CASE REPORT

Acute infection-related glomerulonephritis with disseminated gonococcal infection in a 13-year-old girl

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SUMMARY

Infection-related glomerulonephritis results from glomerular immune complex deposition due to a variety of potential pathogens. Poststreptococcal glomerulonephritis is the best known example. We present a case of acute infection-related glomerulonephritis associated with disseminated gonococcal infection in a sexually active 13-year-old girl, the first report of such an association in the absence of endocarditis. The patient presented with features of acute disseminated gonococcal infection including fever, hypotension, tenosynovitis, polyarthralgias and petechiae. She developed hypocomplementemic glomerulonephritis synchronous with the acute infection. The renal biopsy revealed a diffuse endocapillary proliferative and exudative glomerulonephritis with subepithelial electron-dense humps and granular glomerular capillary wall staining for C3 and IgG, typical of acute postinfectious glomerulonephritis. After treatment and resolution of the gonococcal infection, the serum creatinine, complement levels and urine sediment normalised. The only residual renal damage 16 months later was low-grade proteinuria.

BACKGROUND

Infection-related immune complex-mediated acute glomerulonephritis has been described with a variety of infectious agents including bacteria, viruses, fungi and parasites, either during the acute illness or after a latent period. The most common example of the latter is poststreptococcal glomerulonephritis, which typically occurs 1–3 weeks after pharyngitis and 2–4 weeks after skin infection with beta haemolytic group A *Streptococcus*.

We describe a case of acute glomerulonephritis associated with concurrent disseminated gonococcal infection for rarity of this condition and early recognition of renal involvement.

CASE PRESENTATION

History of present illness

A previously healthy 13-year-old girl was admitted with 1 day of fever, temperature maximum 105°F (40°C), vomiting, pain in the ankles, wrists and proximal right metacarpophalangeal joints, and a rash on the palms, soles and distal legs. She did not give a history of sore throat, headache, visual changes, vaginal discharge, dysuria, urinary urgency or frequency or any drug intake. She had unprotected sex with two male partners 1 month prior.

Physical examination findings on admission

She had a temperature of 102.5°F (39.1°C); heart rate 110 beats/min, blood pressure 95/65 mm Hg, capillary refill <2 s. She had painful petechiae over the palms, soles and lower legs, moderate swelling of both ankle joints and erythema and tenderness of the dorsum of the right foot attributed to acute tenosynovitis. She had no periorbital or pedal oedema, no pharyngitis, no cervical lymphadenopathy and no perianal or genital lesions.

INVESTIGATIONS

Initial laboratory tests

Haematocrit 31%, white cell count $30.8 \times 10^9/L$, with 65% neutrophils and 24% immature neutrophils, C reactive protein 180 mg/L, erythrocyte sedimentation rate 64 mm/hours.

Urinalysis showed protein 100 mg/dL, 41 red blood cells (RBC)/hpf, >182 white blood cells (WBC)/hpf, 4+ WBC clumps. Blood chemistries showed serum creatinine 2.9 mg/dL, blood urea nitrogen 39 mg/dL, serum albumin 3.5 g/dL, normal electrolytes and liver enzymes, complement C3 12 (70–225) mg/dL, C4 14 (14–55) mg/dL, anti-nuclear antibody positive 1:320 titre with homogeneous pattern; and negative antimyeloperoxidase, antiproteinase-3 and anti-DNA antibodies. A rapid streptococcal antigen test from a throat swab was negative.

TREATMENT

Management and hospital course

She was started on vancomycin and ceftriaxone for presumed bacterial sepsis and doxycycline for possible tickborne infection.

On hospital day 2, she became hypotensive with oliguria and required vasopressor support with dopamine despite infusion of 4 L of normal saline (0.9%). Urine PCR was positive for *Neisseria gonorrhoeae* DNA. Testing for other sexually transmitted infections was done and was unremarkable for syphilis, hepatitis C and HIV. She was immune to hepatitis B with presence of hepatitis B surface antibody. There was no growth of bacteria on blood or urine culture. An echocardiogram was normal with no evidence of vegetations.

On hospital day 3, her blood pressure stabilised, fever defervesced, ankle pain improved and serum creatinine decreased to 1.2 mg/dL, but she manifested fluid overload with anasarca and dyspnoea

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Figure 1 A representative glomerulus has global obliteration of glomerular capillaries by endocapillary hypercellularity, including many infiltrating neutrophils. The adjacent periglomerular interstitium is expanded by oedema and mild inflammation (H&E, x400).

requiring supplemental oxygen. The latter resolved with diuretic therapy. The renal and pelvic ultrasound examination showed no evidence of pelvic inflammatory disease or abscess.

