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Diffuse Endocapillary Glomerulonephritis in a Child With IL-17RA Deficiency Emphasizes the Pivotal Role of the Complement Cascade and Anaphylatoxins

Thibaut d'Izarny-Gargas[1], Mathilde Grapin[2], Anne Grunenwald[3], Jean-Paul Duong-Van-Huyen[1], Marion Rabant[1], Romain Lévy[4], Anne Puel[5], Julie Toubiana[6], Olivia Boyer[2], Véronique Frémeaux-Bacchi[3], Marina Charbit[2] and Pierre Isnard[1,7]

[1]Department of Pathology, Necker-Enfants Malades Hospital, APHP, Paris, France; [2]Pediatric Nephrology, MARHEA Reference Center, Imagine Institute, Université Paris Cité, Necker-Enfants Malades Hospital, APHP, Paris, France; [3]Université Paris Cité and Sorbonne Université, INSERM UMRS 1138, Centre de Recherche des Cordeliers, Inflammation, Complement and Cancer Team, Paris, France; Department of Immunology, Assistance Publique-Hôpitaux de Paris, Hopital Européen Georges Pompidou, Paris, France; [4]Pediatric Hematology-Immunology-Rheumatology Unit, Necker-Enfants Malades Hospital, APHP, Paris, France; [5]Laboratoire de Génétique Humaine des Maladies Infectieuses, UMR1163, Imagine Institute, Paris, France; [6]Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants Malades Hospital, APHP, Paris, France; and [7]Université Paris Cité, INSERM U1151, CNRS UMR 8253, Institut Necker Enfants Malades, Département Croissance et Signalisation, Paris, France

Correspondence: Pierre Isnard, Université de Paris, INSERM U1151, CNRS UMR 8253, Institut Necker Enfants Malades, Département Croissance et Signalisation, Faculté de Médecine Necker, 156-160 rue de Vaugirard, 75015 Paris, France. E-mail: pierre.isnard@inserm.fr

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INTRODUCTION

T-helper 17 cell differentiation and downstream interleukin-17 (IL-17) production and signaling is critical for neutrophil granulocyte recruitment and activation and subsequent host defense against *Candida* and *Staphylococcus*.[1] This was highlighted by the description of specific defects of this pathway, such as autosomal recessive *IL17RA* gene or autosomal dominant *IL17F* gene deficiencies, in patients with chronic mucocutaneous candidiasis and staphylococcal skin disease.[2,3] Of interest, in the kidney, IL-17 also plays a significant role in the defense against these pathogens,[4] with IL-17 signaling in renal tubular epithelial cells, rather than hematopoietic cells, acting as a crucial player in disseminated candidiasis immune response. It is thought that IL-17 signaling in renal tubular epithelial cells enables expression of chemokines such as *cxcl1*, *cxcl2*, or *ccl20*, which are instrumental for neutrophil recruitment.[5] Likewise, several studies have highlighted the major role of IL-17 in pathological contexts such as glomerulonephritis (GN).[6,7] Over the past few years, IL-17 was identified as a key player in several models of immune-mediated glomerular injury. For example, in an animal model of autoimmune GN, *Il17ra*$^{-/-}$ mice displayed diminished levels of glomerular neutrophil proliferation, whereas monocyte and macrophage recruitment was similar.[8] In a murine model of antineutrophil cytoplasmic antibodies-associated vasculitis, IL-17 knockout mice exhibited protection from renal injury.[9] These results strongly emphasized the role of the IL-17R signaling pathway in kidney neutrophil recruitment in the setting of GN.

Here, we describe a case of endocapillary GN in a child with complete IL-17 receptor chain A (IL-17RA) deficiency. Our observation demonstrates that multiple pathways can lead to neutrophil recruitment during GN, and that IL-17R signaling may be dispensable for glomerular pathology during infection-associated GN. We provide further evidence suggesting that complement alternative pathway (CAP) activation was instrumental in the disease mechanism of our patient.

