Granulomatous interstitial nephritis associated with influenza A: H1N1 infection – A case report

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SUMMARY

Introduction The causes of acute tubulointerstitial nephritis can be grouped into four broad categories: medications, infections, immunologic diseases, or idiopathic processes. Here we report a 17-year-old female who developed acute kidney injury (AKI) due to granulomatous interstitial nephritis (GIN) associated with influenza A: H1N1 infection.

Case Outline The illness presented after two weeks of respiratory tract infection, skin rash and hypermenorrhea. On admission the patient was febrile, with bilateral pedal edema, macular skin rash, and auscultatory finding that suggested pneumonia. Laboratory investigations showed normocytic anemia, azotemia, hematuria and proteinuria. Renal ultrasound was normal. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, lupus anticoagulant, antiphospholipid antibodies were negative with normal complement. Urine cultures including analysis for *Mycobacterium tuberculosis* were negative. The diagnosis of influenza A: H1N1 infection was made by positive serology. A kidney biopsy showed interstitial nephritis with peritubular granulomas. Glomeruli were normal. Staining for immunoglobulins A, M, G, and E was negative. The girl was treated with oseltamivir phosphate (Tamiflu; Genentech, Inc., South San Francisco, CA, USA) for five days, as well as with tapered prednisone after a starting dose of 2 mg/kg. The treatment resulted in a complete remission during two years of follow-up.

Conclusion We present a severe but reversible case of GIN and AKI associated with influenza A: H1N1 infection. Although a causal effect cannot be confirmed, this case suggests that influenza A: H1N1 should be considered in the differential diagnosis of GIN manifested with AKI in children.

Keywords: acute kidney injury; granulomatous interstitial nephritis; influenza A: H1N1 infection.

INTRODUCTION

Involvement of the tubulointerstitial compartment in renal diseases can be either primary or secondary due to glomerular, vascular, or structural disease. Granulomatous tubulointerstitial nephritis (GIN) is a rare histologic diagnosis found in 0.9% of native renal biopsies and 0.6% of renal transplant biopsies [1]. Although this illness is often reversible, progression to chronic renal disease can occur. While *Streptococcus* was the predominant infectious cause of acute GIN in children before the antibiotic era, nowadays other pathogens have become important causes.

Influenza is an acute febrile illness caused by influenza viruses. Most influenza infections are uncomplicated, with the illness being limited to symptoms of upper respiratory tract infection in combination with a number of constitutional symptoms. Unfortunately, a number of patient groups are at risk of severe illness and complications affecting multiple organ systems.

CASE REPORT

A 17-year-old female patient presented with an acute kidney injury (AKI) after two weeks of respiratory tract infection, skin rash and hypermenorrhea. Excessive bleeding led to hypovolemia and anemia (Hgb = 52 g/l), so she was treated with packed red blood cell transfusions, intravenous antibiotics (ceftriaxone, metronidazole) as well as gestagen (norethisterone) for six days. The treatment was initiated in the regional hospital. On Day 4, serum creatinine had risen from baseline 109 μmol/l to 320 μmol/l corresponding to AKI pRIFLE-F, urging the referral to our institution [2].

Personal medical history revealed premature delivery at week 32 due to preeclampsia. After birth, the patient had neonatal meningitis with consequent hydrocephalus requiring implantation of ventriculoperitoneal shunt. Menarche was registered at the age of 13, with irregular menstrual bleeds since then.

Physical examination on admission revealed pulse rate of 90 beats per minute, blood pressure of 90/60 mmHg, bilateral pedal edema, macular rash at lower extremities, and pneumonia (confirmed by chest X-ray). She had fever and oliguria. Complete blood count showed normocytic anemia. Erythrocyte sedimentation rate was elevated (40 mm/h). Urinalysis showed hematuria with 1+ proteinuria and mild pyuria. Blood chemistry revealed elevated serum creatinine 349 μmol/l with estimated glomerular filtration rate using Schwartz formula (23 ml/min/1.73m2) [3]. Proteinuria was 652 mg in 1,240 ml of 24-hour urine collection.

