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Renal AA Amyloidosis as Rare Presentation of Tumor Necrosis Factor Receptor−Associated Periodic Syndrome in Pediatric Patient

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Received 16 June 2021; revised 13 July 2021; accepted 19 July 2021; published online 27 July 2021

Kidney Int Rep (2021) **6,** 2926–2929; https://doi.org/10.1016/j.ekir.2021.07.016

INTRODUCTION

Here we present a case and review the management of tumor necrosis factor receptor−associated periodic syndrome (TRAPS) presenting with nephrotic syndrome, concurrent acute interstitial nephritis (AIN), and acute kidney injury (AKI) in a pediatric patient. The patient initially presented with nephrotic-range proteinuria. He otherwise had no other signs or symptoms expected of a periodic fever syndrome, most particularly, recurrent fever. He has been successfully managed with the interleukin-1 (IL-1) inhibitor canakinumab, with improvement in his inflammatory markers and stabilization of his amyloid deposition on kidney biopsy.

CASE PRESENTATION

A previously healthy, 10-year-old boy was incidentally found to have persistent proteinuria on routine urinalysis at his primary care physician's office. The degree of proteinuria on dipstick progressed to 3+ over 4 months, so he was referred to Nephrology for evaluation at an outside hospital. At the initial evaluation, the examination findings were unremarkable, besides noting a small child for age (weight at sixth percentile, height at fifth percentile). Systolic blood pressure was elevated to 130 mm Hg. Initial laboratory evaluation showed normal serum creatinine of 0.4 mg/dl and hypoalbuminemia with serum albumin of 2.8 g/dl. Urinalysis showed no blood, >300 mg/dl protein, and spot urine protein-to-creatinine ratio of 6.4 mg/mg.

A few days after seeing a nephrologist, the patient developed vomiting, sore throat, and fever. He was diagnosed with streptococcal pharyngitis (strep throat) and started on amoxicillin and ibuprofen. Three days later, he began to develop periorbital edema, decreased activity, and decreased oral intake. He received a fluid bolus because of concerns about dehydration and was transferred to the hospital for further management because of elevated serum creatinine.

On arrival, the patient looked pale but otherwise appeared well, with mild periorbital and pedal edema, significant abdominal distension, and no scrotal edema. Laboratory evaluation was remarkable for serum creatinine of 4.13 mg/dl and blood urea nitrogen (BUN) of 60 mg/dl, serum albumin of 1.1 g/dl, and C-reactive protein (CRP) of 7.4 mg/dl. Urinalysis showed a urine protein-to-creatinine of 31.4 mg/mg. Kidney ultrasound showed enlarged and echogenic kidneys, and liver ultrasound showed increased echotexture. Echocardiographic results were normal. The patient underwent a kidney biopsy (Figure 1). Results were remarkable for amyloid deposition and AIN. Serum amyloid A (SAA) at time of presentation was 316 mg/l (with a level <10 mg/l normal).

Prior to kidney biopsy, it was discovered that the patient's mother had developed kidney failure as a late teenager, requiring dialysis and eventually a kidney transplant. She later developed both kidney and liver failure, eventually passing away at age 31 years. Per the patient's father, she carried a diagnosis of familial Mediterranean fever, as did the mother's father.

To treat AIN, the patient received a 4-day course of i.v. methylprednisolone, then transitioned to oral

