A 17-Year-Old With Steroid-Resistant Nephrotic Syndrome

Molly E. Band, MHS, PA-C,[a] Candice Sheldon, MD,[b] John Brancato, MD,[a] Nehal S. Parikh, MD,[a] Cynthia D'Alessandri-Silva, MD[a]

abstract

A 17-year-old girl presented with facial swelling and shortness of breath to an outside emergency department. She was treated for an allergic reaction with steroids and antihistamines, and discharged from the hospital. Subsequently, she was referred as an outpatient to pediatric nephrology for recurrent edema and proteinuria. Initial laboratory workup by nephrology was significant for a normal complete blood count and reassuring electrolyte panel. Pertinent laboratories were a creatinine of 0.5 mg/dL (0.4–1.1 mg/dL) and an albumin 2.3 g/dL (3.5–5.0 g/dL). The urine protein-to-creatinine ratio was >7 (<0.2). A renal ultrasound showed symmetrically sized kidneys with normal echotexture. The patient's renal biopsy results were consistent with minimal change disease. Based on the biopsy results, prednisone was started. Due to a poor response to prednisone, an alternate immunomodulator therapy was selected. Her subsequent complete blood counts showed a downward trend of all cell lines and an elevated serum uric acid. Concurrently, she reported worsening fatigue, low back pain, nausea, vomiting, night sweats, and pruritus. More details of her case and the outcome are presented.

CASE HISTORY WITH SUBSPECIALITY INPUT

Dr Candice Sheldon (Pediatrics, Chief Resident)

A 17-year-old girl presented to an outside emergency department (ED) with significant edema, lip swelling, facial flushing, tachycardia, rash, and difficulty breathing. She started bupropion for depression and anxiety 2 days before her ED visit.

Dr John Brancato, is this history and examination consistent with an allergic reaction? What else is on the differential diagnosis?

Dr Brancato (Pediatric Emergency Medicine)

Patients present to EDs frequently with symptoms suggestive of allergic reaction, including urticaria and angioedema. Anaphylaxis or acute multisystem type 1 hypersensitivity reaction may also include tachycardia, wheezing, pruritus, and gastrointestinal symptoms. Although tachycardia is an adverse reaction of bupropion in >10% of patients who take it, facial or other edema is much less common, and given the time frame of days (instead of hours), it would be important to approach the chief complaint of edema broadly.[1,2] Most important on an initial ED visit would be to establish whether the edema is localized to the face and lip or not, as generalized edema would lead to a much broader differential diagnosis, including heart failure, vasculitis, and liver and renal disease. Given the adage "common things are common," in the absence of generalized edema, a presumption of drug reaction is not unreasonable. The patient was sent

[a]*Connecticut Children's Medical Center, Hartford, Connecticut; and* [b]*Division of Nephrology, Department of Pediatrics, Stanford School of Medicine, Stanford University, Palo Alto, CA*

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Address correspondence to Molly E. Band, MHS, PA-C, Connecticut Children's Medical Center, 282 Washington St, Hartford, CT 06106. E-mail: mband@connecticutchildrens.org

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home with an allergic reaction to bupropion.

Dr Sheldon

The patient received steroids, diphenhydramine, and intravenous fluids at the outside ED and was discharged from the hospital with a prescription for prednisone. Two days later she developed the same symptoms and went back to the outside ED.

Dr Brancato, how do you approach a patient who returns with these symptoms?

Dr Brancato

Any return visit to an ED warrants an even more meticulous history of the present illness, as well as a careful review of systems and thorough examination. In this case, elucidating any evidence of more widespread edema and the nature of the respiratory symptoms would be essential. A urine dipstick to evaluate for proteinuria would be an easy, noninvasive screening test and, if positive, would lead us to evaluate in greater detail for possible nephrotic syndrome. If the vital signs and respiratory examination were not normal, a chest radiograph, looking for any evidence of inflammation, infection, or failure, might also guide further workup. At this point in the patient's workup, a urine sample to evaluate for proteinuria would have helped rule in or out renal disease, such as nephrotic syndrome. Intravenous fluids exacerbate systemic edema in patients with active nephrotic syndrome. Given the patient had recurrent edema resistant to antihistamine and anti-inflammatory treatment, allergic reaction is lower on the differential diagnosis. Given these findings, the use of systemic steroids ultimately caused a delay in diagnosis.

