STUDENT ARTICLE

The Challenge of Diagnosing Common Variable Immunodeficiency in the Face of Immunosuppression and Nephrotic Syndrome

Jacob Diamond, MS[1]; Douglas Nordli, MD[2]; Matthew Garber, MD[3]; Suzanne Bilyeu, MD[4]
[1]MS4 Medical Student, University of Florida College of Medicine
[2]PGY-3 Resident Physician, University of Florida Jacksonville
[3]Pediatric Professor & Chief UF Health Jacksonville
[4]Division of Hospital Pediatrics Wolfson Children's Hospital

Children with common variable immunodeficiency are often challenging to diagnose. We present a case of common variable immunodeficiency and nephrotic syndrome and discuss features, including immunosuppression, which made the diagnosis challenging. This case underlines the importance of suspecting underlying immunodeficiencies in children who are therapeutically immunosuppressed, but infections persist once such therapy is stopped.

INTRODUCTION

Combined variable immunodeficiency (CVID) represents a heterogeneous group of disorders characterized by hypogammaglobinemia, poor or absent response to immunization, and increased susceptibility to recurrent and chronic infection.[1] Diagnosis of CVID typically occurs in the third decade of life. However, the second-highest incidence falls between ages 5 to 10 years. Typical presentation in both adults and children include pneumonia, sinusitis, gastroenteritis and otitis media. Autoimmune disorders, splenomegaly, and bronchiectasis are also common findings.[1,2] Typical presentations of CVID may require extensive evaluations and time to diagnose.

We present the second reported case of CVID in a patient with a history of nephrotic syndrome caused by minimal change disease (MCD). Unlike the first reported patient, the diagnosis of nephrotic syndrome and subsequent immunosuppressive therapy preceded the diagnosis of CVID, making the diagnosis of CVID even more challenging.

Recurrent infections in patients taking immunosuppressive medications requires the clinician to distinguish medication-induced complications from possible underlying conditions.

CASE REPORT

A 9-year-old boy with nephrotic syndrome, recurrent infections, and a chronic cough presented to his pediatrician in April with one day of fever up to 105.4°F and one episode of non-bloody, non-bilious emesis. The pediatrician obtained a complete blood count which was notable for a leukocyte count of 26,000 cells per μL with a neutrophil predominance and then referred the child to the emergency department (ED).

In the ED, the patient presented with fever and otherwise normal vital signs. The patient was in no distress, and other than the fever, had a normal physical examination including clear lungs bilaterally. C-reactive protein was elevated to 9.2mg/dL. A chest X-ray showed consolidation of the left lower lobe. Medical record review revealed 4 prior pneumonias in the last 2 years, with two hospitalizations in 2020, prompting a more thorough history.

The patient was born at term without complications. His early childhood was complicated with recurrent ear infections and multiple ED presentations for fever. At 20 months of age, following five episodes of otitis media in a six-month period and persistence of middle ear effusions, the patient underwent bilateral tympanostomy tube placement that ultimately did not resolve the ear infections.

In 2012, at 27 months of age, he presented to the ED with testicular swelling. Urinalysis indicated significant proteinuria resulting in an evaluation by nephrology and a diagnosis of nephrotic syndrome. Because the patient relapsed during steroid therapy, a renal biopsy was obtained which demonstrated minimal change disease (MCD). For the next 2 years the patient experienced multiple relapses requiring escalation from steroids to cyclosporine, tacrolimus, and rituximab.

Despite gaining better control of edema and proteinuria with initiation of tacrolimus in 2014, his frequent presentations for otitis media, pneumonia and diarrhea continued and were attributed to immunocompromised status secondary to pharmacotherapy for nephrotic syndrome. Tacrolimus therapy was discontinued in late 2017, and the patient achieved remission of nephrotic syndrome in January 2018. He continued to follow-up with nephrology. In February he 2020 was found to have a low serum IgA level of 8mg/dL during a gastroenterology evaluation for his recurrent diarrhea.