On day 5, serum creatinine increased to 2.3 mg/dL despite normal blood pressure and perfusion. Urinalysis showed protein 300 mg/dL and several RBC, and mixed cellular casts and urine protein/creatinine ratio was 1.1 mg/mg (normal <0.2). Antistreptolysin titre was 860 Todd units/mL (<330) and anti-DNAase B was <250 U/mL (<310 U/mL). Serum complement levels were as follows: C3 6 mg/dL (83–177), C4 9 mg/dL (15–45), CH50 10 (40–62) U/mL, C5 3 (7–20) mg/dL, C6 36.3 (28–69) µg/mL, C7 56.4 (35.3–96.5) µg/mL, C8 43 (49–106) µg/mL, C9 71.3 (33–95) µg/mL. Serum parvovirus IgM was not sent as the rash was petechial and purpuric rather than typical malar or reticulated erythema seen with parvovirus. Also given abrupt onset of clinical symptomatology and absence of any identifiable chronic infection or chronic autoimmune condition, the index of suspicion for cryoglobulinaemia was low, and cryoglobulin testing was not done.

Figure 2 Immunofluorescence staining for C3 shows granular 'starry sky' pattern of positivity involving the mesangium and glomerular capillary walls (x400).

Figure 3 An electron micrograph shows several hump-shaped subepithelial electron-dense deposits (large arrows) with overlying foot process effacement as well as few smaller subendothelial electron-dense deposits (small arrows), (x30 000).

On day 6, serum creatinine was 2.7 mg/dL, serum albumin 2.6 g/dL and cholesterol 116 mg/dL. She never manifested nephrotic range proteinuria, and thus the low serum albumin was attributed to haemodilution associated with fluid retention and protein catabolism.

A renal biopsy was performed on hospital day 6.

Renal biopsy findings

All 19 glomeruli sampled for light microscopy showed diffuse and global severe endocapillary proliferative and exudative glomerulonephritis with many infiltrating neutrophils (figure 1). Patchy interstitial inflammation and oedema occupied 15%–20% of the cortical parenchyma. Focal RBC and WBC casts were seen. Immunofluorescence microscopy of 5 glomeruli showed dominant 2–3+ granular deposits of C3 involving the glomerular capillary walls and mesangium in a 'starry sky' pattern (figure 2), with 1–2+ IgG, negative IgM, trace to 1+ IgA and trace sparse C1q. Electron microscopy performed on five glomeruli showed marked diffuse and global proliferation of mesangial and endothelial cells, numerous infiltrating neutrophils, abundant subepithelial hump-shaped electron-dense deposits without spike formation and scattered small segmental mesangial and subendothelial electron-dense deposits (figure 3).

OUTCOME AND FOLLOW-UP

Follow-up

She received intravenous ceftriaxone for 10 days, oral doxycycline for 7 days, amlodipine 5 mg daily for 3 weeks for hypertension and enalapril 10 mg daily for 16 months.

Serum C4 normalised 10 days after admission and C3, C5 and C8 values returned to normal 5 weeks after admission. Serum creatinine improved to 0.7 mg/dL 6 weeks after admission. The urine protein/creatinine ratio was 0.3–0.36 for the next 6 months and has been stable around 0.22 g thereafter. Urinalysis 16 months after disease onset showed 100 mg/dL protein and 1–3 RBC/hpf.

DISCUSSION

We report an adolescent girl with acute glomerulonephritis temporally associated with concurrent disseminated gonococcal infection. To our knowledge, this is the first report of acute glomerulonephritis related to *N. gonorrhoeae* infection in the absence of endocarditis. A case of chronic gonococcaemia with endocarditis

and immune complex glomerulonephritis was reported in 1980.¹ Over the past three decades, disseminated gonococcal infection has become a rarity. Our patient presented with signs and symptoms consistent with disseminated gonococcal infection including fever, vasculitic petechiae, tenosynovitis, arthralgias and arthritis.^{2,3} Gonococcal DNA was detected in urine by PCR.

While the most common presentation of sexually transmitted *N. gonorrhoeae* infection is cervicitis in women and urethritis in men,⁴ history of recent symptomatic genital infection is uncommon in patients with disseminated gonococcal infection. The latter condition generally presents with abrupt onset of malaise, tenosynovitis, skin lesions of haemorrhagic macules, pustules or vesicles, polyarthralgias and asymmetric polyarthritis. The skin lesions generally involve distal extremities and are often transient, as in our case.⁵ The risk of dissemination probably depends on microbial virulence as well as host immune factors.