Dr Sheldon

At this outside ED visit, she was restarted on a prednisone taper of 1-week duration and hydrochlorothiazide 12.5 mg daily for edema thought to be secondary to allergic reaction. Her urine was checked at a follow-up primary care physician visit and was notable for large protein. At this point, recommendation was made to follow up with Nephrology for suspicion of nephrotic syndrome.

The patient's past medical history is notable being a full-term infant and has been followed by a psychiatrist for anxiety and depression. Her family history is not significant for any renal diseases, although a distant cousin has had a kidney transplant for an unknown etiology. The patient's mother carries a diagnosis of bipolar disorder. Socially, the patient lives with her mother and father.

When she presented to the pediatric nephrology clinic, her initial laboratory results showed an unremarkable complete blood count with a hemoglobin of 13.4 g/dL (11.7–15.7 g/dL) and a hematocrit of 40.5% (35.0%–47.0%), platelets of 450 000/μL (150–450 000/μL), and white blood count of 12.4 × 10^3/μL (4–11 × 10^3/μL). Her renal function panel results were as follows: creatinine 0.5 mg/dL (0.4–1.1 mg/dL), total calcium 8.7 mg/dL (9.2–11.0 mg/dL), albumin 2.3 g/dL (3.2–4.5 g/dL), with her other electrolytes within normal limits. Complement C3 244 mg/dL (90–180 mg/dL) and C4 62 mg/dL (10–40 mg/dL), antinuclear antibody screen was negative, and an acute hepatitis panel was negative. Her random urine protein-to-creatinine ratio was >7. Her renal ultrasound showed 2 normal, symmetrically sized kidneys with normal echotexture.

Dr D'Alessandri-Silva, is this presentation consistent with nephrotic syndrome? Would you perform any further workup?

Dr Cynthia D'Alessandri-Silva (Pediatric Nephrologist)

Nephrotic syndrome classically consists of a triad of edema, proteinuria, and hypoalbuminemia.[3] This patient met all 3 of these criteria with her edema on examination, her urine protein-to-creatinine ratio was well over the normal cutoff of 0.2, indicating a significant amount of proteinuria, and her albumin was low. Idiopathic nephrotic syndrome (INS) is most commonly seen in younger ages, 1–6 years.[4] An adolescent patient presenting with nephrotic syndrome may have other etiologies for their presentation, including infectious causes (viral infections, diabetes mellitus, myasthenia gravis, and immunizations), drugs (nonsteroidal anti-inflammatory drugs, gold, mercury, lithium), or malignant disease (lymphoma, carcinoma).[3] A renal biopsy needs to be considered in children older than 12 to help determine the underlying pathology before starting steroids, particularly if systemic symptoms or the history and physical are suggestive of these secondary causes of nephrotic syndrome.[5] The recommendation is that at least 25 glomeruli are needed in a biopsy to provide appropriate diagnosis.[6]

Dr Sheldon

A renal biopsy was performed with 20 glomeruli sampled. The pathology findings were consistent with INS with lack of any other findings. There was no evidence of focal segmental glomerulosclerosis. The immunofluorescence revealed trace mesangial staining for immunoglobulin G, immunoglobulin M, κ, and λ. Electron microscopy revealed complete effacement of foot processes (Fig 1). Periodic acid-Schiff stain was also performed, revealing normal glomeruli and tubules (Fig 2). Overall, given the renal biopsy findings, and the patient's benign presentation, these findings are

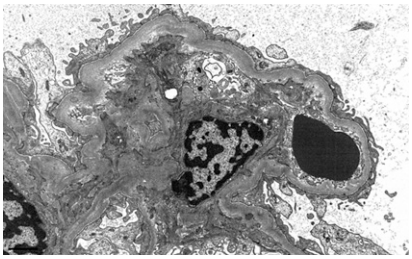

FIGURE 1
Histology showing complete foot process effacement on electron microscopy.