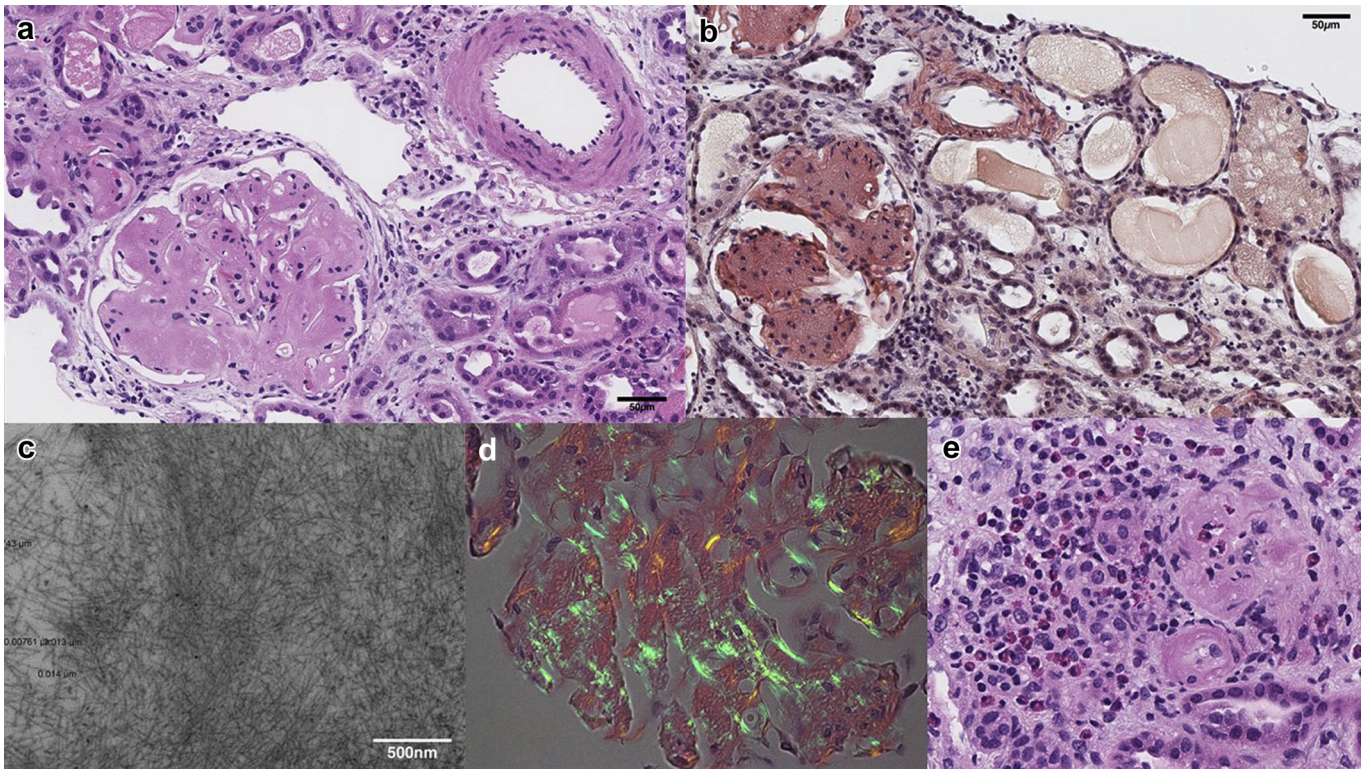

Figure 1. Biopsy specimen at presentation. (a) (Top left): Hematoxylin and eosin, original magnification ×250. Glomeruli have mesangium expanded by amorphous eosinophilic acellular material, few inflammatory cells. (b) (Top right): Congo red, original magnification ×250. Material deposited in glomeruli is brightly Congophilic (bright red). (c) (Bottom left): Original magnification ×15,000. Deposited material is identified as haphazardly arranged fibrils, consistent with amyloid. (d) (Bottom center): Material deposited in glomeruli demonstrates green birefringence on polarization. (e) (Bottom right): Hematoxylin and eosin, original magnification ×250, interstitial inflammation with eosinophilic inflammation, consistent with acute interstitial nephritis (AIN).

steroids 2 mg/kg. For the amyloidosis, he was started on colchicine at a low dose (0.6 mg) daily, adjusted for his renal function. Genetic evaluation revealed a heterozygous mutation at the *TNFRSF1A* gene, c.175T>C (p.Cys59Arg), located in exon 2, with known pathogenicity, consistent with a diagnosis of autosomal dominant tumor necrosis factor receptor–associated periodic syndrome (TRAPS). In addition to colchicine, the patient was started on canakinumab, a human monoclonal antibody targeted at IL-1 to be given subcutaneously every 4 weeks.

