Pediatric Blood & Cancer

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LETTER TO THE EDITOR OPEN ACCESS

Paraneoplastic Lupus Nephritis in a Child With Neuroblastoma Recurrence

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Received: 5 February 2026 | **Revised:** 14 February 2026 | **Accepted:** 18 February 2026

To the Editor:

Neuroblastoma is the most common solid tumor in children under 5 years of age. It arises from neural crest cells of the sympathetic nervous system, and it is associated with various paraneoplastic syndromes [1]. Paraneoplastic glomerular disease is rare in children and mostly described in adults, where membranous nephropathy, minimal change disease, and membranoproliferative glomerulonephritis represent the most common histological patterns [2], while lupus nephritis (LN) has rarely been reported with malignancies and never with neuroblastoma in pediatric patients. We describe a biopsy-proven case of LN occurring during neuroblastoma relapse in a child, expanding the spectrum of paraneoplastic renal involvement in pediatric oncology.

In January 2017, a 4-year-old girl was diagnosed with a poorly differentiated neuroblastoma with a minor schwannomatous component, originating from the left adrenal gland and presenting with disseminated lymph node and bone metastases. From February to April 2017, she received induction chemotherapy (vincristine, carboplatin, etoposide, cyclophosphamide), followed by two cycles of high-dose chemotherapy and autologous stem cell transplantation. By November 2017, she achieved metabolic remission and completed 13-cis-retinoic acid maintenance until March 2018. In July 2022, she developed chronic hypoalbuminemia, serous effusions, and diffuse edema, requiring albumin infusion and corticosteroid therapy. Cardiac, hepatic, and renal function were normal, and fecal α1-antitrypsin was elevated (2425 µg/g), suggesting a protein-losing enteropathy. Neuroblastoma relapse was confirmed by biopsy of a left renal hilum lymph node, showing poorly differentiated disease with MYCN amplification and negative anaplastic lymphoma kinase status. She was referred to Gaslini Children's Hospital in December 2022 and received three cycles of topotecan–cyclophosphamide, followed by irinotecan–temozolomide and subsequent anti-GD2 immunotherapy with 13-cis-retinoic acid. Chemotherapy was discontinued in January 2024, and she remained under follow-up. In June 2024, she was hospitalized with polyserositis, including ascites and pleural and pericardial effusions, requiring continuous albumin infusion and diuretics. Due to persistent disease, subcutaneous anakinra was initiated. She subsequently developed progressive renal dysfunction, with stage 3 acute kidney injury (serum creatinine 1.21 mg/dL), nephrotic-range proteinuria (5.7 g/24 h), and active urinary sediment with 20%–30% dysmorphic erythrocytes, hyaline and granular casts. Autoimmunity testing revealed hypocomplementemia (C3 35 mg/dL, C4<3 mg/dL), positive antinuclear antibodies (ANA, titer 1:640, speckled pattern), anti-Sjogren's syndrome-related antigen A (anti-SSA/Ro) antibodies, and an elevated erythrocyte sedimentation rate (77–80 mm/h) with normal C-reactive protein. Anti-double-stranded DNA antibodies were negative, and no extrarenal features of SLE were observed. Kidney biopsy demonstrated crescentic glomerulonephritis characterized by cellular extracapillary proliferation. Immunofluorescence showed a characteristic "full-house" granular capillary staining for IgG, IgM, IgA, C3, and C1q, consistent with class IV LN (Figure 1). Due to rapidly progressive disease, immunosuppressive therapy with intravenous methylprednisolone pulses followed by a single dose of rituximab (375 mg/m^2) was administered, while cyclophosphamide was avoided due to frailty.

