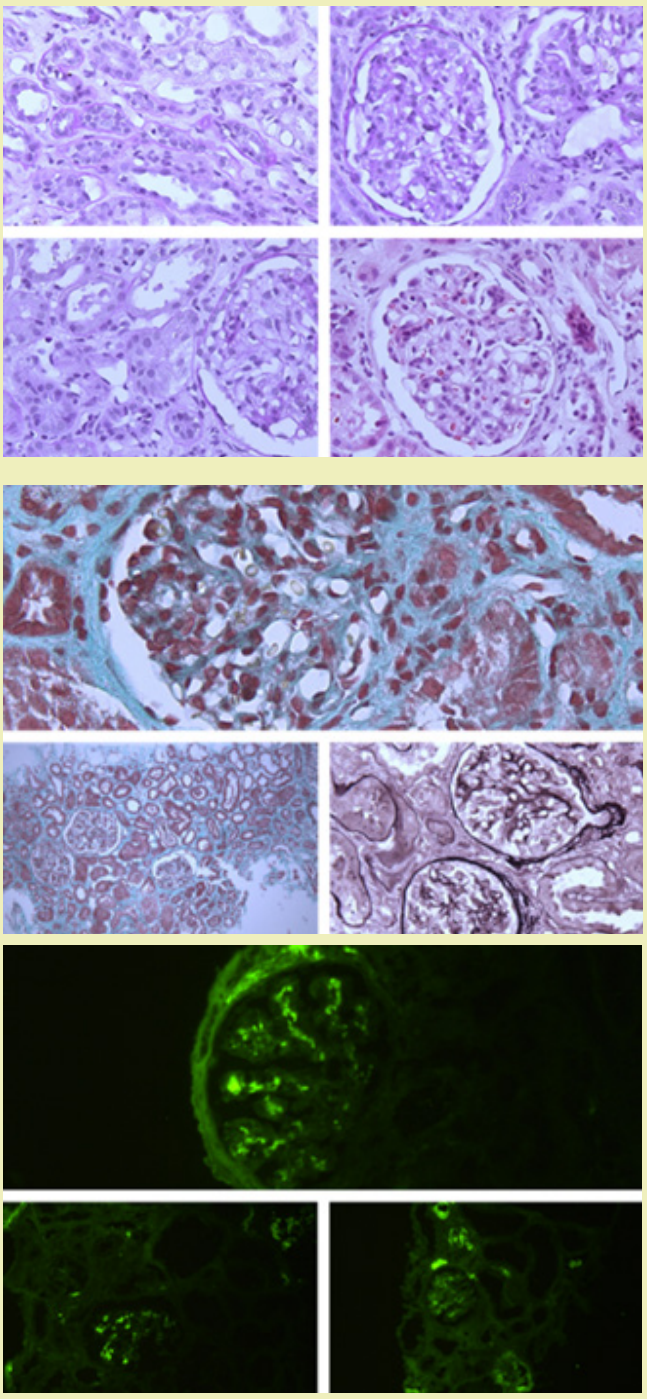


Figure 1: CT angiogram showing the LRV compression by the SMA with an evident difference in calibers between the tract prior and post the compression



Figures 2-4: Light microscopy: diffuse segmental mesangial hypercellularity, and focal segmental increased matrix and endocapillary hypercellularity. Very mild glomerular basement membrane thickening. Tubules showed dilatation, vacuolization, protein droplets and red blood cells casts, but mild tubular atrophy. Immunofluorescence demonstrated IgA-dominant staining of mesangium

Case 2

A 13-year-old boy with a family history of Antiphospholipid Antibody Syndrome and Sjögren's Syndrome came to our attention after experiencing a single episode of gross hematuria without any other associated symptoms. Initially evaluated at another center, his blood tests showed normal renal function, ANA negativity, no hypocomplementemia, and a negative antistreptolysin O titer. Urine tests revealed non-nephrotic proteinuria and hematuria, and an abdominal ultrasound was normal. He was subsequently discharged and placed on follow-up, during which he exhibited persistent microhematuria and occasional episodes of gross hematuria following physical exertion.

Approximately one month after his first symptoms, the patient presented to our center. We repeated all the tests previously performed, which confirmed normal results. Urine tests remained consistent with non-nephrotic proteinuria and hematuria, and UEM evaluation was inconclusive.

Given the association between gross hematuria and physical activity, we suspected Nutcracker Syndrome (NS). An abdominal CT angiogram Figure 5 revealed a 5mm reduction in the caliber of the left renal vein (LRV) caused by compression from the superior mesenteric artery (SMA), with associated proximal dilation (15 mm). The aortomesenteric angle was reduced to 32 degrees, and the left kidney was larger than the right (length 11.18cm, 95th percentile vs 9.13cm, 50th percentile). A diagnosis of NS was made, and the patient began regular follow-up.