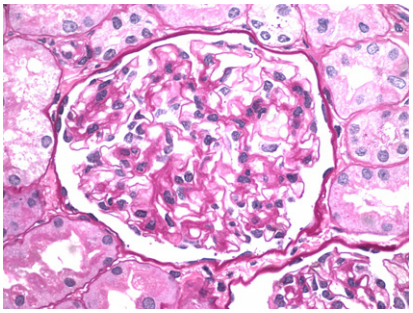

FIGURE 2
Histology showing normal glomerulus and tubules with periodic acid-Schiff stain.

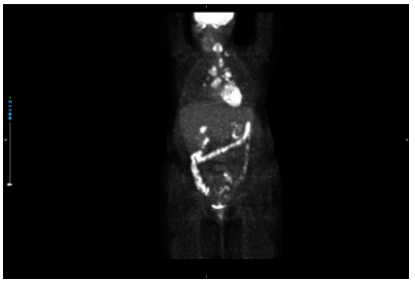

FIGURE 3
Positron emission tomography scan at diagnosis.

suggestive of INS without obvious secondary etiologies.

Dr D'Alessandri-Silva, with these renal biopsy results, how would you approach managing this patient?

Dr D'Alessandri-Silva

Given that these results are consistent with INS in combination with the lack of systemic symptoms concerning for other etiologies of INS, I would start the patient on the standard course of steroids (prednisone 2 mg/kg per day, with a maximum of 60 mg/day) for 6 weeks as first-line therapy, with a salt-restricted diet.[5]

Dr Sheldon

The patient was started on prednisone 60 mg daily with a low-salt diet. Over the next 4 weeks, she experienced rapid weight gain, increased edema, and decreased appetite and emesis. She was thought to be steroid nonresponsive.

Dr D'Alessandri-Silva, what is your approach to patients with steroid-resistant nephrotic syndrome?

Dr D'Alessandri-Silva

The minimal amount of time that a patient is given steroids before he or she is deemed steroid resistant is unclear. A commonly used definition is 8 weeks of steroids.[7] If not already done, a kidney biopsy is recommended to help define the underlying histopathology as well as estimating glomerular filtration rate to help assess kidney function. Treatment of steroid-resistant nephrotic syndrome is not well-defined. An immunosuppressive agent, such as a calcineurin inhibitor should be considered for steroid-resistant nephrotic syndrome. The rationale for using different treatment is to avoid kidney failure.[5]

Dr Sheldon

The patient was started on tacrolimus with a rapid taper of prednisone. Soon after starting the tacrolimus, she was admitted to the hospital with complaints of continued weight gain, fatigue, low back pain, nausea, and vomiting. Her laboratories at this time revealed a decreasing trend in all cell lines and a uric acid of 9.8 mg/dL (3.4-7.0 mg/dL).

Dr Parikh, are you concerned about hyperuricemia in a nephrotic patient? What is your approach to a patient with hyperuricemia?

Dr Nehal Parikh (Pediatric Oncologist)

I was concerned that this could be a malignant process. There are many causes of hyperuricemia in children. Hyperuricemia occurs due to either reduced clearance of uric acid or increased production of uric acid. We have seen increased uric acid levels in patients with high cell turnover, such as a newly diagnosed patient with leukemia or lymphoma. We have occasionally seen elevated uric acid levels in patients with solid tumors, although this is uncommon. Other causes to consider in the absence of clinical or laboratory evidence of malignancies are dehydration, lactic acidosis, starvation, diuretic therapies, or renal diseases.[8,9] Typically, when I see elevated uric acid, I am concerned about a malignant process. I obtain lactate dehydrogenase, erythrocyte sedimentation rate, and further evaluations based on clinical scenarios.