In disseminated gonococcal infection, the blood culture is positive in less than half of cases and the skin culture is positive in 10%–15% of cases. This is due to the fastidious nature of *N. gonorrhoeae*, as its viability is dependent on proper transport in a humid and carbon dioxide-rich atmosphere, as well as the proper use of chocolate blood agar for culture. By contrast, *N. gonorrhoeae* can be isolated from a mucosal site in about 80% of cases, as occurred in our patient.⁶

Deficiencies in the complement system have been associated with disseminated disease.⁷ Our patient had low C3, C4, C5 and C8 levels during the acute illness but they normalised within 5 weeks, providing evidence against congenital complement deficiency and supporting active complement consumption associated with acute nephritis.

Our patient presented with hypocomplementemic acute nephritic syndrome including reduced glomerular filtration rate, fluid overload, haematuria, leucocyturia and proteinuria. While the serum creatinine improved transiently with haemodynamic support, she subsequently manifested significant but non-nephrotic range proteinuria, further decrease in glomerular filtration rate and anasarca from fluid retention, reflecting an evolving glomerulonephritis temporally associated with active systemic infection. The kidney biopsy findings of diffuse proliferative glomerulonephritis with many infiltrating neutrophils and hump-shaped subepithelial immune complex deposits of IgG and C3 resemble the changes seen in acute poststreptococcal glomerulonephritis. The patient, however, did not have any preceding sore throat or impetigo. A rapid streptococcal antigen test was negative at presentation; therefore, no throat culture was obtained. An elevated streptolysin titre together with a normal anti-DNAase B level is a discordant antibody response. This serology in the setting of lack of preceding or current pharyngitis or skin infection provides evidence against a bona fide streptococcal infection. In addition, poststreptococcal glomerulonephritis typically presents 2–4 weeks after an episode of exudative pharyngitis or streptococcal impetigo,⁴ whereas our patient had acute glomerulonephritis concurrent with active disseminated gonococcal infection.

Most patients with poststreptococcal glomerulonephritis show only low serum C3 reflecting activation of the alternative complement pathway, while only a minority of patients also has low C4. Our patient had decreases in both C3 and C4. The C4 value returned to normal within 10 days while the C3 value normalised later at 5 weeks, suggesting possible involvement of both the classical and alternative pathways of complement. In a recent study of acute infection-related glomerulonephritis, a third of patients showed both low C3 and C4 levels,⁷ similar to the findings in our patient.

The fact that infection-related glomerulonephritis can be caused by so many different pathogenic organisms but develops in only a minority of infected patients argues for critical pathogen and host factors in disease susceptibility. A high attack rate (38%) of sporadic post streptococcal glomerulonephritis has been reported in siblings, reflecting genetic susceptibility.⁸ Acquired dysregulation of the complement pathway may be a plausible host susceptibility factor.

N. gonorrhoeae has two immunochemically distinct groups based on porin proteins, named Por A and Por B. These groups in turn have been divided into 26 and 32 serovars, respectively, indicating broad strain diversity. As there are limited numbers of nephritogenic strains of beta haemolytic group A streptococci, we postulate there are likely to be a limited number of newer strains of *N. gonorrhoeae* with nephritogenic properties. This may explain the lack of prior reports of gonococcal-related acute glomerulonephritis. The putative nephritogenic gonococcal antigens could mediate glomerular injury by multiple potential mechanisms similar to those considered for acute poststreptococcal glomerulonephritis.⁷ These include the following: (1) passive glomerular entrapment of circulating gonococcal antigen–antibody immune complexes that can activate the complement pathways, (2) penetration of a cationic gonococcal antigen through the polyanionic glomerular capillary wall followed by binding of antibodies to the planted antigen in situ, (3) cross reaction of gonococcal antigen with a component of the glomerular capillary wall (molecular mimicry) and production of antibodies that bind in situ to the neoantigen.

Learning points

- Consideration of disseminated gonococcal infection in sexually active adolescents presenting with consistent signs and symptoms. There has been an increase in the incidence of gonococcal infections, however disseminated infection is a rarity (0.5%–3%).
- Early recognition of concurrent gonococcal infection-related glomerulonephritis to allow timely management.
- Exclusion of any host immunodeficiency such as underlying complement deficiency (C6, C7 and C8).
- In case of infection-related glomerulonephritis, the workup should include testing for other common causes, such as poststreptococcal glomerulonephritis, *Staphylococcus* bacteraemia, hepatitis B and hepatitis C infections.

Contributors AN: participated in the design of the case report, data collection, drafting and revision of the manuscript. LRK: participated in data collection, drafting and revision of the manuscript. VD'A: provided images of the renal pathology and revised the manuscript. MC: supervised the project, participated in study design and implementation, and revised the manuscript. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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