CASE PRESENTATION

A 9-year-old boy was referred to our nephrology department after the discovery of hematuria and proteinuria. His medical history was remarkable for

chronic mucocutaneous candidiasis and recurrent staphylococcal skin disease related to IL-17RA deficiency that was previously diagnosed with whole-exome sequencing.[3] He presented to the emergency department with fever, right flank pain and gross hematuria. Physical examination was remarkable for moderate ascites, without lower limb edema or hypertension. A chest X-ray revealed a right upper lobe opacity suggestive of lobar pneumonia. The patient was admitted and received ceftriaxone. The biological workup was remarkable for hyperleukocytosis, elevated C-reactive protein, and acute kidney injury (creatinine 0.96 mg/dl) with nephrotic syndrome (urine protein-to-creatinine ratio 5.3 g/g, albuminemia 19.9 g/l). Complement studies revealed lowered CH50 (20%) with decreased C3 level (83 mg/l, normal >650 mg/l), normal C4 (182 mg/l) and elevated soluble C5b9 (>1.9 mg/l).

RESULTS

Given the atypical history for childhood acute post-infectious GN (APIGN) (no documented streptococcal infection, no infection-free latent period, no hypertension) and the peculiar immunological history of our patient, we decided to perform a kidney biopsy (Supplementary Methods). Microscopic examination revealed exudative, neutrophilic endocapillary proliferation in all the sampled glomeruli (Figure 1a and b). There were no crescents. Many extramembranous deposits in the form of humps were noted. Immunofluorescence studies were positive for IgA and IgG, as well as C3, which was the dominant stain. An immunological workup detected no anticomplement factor B autoantibodies, but high titers of anti-C3b autoantibodies. The patient was also positive for anti-streptolysin O antibodies. A repeat analysis of the exome sequencing data available for this patient did not detect any mutation known to be associated with complement dysregulation.

Further histological studies demonstrated diffuse glomerular capillary wall deposition of C4d and C5b9 (Figure 1c and d). In order to determine whether the observed polymorphonuclear neutrophil capillary infiltrate was triggered by local anaphylatoxin (C5a) derived from complement activation, we performed C5R immunostaining (Supplementary Methods). Of particular interest, we observed positive cytoplasmic signal in polymorphonuclear neutrophil–like cells within glomerular and peritubular capillaries (Supplementary Figure S1A and B), suggesting that complement