Dr Sheldon

The patient was treated with rasburicase and allopurinol for her hyperuricemia. A positron emission tomography scan showed areas of intensity in the neck, mediastinum, chest, abdominal, and sacral lymph nodes (Fig 3). Oncology was consulted and a bone marrow biopsy, bone marrow aspirate, and sacral biopsy were all nondiagnostic.

Dr Parikh, what role do you think her steroids may have played in her biopsy results?

Dr Parikh

I believe steroids masked our patient's underlying disease, which led to a delay in the diagnosis of the Hodgkin lymphoma. Leukemia and lymphoma can be very sensitive to treatment with steroids. Partial treatments can alter pathologic features within the diagnostic tissue samples and lead to inconclusive results.[10,11] In certain cases of a very responsive disease, we may see disease remission with use of

steroids as a single agent, although this remission is typically not sustainable. It is not evident that patients with Hodgkin lymphoma who have been previously treated with steroids will have a poorer disease outcome. However, partial response to steroids alters the clinician's ability to accurately use the current standards of delivering response-adapted therapy in Hodgkin lymphoma. Therefore, a patient may receive more cytotoxic therapy than would have been otherwise necessary to achieve the same outcome.

Dr Sheldon

The patient was tapered off steroids and the biopsies were repeated. A cervical lymph node biopsy showed classic Hodgkin lymphoma.

Dr Parikh, based on the information presented, are there any oncologic syndromes that could explain her nephrotic syndrome in conjunction with her Hodgkin lymphoma?

Dr Parikh

There are numerous reports of malignancies in patients previously diagnosed with nephrotic syndromes. In a large cohort of patients with nephrotic syndrome, it has been reported that the patients with nephrotic syndrome have a >70% increased risk for cancer during their lifetime. The greatest risk is in the first year after being diagnosed with nephrotic syndrome.[12] Approximately 0.1% to 0.5% of patients with Hodgkin lymphoma have nephrotic syndrome.[13] The predominant subtype of nephrotic syndrome has been minimal change disease.[13]

FINAL DIAGNOSIS AND DISCUSSION: PARANEOPLASTIC NEPHROTIC SYNDROME

Dr D'Alessandri-Silva

Nephrotic syndrome is a well-described paraneoplastic manifestation of Hodgkin lymphoma. Recent large studies have published the incidence of nephrotic syndrome and Hodgkin lymphoma to be 0.4% to 0.6%[14] in adult and pediatric patients, respectively. The clinical presentation of Hodgkin lymphoma–associated INS is the same as classic INS. The diagnosis of Hodgkin lymphoma should be considered when patients have atypical features, including older age at presentation and are unresponsive or partially responsive to steroid treatment. The temporal relationship between nephrotic syndrome with respect to Hodgkin lymphoma is variable but has been reported to occur afterward in 42% of cases.[14] The diagnosis of Hodgkin lymphoma can be delayed with steroid usage, as it was in this patient. The treatment of the underlying lymphoma almost always results in remission of the nephrotic syndrome. In summary, INS is a rather common and not devastating disease in the pediatric population. However, when children present at older ages, INS is less likely and Hodgkin lymphoma is a rare but treatable etiology in this age group. Standard chemotherapy regimens are the first and best line of treatment in patients with INS-associated Hodgkin lymphoma.

Dr Parikh

Although an immune mechanism has been suggested as the causative event for development of Hodgkin lymphoma in a patient with nephrotic syndrome, there has been no clear pathomechanism outlining how exactly autoimmunity leads to development of Hodgkin lymphoma.[15] Some reports suggest T-lymphocyte dysregulation.[16] In our patient, her initial diagnosis of nephrotic syndrome followed by Hodgkin lymphoma is evident of the observed paraneoplastic syndrome and provides an excellent opportunity to learn from such unique presentations.

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ABBREVIATIONS

ED: emergency department
INS: idiopathic nephrotic syndrome

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