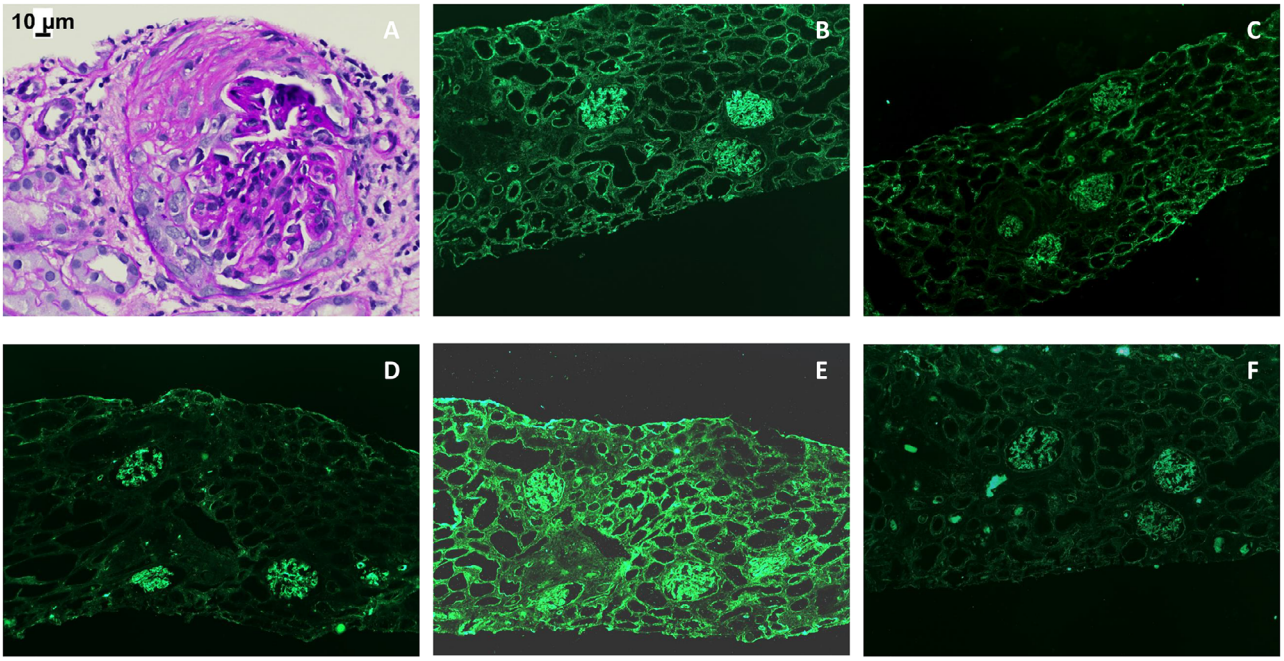

FIGURE 1 | Light microscopy of a glomerulus showing a cellular crescent, formalin-fixed paraffin-embedded (FFPE) section, periodic acid–Schiff (PAS) stain, original magnification, ×60 (A). Immunofluorescence images illustrate glomerular deposition of C1q (B), C3 (C), IgA (D), IgG (E), and IgM (F).

Concurrent oncologic reassessment with abdominal magnetic resonance imaging and [^{18}F]-dihydroxyphenylalanine positron emission tomography confirmed recurrent neuroblastoma. In August 2024, oral etoposide chemotherapy was started. The patient showed a good clinical response, showing improvement in pleural and pericardial effusions, recovery of renal function (serum creatinine 0.35 mg/dL), and remission of proteinuria and hematuria.

LN is rarely associated with malignancies, and reports in pediatric patients are particularly scarce. To date, paraneoplastic LN has not been reported in association with neuroblastoma, nor has it been previously described in the pediatric population. The pathophysiological mechanisms linking malignancy to LN remain incompletely understood. Proposed hypotheses include direct cytotoxic effects of tumor-derived products on renal tissue and, more compellingly, tumor-mediated immune dysregulation. Tumor-associated antigens may break immune tolerance, leading to the production of autoantibodies that cross-react with self-antigens. These autoantibodies contribute to immune complex formation and their deposition in the glomeruli, triggering complement activation and subsequent kidney injury. While ANA and anti-SSA/Ro antibody positivity, classically associated with SLE, may also occur in patients with malignancies, independent of autoimmune disease [3, 4]. The biological significance of these autoantibodies remains uncertain, but they likely reflect immune dysregulation driven by the tumor or its treatment. In our patient, complement consumption, immunocomplex deposition in tissues, and absence of human leukocyte antigen polymorphisms typically associated with SLE susceptibility collectively support paraneoplastic rather than primary autoimmune etiology. Only a few cases of malignancy-associated LN have been reported in adults, in association with lymphoproliferative disorders, trophoblastic tumors [5–8] or benign tumors [9, 10]. Across these cases, therapeutic strategies varied depending on the underlying neoplastic condition and the histological class of LN. Nonetheless, immunosuppressive therapy targeting LN yielded only partial clinical responses, with complete remission achieved only after treatment of the underlying tumor. This trend reinforces the hypothesis that the tumor itself may act as the primary immunological driver of glomerular injury, rather than LN occurring as a distinct autoimmune process. In our case, induction immunosuppressive therapy was initiated because of rapidly progressive glomerulonephritis and was followed by renal remission, consistent with an immune complex–mediated mechanism. Chemotherapy was started shortly thereafter, making it difficult to separate the early effects of immunosuppression from those of oncologic treatment. However, unlike standard management of class IV LN, the patient did not receive prolonged maintenance immunosuppression with agents such as mycophenolate mofetil or low-dose corticosteroids, remaining in sustained renal remission for two years, with no laboratory evidence of ongoing autoimmunity, complement consumption, or clinical flares of SLE. The persistence of remission in the absence of maintenance immunosuppression, together with its close temporal association with tumor relapse, is highly atypical for classical SLE and strongly supports a tumor-driven, paraneoplastic immune mechanism.

In conclusion, this case highlights the need to consider paraneoplastic processes in the differential diagnosis of LN, even in pediatric patients. Prompt recognition and treatment of the underlying malignancy may be crucial for sustained renal remission. Further research is essential to elucidate the immunopathogenic link between cancer and LN in pediatric populations, where current data are extremely limited.

Acknowledgments

We would like to express our sincere gratitude to Abeo Liguria, Alecrim, Progetto Giada, and Collina degli Elfi associations for their valuable help and unwavering support to the patient and her family.

Conflicts of Interest

The authors have no financial disclosures or conflicts of interest relevant to this topic.

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