Within about 2 months after discharge from the hospital, serum creatinine had returned to a baseline of 0.42 mg/dl. At 6 months postpresentation, the patient's edema and abdominal distention had resolved. Laboratory evaluation showed normalization of CRP (<0.40 mg/dl) and serum SAA level (<3.5 mg/l; normal <10). Steroids were weaned off by 6 months postpresentation. By 1 year postpresentation, the urine protein-to-creatinine ratio decreased to 1-2 mg/mg. The patient's kidney function showed serum creatinine of 0.77 mg/dl and estimated glomerular filtration rate by cystatin C of 51 ml/min/1.73 m^2. His hypertension is well controlled on long-acting nifedipine and lisinopril. A 1-year follow up kidney biopsy showed resolution of AIN and stable amyloid deposition (Figure 2). The patient's younger brother was also discovered to have the same mutation. Although he does not have any kidney disease, he is showing signs of typical TRAPS symptoms, including recurrent fevers and arthralgias.

DISCUSSION

This patient with TRAPS presented with nephrotic syndrome that was exacerbated by AIN. TRAPS is an autoinflammatory disease that typically presents with flares of varying duration and can involve a variety of symptoms, including fevers, abdominal pain, rash, and joint pains,[1–3] which was the presentation in the patient's mother and grandfather. There have been reports of nonfebrile TRAPS, although patients typically endorse other symptoms associated with the syndrome, such as arthralgia, abdominal pain, and myalgias.[4] The Eurofever International TRAPS Registry recruited 158 patients, including 53 pediatric patients, and found that the median age of symptom onset was 4.3 years. Among the pediatric population, the most common presenting manifestations were myalgias, arthralgias, abdominal pain, and fever.[1] Similarly, in a recent case

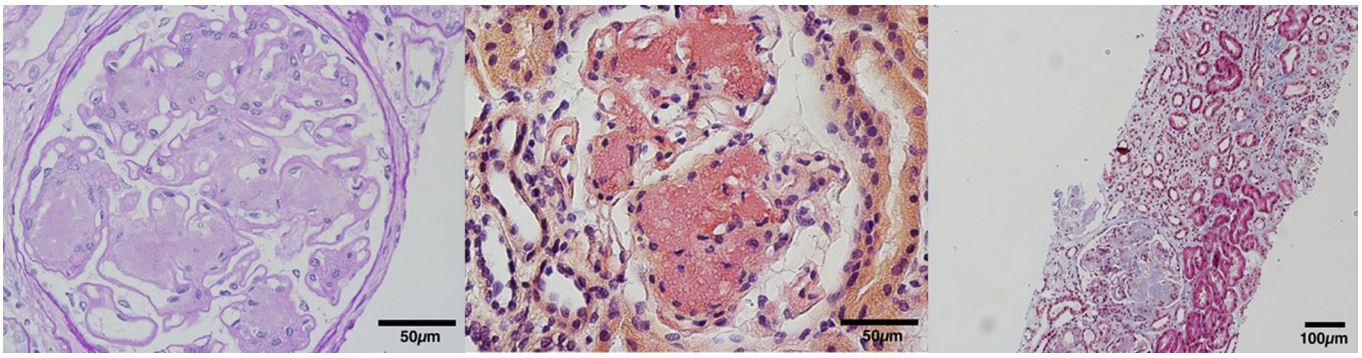

Figure 2. Biopsy specimen 1 year later. (Right) Hematoxylin and eosin, original magnification ×400, shows stable amorphous infiltrate. (Center) Congo red stain, original magnification ×400; amorphous material is congophilic, consistent with amyloid deposition. (Left) Trichrome stain, original magnification ×100, shows patchy interstitial fibrosis and tubular atrophy, resolved interstitial nephritis.

series from France, 41 patients had a diagnosis of TRAPS, with a median age of onset of symptoms being 5 years of age.[2] However, the amyloidosis diagnosis was not made until an average age of 40 years, with the youngest at 13 years.

The presentation of TRAPS in our patient was quite atypical, as his presenting feature was nephrotic syndrome and hypertension, and he had none of the typical presenting symptoms of the TRAPS phenotype, such as fever, arthralgia, rash, or abdominal pain. In addition, he displayed a different phenotype from that of his mother and grandfather, who presented with symptoms consistent with autoinflammatory syndrome. Although they were diagnosed with familial Mediterranean fever (FMF), we suspect that the mother and grandfather had same genetic mutation as the patient, and that their autoinflammatory disease was secondary to TRAPS. Although the patient's age is within range for presenting with TRAPS symptoms, he is younger than has been reported to be diagnosed with AA amyloidosis associated with TRAPS.