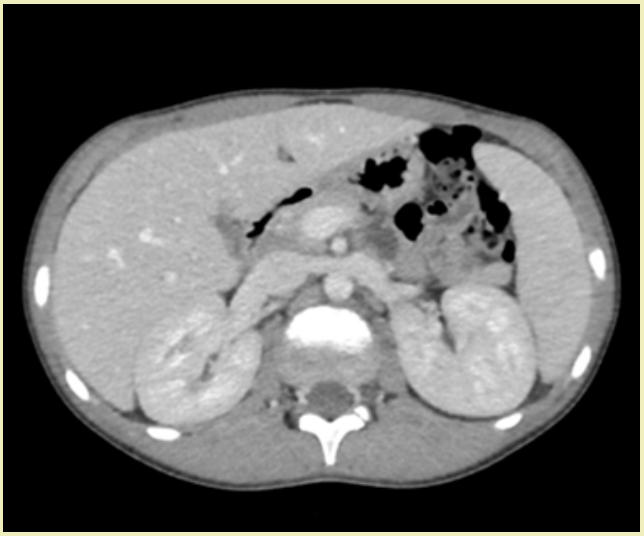
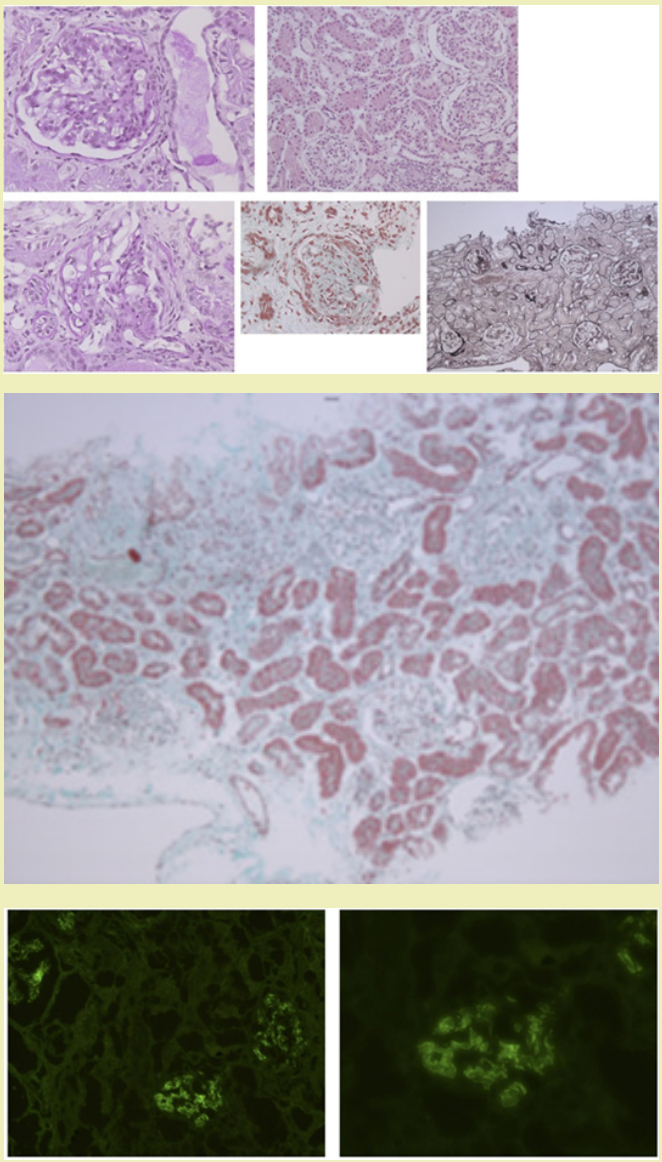


Figure 5: CT angiogram showing the LRV compression by the SMA

In the following months, the patient experienced three episodes of gross hematuria following viral infections, with the last episode complicated by impaired renal function and persistent non-nephrotic proteinuria. Therefore, a kidney biopsy was performed. Light microscopy showed 11 glomeruli, with segmental glomerulosclerosis in one and global glomerulosclerosis in another. The remaining glomeruli showed focal segmental mesangial hypercellularity (>4 cells/mesangial area), segmental increased matrix and endocapillary hypercellularity. No crescents were observed. Tubules showed protein droplets and hyaline casts, and mild tubular atrophy (<25%). Mild interstitial fibrosis was observed, with few, mainly periglomerular, inflammation. Vessels were normal. Immunofluorescence demonstrated IgA-dominant staining of mesangium accompanied by C3, and low IgM and

fibrinogen staining. Electron microscopy confirmed mesangial electron-dense deposits Figures 6-8. IgA nephropathy (grading according to the Oxford Classification: M1E1S1T0C0) was then diagnosed and corticosteroid therapy according to Pozzi protocol[5] and ACE inhibitors treatment were started.