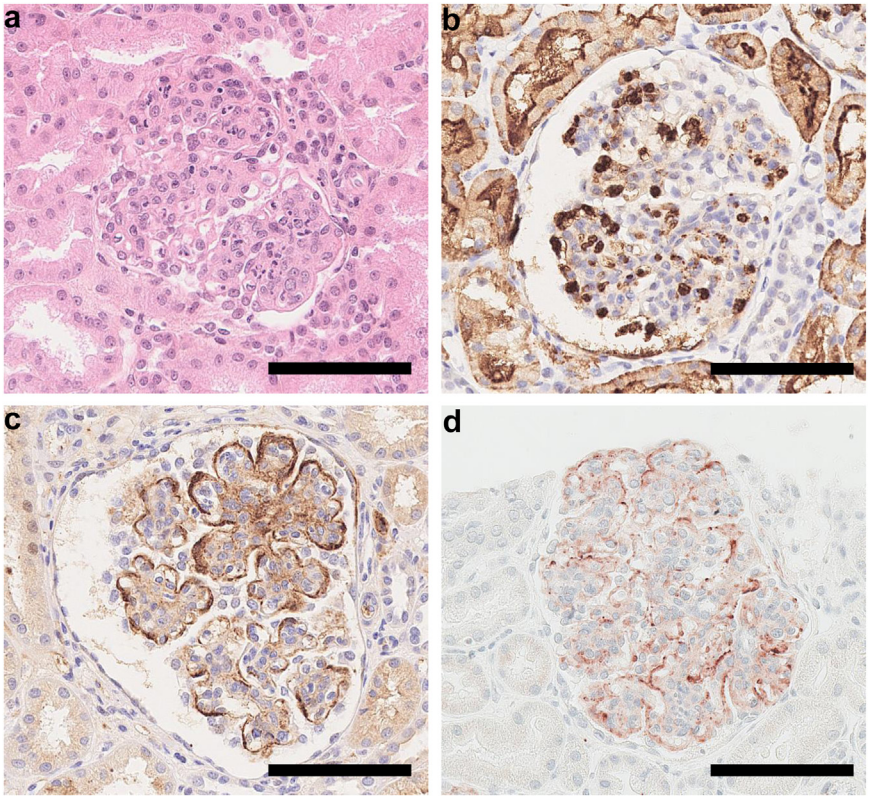

Figure 1. Light microscopy and immunohistochemistry analysis of the kidney biopsy. (a) Light microscopy using hematoxylin and eosin staining showing global endocapillary proliferation composed of polymorphonuclear leukocytes. (b) Immunohistochemistry targeting CD15 identifies endocapillary cells as neutrophils. (c) Immunochemistry targeting C4d and (d) C5b9 unveils extensive complement deposition along the glomerular capillary walls. Original magnification for all images, ×400.

activation and consecutive release of C5a anaphylatoxin is a crucial mediator of neutrophil migration and activation in this case of GN. Given the diagnostic challenge between classical APIGN or infection-triggered initial episode of C3 glomerulopathy (C3G), we made a collegial decision to treat the patient with corticosteroids. He received intravenous methylprednisolone pulses (500 mg/m^2/d for 3 days) and oral prednisone (60 mg/d initially, with a gradual taper and discontinuation after 2 months). He promptly recovered a normal kidney function. A light proteinuria and microscopic hematuria remained for over 3 months but were absent at 1 year follow-up. The anti-C3b autoantibodies disappeared after 3 months. However, after 2 years of follow-up, he exhibits persistent signs of CAP activation (low C3 at 204 mg/l, elevated sC5b9 >1750 ng/ml, with normal C4 at 147 mg/l).

DISCUSSION

Here, we report a case of acute GN in a patient with defective IL-17RA signaling. We were intrigued by the significant neutrophil endocapillary proliferation in the kidney biopsy, given the patient's medical record. As stated previously, IL-17 has been identified as a key mediator of disease in various models of immune-mediated GN.[8,9] A recent work revealed that IL-17R signaling in renal tubular epithelial cells was a critical pathway in the murine model of antiglomerular basement membrane GN, with *Il17ra*$^{fl/fl}$ *Cdh16*^{Cre} mice (mice selectively depleted for IL-17RA in renal tubular epithelial cells) being protected from glomerular injury, whereas chimeric wild-type animals with adoptive transfer of *Il17ra*$^{-/-}$ bone marrow suffered from GN.[S1] This result was further complemented by another study that unveiled an IL-17 autocrine negative feedback loop at play in T-helper 17 cells during experimental GN, whose disruption led to increased GN severity.[S2] It should be noted, however, that the relationship between IL-17 signaling and neutrophil influx is complex, and may vary along glomerular disease progression.[7,S2,S3]

The role of IL-17R signaling has not been studied in the context of postinfectious GN. Infection-associated GN is thought to involve immune complexes containing bacterial antigens that are deposited in the glomerular capillary tuft.[S4] This may result in complement activation and consecutive release of anaphylatoxins such as C3a and C5a, which are important mediators of neutrophil migration and activation.[S5] Our group recently demonstrated the role of transient anti-factor B autoantibodies during childhood APIGN,[S6] suggesting that the observed pathology might result from CAP activation, and strengthening the pathogenic link between APIGN and C3G.

During the course of these diseases, inflammatory cell recruitment and activation could be mediated by the anaphylatoxins (C3a and C5a) that are generated by the complement cascade following CAP activation.[S7] In fact, the prominent neutrophil endocapillary influx seen in our patient strongly suggests that IL-17R signaling is a dispensable mechanism for disease pathogenesis and neutrophil recruitment during infection-associated GN and/or C3G. It illustrates the multiplicity and redundancy of neutrophil recruitment pathways during glomerular injury, which likely depend on the underlying disease process. In the case of our patient, immunohistochemistry revealed complement deposits along the capillary walls. We further performed immunofluorescence on the kidney biopsy, which revealed marked expression of the C5a receptor on neutrophils cell surface (Supplementary Figure S1). The low C3 assay in our patient may indicate that anaphylatoxin-mediated neutrophil recruitment in the glomeruli could occur independently of any IL-17-related pathway. Taken together, these results should prompt us to investigate anaphylatoxin-signaling inhibitors for this type of GN, such as avacopan, a small-molecule C5aR1 inhibitor which was recently studied in a clinical trial involving patients with antineutrophil cytoplasmic antibodies-associated vasculitis.[S8]