The production of precursor proteins, leading to amyloid A (AA amyloidosis), is commonly seen in chronic inflammatory diseases and is the most common type of amyloidosis in children. AA amyloidosis occurred in a total of 16 cases (10%), at a median age of 43 years, with a range of 20 to 77 years. The authors noted that 7 patients had cystine variants, as cysteine has been associated with a higher penetrance, more severe disease phenotype and higher risk of AA amyloidosis.[1,3]

AA amyloidosis diagnosis is dependent on clinical suspicion and urinalysis results, prompting renal biopsy.[5,6] There has been no demonstrable relationship between the extent of amyloid deposition and the severity of clinical manifestations.[5] The median patient survival has been reported at 6 to 9 years, with improved prognosis associated with underlying periodic fever syndromes, in particular, the ability to suppress circulating SAA levels.[6] In our patient, a strong family history of autoinflammatory syndrome made us consider amyloidosis before kidney biopsy results were available. However, his presentation with significant acute kidney injury and an acute increase in proteinuria also suggested an alternative diagnosis. Most likely, AIN in this patient was secondary to either the amoxicillin or ibuprofen that he received for strep throat.

Current treatment recommendations for TRAPS include directed therapy with anti−IL-1, as evidence has shown better response than with anti−tumor necrosis factor agents.[3,7,8] There is also some evidence for continued colchicine use, with improvement in some patients when used as a monotherapy.[7,9] Monitoring parameters for treatment efficacy include flare frequency and severity and inflammatory markers, including CRP and SAA. As seen in this patient, a combination of anti−IL-1 monoclonal antibody (canakinumab) and colchicine has been effective in normalizing inflammatory markers, both CRP and SAA (Table 1).

Table 1. Teaching points

Amyloidosis	Can be a complication of untreated autoinflammatory syndromes such as TRAPS with poor outcome, including ESKD and death
TRAPS diagnosis	Depends on high clinical suspicion, including family history, presence of clinical symptoms, and genetic diagnosis; however, given the cyclical nature and vague symptoms, proteinuria or nephrotic syndrome can be a presenting symptom
TRAPS treatment	Current recommendations are directed IL-1 monoclonal antibody therapy such as canakinumab, targeting normalization of inflammatory markers, particularly CRP and SAA

CRP, C-reactive protein; ESKD, end-stage kidney disease; IL-1, interleukin-1; SAA, serum amyloid A; TRAPS, tumor necrosis factor receptor−associated periodic syndrome.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

Patient consent was provided.

REFERENCES

1. Lachmann HJ, Papa R, Gerhold K, et al. The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EURO-TRAPS international registry. *Ann Rheum Dis*. 2014;73:2160–2167.
2. Delaleu J, Deshayes S, Rodrigues F, et al. Tumor necrosis factor receptor-1 assciated periodic syndrome (TRAPS) related AA amyloidosis: a national case series and systematic review [e-pub ahead of print]. *Rheumatology (Oxford)*. https://doi.org/10.1093/rheumatology/keab252. Accessed July 8, 2021.
3. Cudrici C, Deuitch N, Aksentijevich I. Revisiting TNF receptor-associated periodic syndrome (TRAPS): current perspectives. *Int J Mol Sci*. 2020;21.
4. Kallinich T, Haffner D, Rudolph B, et al. "Periodic fever" without fever: two cases of non-febrile TRAPS with mutations in the TNFRSF1A gene presenting with episodes of inflammation or monosymptomatic amyloidosis. *Ann Rheum Dis*. 2006;65:958–960.
5. Bilginer Y, Akpolat T, Ozen S. Renal amyloidosis in children. *Pediatr Nephrol*. 2011;26:215–1227.
6. Papa R, Lachmann HJ. Secondary, AA, amyloidosis. *Rheum Dis Clin North Am*. 2018;44:585–603.
7. Ter Haar N, Lachmann H, Ozen S, et al. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis*. 2013;72:678–685.
8. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med*. 2018;378:1908–1919.
9. Vitale A, Sota J, Obici L, et al. Role of colchicine treatment in tumor necrosis factor receptor associated periodic syndrome (TRAPS): real-life data from the AIDA Network. *Mediators Inflamm*. 2020;2020:1936960.