Figures 6-8: Light microscopy: focal segmental mesangial hypercellularity, seg mental increased matrix and endocapillary hypercellularity. Segmental glomerulosclerosis in one glomerulus and global glomerulosclerosis in another on Tubulointerstitial compartment: protein droplets and hyaline casts in tubuli, with mild tubular atrophy and interstitial fibrosis. Immunofluorescence: IgA-dominant staining of mesangium

Discussion

IgA nephropathy is the most common cause of glomerular disease worldwide,[1] and the typical manifestation is represented by an episode of hematuria during an upper respiratory or, less frequently, during a gastrointestinal infection, differently from the post-infectious glomerulonephritis which has a 2-3 weeks gap.[1,6] The diagnosis can be made only by a renal biopsy, which is an invasive procedure performed in patients with persistent symptoms and impairment of renal function. NS is an increasing cause of hematuria due to the presence of more diagnostic tests. Symptoms vary from left flank pain to hematuria associated with physical exercise,[2-3] but there is still a lack of consensus of diagnostic criteria, especially on imaging cut-offs[7] and sometimes patients have borderline pathological characteristics, as our CASE 1, which don't permit us to make a sure diagnosis.

Several case reports have highlighted the coexistence of NS and IgAN, also in pediatric populations. Wang[8] reported a 15-year-old patient with both conditions, who experienced recurrent episodes of gross hematuria, fatigue, and abdominal symptoms. Similarly, Shin.[9] described a case of a 9-year-old girl with NS and IgAN, presenting with recurrent hematuria after an upper respiratory infection.[8] These cases, along with our patient's presentation, underscore the diagnostic difficulty in determining whether NS or IgAN is the primary driver of hematuria.

Although the prevalence of NS in patients with IgAN has been estimated at 6.8%, the potential causal relationship between these two conditions is still debated.[9]

In patients with both NS and IgAN, as in our case, Doppler ultrasound plays a critical role in diagnosing NS by measuring the LRV peak velocity ratio.[8] However, this alone is insufficient to rule out glomerular disease, as IgAN can also present with hematuria. Renal biopsy remains essential for definitive diagnosis, especially in the presence of recurrent hematuria, proteinuria, or impaired renal function.[8-9] Both Wang and Shin emphasized the importance of biopsy to clarify the overlapping symptoms of NS and IgAN, as seen in our patient.

IgA nephropathy typically has a favorable long-term prognosis unless complicated by hypertension, significant proteinuria, or impaired renal function. However, up to one-third of patients may progress to end-stage renal disease within 20 years.[10] Early detection and timely treatment with immunosuppressive therapy are crucial in improving outcomes. In this context, renal biopsy becomes a key diagnostic tool, particularly in patients with recurrent gross hematuria or persistent proteinuria initially diagnosed with Nutcracker Syndrome (NS).

Conclusions

Given the overlap in symptoms between NS and glomerulopathies, such as IgA nephropathy, clinicians should maintain a high index of suspicion for glomerular disease in patients with NS who experience recurrent episodes of gross hematuria. While the coexistence of NS and IgA nephropathy may seem coincidental, their association is well-documented and warrants thorough investigation. Renal biopsy should be strongly considered in these cases to establish an accurate diagnosis and guide appropriate management.

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Conflict of Interest

Regarding the publication of this article, the authors declare that they have no conflicts of interest.

References

1. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402-2414.
2. Nastasi DR, Fraser AR, Williams AB, et al. A systematic review on nutcracker syndrome and proposed diagnostic algorithm. *J Vasc Surg Venous Lymphat Disord.* 2022;10(6):1410-1416.
3. Mazzoni MB, Milani GP, Persico C, et al. Nutcracker phenomenon and idiopathic IgA nephropathy. *NDT Plus.* 2011;4:453-454.
4. Suzuki T, Imai N, Hisamichi M, et al. Can nutcracker phenomenon cause glomerular hematuria? *Nephrology (Carlton).* 2018;23(5):495.
5. Pozzi C, Bolasco PG, Fogazzi GB, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. *Lancet.* 1999;353(9156):883-887.
6. Pattrapornpisut P, Avila Casado C, Reich HN. IgA Nephropathy: Core Curriculum 2021. *Am J Kidney Dis.* 2021;78(3):429-441.
7. Heilijgers F, Gloviczki P, O'Sullivan G, et al. Nutcracker syndrome (a Delphi consensus). *J Vasc Surg Venous Lymphat Disord*. 2024:101970.
8. Wang C, Wang F, Zhao B, et al. Coexisting nutcracker phenomenon and superior mesenteric artery syndrome in a patient with IgA nephropathy: A case report. *Medicine.* 2021;100(28):e26611.
9. Shin JI, Park JM, Shin YH, et al. Nutcracker syndrome combined with IgA nephropathy in a child with recurrent hematuria. *Pediatr Int.* 2006;48(3):324-326.
10. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int.* 2021;100(4):753-779.