Given the patient's history of recurrent infections before immunosuppressive therapy commenced and which continued after the treatment had stopped, we initiated a workup for immune deficiency. The evaluation revealed low serum levels of IgG (235.2 mg/dL), IgM (<15 mg/dL), and IgA (5.3 mg/dL) with poor pneumococcal antibody titers after immunization consistent with CVID. He received IVIG on the second day of hospitalization with no adverse reactions and remained afebrile without use of antipyretics for the duration of his hospital stay. He was discharged with antibiotics and follow up with infectious disease for monthly IVIG infusions.

DISCUSSION

Our patient presented with persistent infections in his first two years of life, but his diagnosis of CVID was not made until he was 9-years-old. This is not uncommon. In a study of 95 patients with CVID, mean time from first presenting symptoms to correct diagnosis was 8.5 years.[3] Although autoimmune processes are often implicated in nephrotic syndrome, and CVID is strongly associated with autoimmune disease, this is only the second reported case of nephrotic syndrome in a patient with CVID. In fact, in a 30-year retrospective review of both pediatric- and adult-onset CVID, cytopenias such as autoimmune thrombocytopenia and autoimmune hemolytic anemia made up the largest proportion (33%) of autoimmune disorders with no mention of kidney disease.[4]

Renal involvement is rare in both pediatric and adult populations carrying a diagnosis of CVID.[5] In a cohort study, excluding infectious etiologies like urinary tract infection and pyelonephritis, only one out of 69 pediatric patients with CVID developed renal sequelae over a follow-up period of five years.[1] Concurrent MCD and CVID appear only once in a comprehensive literature search. In a 2008 case report, a 12-year-old patient with known CVID developed nephrotic syndrome while receiving monthly IVIG infusions.[6] The diagnosis of nephrotic syndrome is usually straightforward given the recognizable signs and symptoms of edema, proteinuria and hypoalbuminemia, even in a patient with other co-morbidities. Aside from other edematous states, most co-morbidities would not delay the diagnosis of nephrotic syndrome, but the opposite is not true. Complications of the immunosuppressive treatment of nephrotic syndrome can mimic immune deficiencies and further obscure the already challenging diagnosis of CVID. Our patient continued to develop pneumonias after discontinuation of immunosuppressive therapy and was even known to have low IgA and recurrent diarrhea. We suspect that anchoring and availability bias may have contributed to the delay in diagnosis given his long history of immunosuppression and infections.

Our case highlights an important presentation of MCD and CVID given the challenges of diagnosing CVID with concurrent immune suppression. Obtaining a thorough history, including recurrent, chronic and unusual infections is of utmost

importance before prescribing immunosuppressant therapy. Understanding the expected frequency, type and severity of infections intrinsic to each medication or combination of medications is also important, though complex, and may require consultation with infectious disease experts. Finally, a patient's susceptibility to infections should normalize once immunosuppressant therapy ceases. Clinicians should discuss this expectation with patients and families, and in partnership with them, monitor for continued infections allowing for earlier recognition of an underlying immunodeficiency.

REFERENCES

1. Mohammadinejad P, Aghamohammadi A, Abolhassani H, et al. Pediatric patients with common variable immunodeficiency: long-term follow-up. *J Investig Allergol Clin Immunol*. 2012;22(3):208-14. PMID: 22697011.
2. Gathmann B, Mahlaoui N, Gérard L, et al. European Society for Immunodeficiencies Registry Working Party. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2014 Jul;134(1):116-26. doi: 10.1016/j.jaci.2013.12.1077. Epub 2014 Feb 28. PMID: 24582312.
3. Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. *J Clin Immunol*. 2001 Mar;21(2):145-9. doi: 10.1023/a:1011012023616. PMID: 11332653.
4. Baloh C, Reddy A, Henson M, et al. 30-Year Review of Pediatric- and Adult-Onset CVID: Clinical Correlates and Prognostic Indicators. *J Clin Immunol*. 2019 Oct;39(7):678-687. doi: 10.1007/s10875-019-00674-9. Epub 2019 Aug 3. PMID: 31377970; PMCID: PMC6754754.
5. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999 Jul;92(1):34-48. doi: 10.1006/clim.1999.4725. PMID: 10413651.
6. Garimella-Krovi S, Panner BJ, Springate JE. Renal disease in common variable immunodeficiency—Case report and literature review. *Pediatr Asthma, Allerg Immunol*. 2008;21(1):35–9.