To the best of our knowledge, this is the first report of GN in the context of IL-17RA deficiency. Whether the history of recurrent staphylococcal skin infections of this young boy may have made him more susceptible to the disease remains hypothetical; however, patients with C3G with anti-C3b autoantibodies frequently present with documented infection.[S9] In our patient, the ultimate diagnostic category may remain undefined for the time being, because his clinical course (acute disease with complete and durable remission) is reminiscent of APIGN; nevertheless, the absence of anti-factor B autoantibodies, presence of anti-C3b autoantibodies, and long-term persistence of CAP activation may rather point to a diagnosis of C3G, of which the first episode may rarely be triggered by an infectious episode. Anti-C3b autoantibodies have been described in some patients with C3G and immunoglobulin-associated membranoproliferative GN. They may drive pathogenesis by stabilizing C3 convertase and preventing C3b from binding to regulatory proteins, thereby enhancing the activation of the CAP. Similarities between C3 coding sequences and streptococcal peptides have been identified. Autoantibodies recognizing activated forms of C3 have long been documented after viral or bacterial infections, and persist at high titers over time in animal models of chronic infection.[S9,S10]

GN is not a feature that was reported in other immune deficiencies targeting the IL-17 pathway, such as *IL17F*

Table 1. Teaching points

IL-17 production and signaling is critical for neutrophil recruitment and activation in the context of host defense against *Candida* and *Staphylococcus*. This cytokine is also instrumental in several models of immune-mediated GN.
Childhood APIGN has recently been associated with transient anti-factor B autoantibodies, driving activation of the CAP. This finding strengthens its pathogenetic links with C3G, a chronic GN during which uncontrolled CAP activation is implicated.
We describe a case of infection-associated acute GN in a child with defective *IL-17* gene signaling due to IL-17RA deficiency. The prominent, diffuse endocapillary influx of neutrophils encountered in the kidney biopsy illustrates how the IL-17 pathway is dispensable for neutrophil recruitment during this type of GN.
Using both serum and tissue complement investigations, we argue that CAP activation and subsequent anaphylatoxin secretion were instrumental for neutrophil recruitment and activation in the glomerular capillary loops.

APIGN, acute postinfectious glomerulonephritis; C3G, C3 glomerulopathy; CAP, complement alternative pathway; GN, glomerulonephritis; IL-17, interleukin-17; IL-17RA, interleukin-17 receptor chain A.

dominant negative mutations, or *STAT1* gain-of-function variants. During autoimmune polyendocrine syndrome type 1, a complex autoimmune monogenic disorder in which chronic candidiasis mediated by anti-IL-17 antibodies is a prominent feature, renal impairment has been seldom reported and consists mostly of interstitial nephritis.[S11] Considering that most of these disorders were described recently, it will be important in the future to study and report any immune-mediated manifestation that may arise in these predominantly young children. This may provide valuable clues on the natural history of defective IL-17 signaling and the various roles of this cytokine in health and disease.

CONCLUSION

In summary, we report the clinical course and histological analysis of a case of infection-association endocapillary GN in a child with inborn IL-17RA deficiency. The diffuse neutrophil recruitment at the site of injury despite genetically impaired IL-17 pathway points to complement activation and downstream anaphylatoxin release and signaling as a decisive mechanism for glomerular inflammation during this type of GN, as evidenced by serum and tissue complement investigations in our patient (Table 1).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The patient's parents provided written informed consent.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF).

Supplementary Methods.

Supplementary References.

Figure S1. Immunofluorescence analysis of the kidney biopsy targeting C5aR1.

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