Case Description

A 15-year-old woman was admitted to the hospital with a new diagnosis of SLE. She presented with a 1-year history of intermittent fevers, joint pain, myalgias, and subcutaneous nodules. Laboratory evaluation revealed her hemoglobin was 6.8 g/dl, white blood cell count was 3.7 \times 10^3/L, serum creatinine was 0.97 mg/dl (eGFR of 72 ml/min per 1.73^2 by the Schwartz 2009 equation), and she had undetectable complement C3 and C4 levels, positive antinuclear antibody test with a titer of 1:1280, and positive double-stranded DNA antibodies with a titer of 34. A 24-hour urine collection revealed 944 mg protein (25 mg/m^2 per hour).

After transfusion of packed red blood cells and pulse intravenous methylprednisolone, her serum creatinine improved to 0.57 mg/dl (eGFR of 122 ml/min per 1.73^2 by the Schwartz equation). She underwent a kidney biopsy, with light microscopy of the biopsy specimen demonstrating glomerular basement membrane thickening and lymphoplasmacytic infiltrates in the interstitium (Figure 1A). Curiously, numerous interstitial plasma cells were positive for IgG4 (Figure 1B). Immunofluorescence revealed “full-house” positivity and electron microscopy demonstrated tubulocapillary inclusions, and multiple subepithelial, intramembranous, and subendothelial electron-dense deposits (Figure 1C). Overall, the pathology was consistent with membranous lupus nephritis, International Society of Nephrology/Renal Pathology Society (ISN/RPS) class V. However, the plasma cell infiltrate also raised concern for potential overlapping tubulointerstitial nephritis (TIN) due to IgG4-related disease (IgG4-RD). Specifically, there were 10–50 IgG per high-power field, no evidence of storiform fibrosis or obliterative phlebitis, and the IgG4/IgG ratio was unable to be determined due to the presence of high background staining. The patient did not have other known end-organ findings characteristic of IgG4-RD.

Potential co-occurrences of IgG4-RD and SLE with and without nephritis have previously been reported in adult patients, but not in pediatric ones (1,2). Diagnostic criteria for IgG4-RD are outlined in a 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) report and include clinical, radiologic, or pathologic evidence of involvement of a typical organ, exclusion of mimicking conditions, and a weighted point total of other common clinical manifestations (3).

Histologic criteria for IgG4-RD diagnosis include the need for identification of a dense lymphocytic infiltrate with a high IgG4+/IgG+ ratio, obliterative phlebitis, and presence of storiform fibrosis (3). With regard to IgG4 infiltrates in the presence of SLE, a 2015 case series reviewed biopsy specimens from 65 adult patients with membranous lupus nephritis (4). Of these patients, 37% were isolated class V and the others had combined proliferative and membranous patterns. Seven of the samples (10%) contained IgG4 deposits, and this subset of patients was more likely to have kidney involvement as their first manifestation of SLE. A separate review of 100 kidney biopsy specimens of various underlying primary pathologies concluded an abundance of IgG4-positive plasma cells may be requisite to a diagnosis of IgG4-RD TIN, but the finding was not specific nor alone sufficient to make the diagnosis as an overlapping process (5).

In this case, the presence of positive double-stranded DNA would be considered an exclusion from IgG4-RD diagnosis per the 2019 ACR/EULAR criteria (3). The lack of histologic and clinical criteria for IgG4-RD in this case suggests the lymphocytic infiltrate is a nonspecific manifestation of lupus TIN. However, the finding of lupus nephritis with IgG4 deposits is not commonly reported in pediatric patients and it is important to acknowledge the potential clinical significance, because IgG4 deposits present at the time of SLE diagnosis portend a worse overall kidney prognosis with regard to dialysis dependence (4). Both adult and pediatric clinicians should recognize and be aware of this finding, because it may have implications on management and prognosis.

Teaching Points

- Membranous lupus nephritis (ISN/RPS class V) is histologically characterized by subepithelial immune complex deposits in the absence of diffuse or focal proliferative changes and “full-house” staining by immunofluorescence.
IgG4-RD TIN should be suspected when kidney biopsy specimen histology reveals a dense lymphocytic infiltrate with a high IgG4+/IgG+ ratio, obliterator phlebitis, and presence of storiform fibrosis.

Although it is not sufficient for diagnosis alone, the presence of interstitial plasma cells in a kidney biopsy specimen should prompt consideration of IgG4-RD and independently portends a poor prognosis when found in the setting of lupus nephritis.

Disclosures
All authors have nothing to disclose.

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Author Contributions
C.R. Crane conceptualized the study and wrote the original draft; E. Ingulli supervised the study; and E. Ingulli and K. Shayan reviewed and edited the manuscript.

References

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Figure 1. Kidney biopsy findings. (A) Light microscopy (hematoxylin and eosin staining) demonstrates lymphocytoplasmic interstitial infiltrate. (B) Light microscopy reveals IgG4 immunostaining of the tubulointerstitium. (C) Electron microscopy shows tubuloreticular inclusions, and multiple subepithelial, intramembranous, and occasional subendothelial electron-dense deposits.