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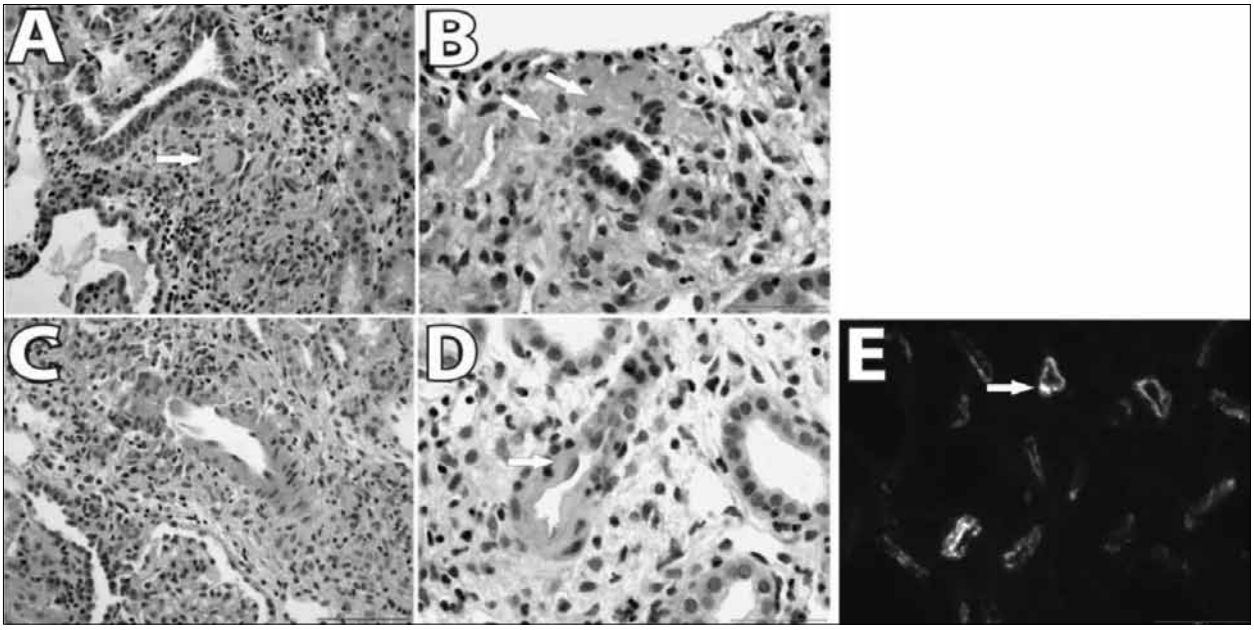

Figure 1. (A–E). Granulomatous interstitial nephritis (GIN); PAS staining (A, C), ×200; PAS staining (B, D), ×400.

A) Interstitial granulomatous lesion with giant cell (arrow); B) Peritubular fibrinoid necrosis (arrows); C) Heavy perivascular infiltrate; D) Edema of endothelial cell (arrow); E) C3 complement component positivity along the tubular basement membrane

Ultrasound showed normal size kidneys with normal corticomedullary differentiation.

Levels of complement proteins C3 and C4 were normal, and all immunological investigations performed (antinuclear antibodies, antineutrophil cytoplasmic antibodies, lupus anticoagulant, antiphospholipid antibodies, and anti-transglutaminase antibodies) were negative. Urine culture for Mycobacterium tuberculosis and Mantoux test were performed, and all results were negative. Coagulation screen (PT, aPTT) was normal, as well as upper gastrointestinal endoscopy and fecal occult blood test. Diagnosis of influenza A:H1N1 infection was confirmed by real-time polymerase chain reaction assays in respiratory specimens.

Percutaneous renal biopsy was performed to identify the cause of AKI, and light microscopy showed normal glomeruli (five out of five). Interstitium showed peritubular granulomas with giant cells and fibrinoid necrosis. Several foci of mononuclear cell infiltrate comprising mainly lymphocytes and monocytes were also found in interstitium. Similar inflammatory infiltrates were seen around large blood vessels and a greater infiltrate around one arteriole. Immuno-morphologically, C3 complement component positivity along the tubular basement membrane was revealed. Staining for immunoglobulins A, M, G, and E was negative. A diagnosis of GIN was made (Figure 1. A–E).

The patient was treated with oseltamivir phosphate (Tamiflu; Genentech, Inc., South San Francisco, CA, USA) orally (150 mg/d) combined with glucocorticoids (oral prednisolone 60 mg/m^2/24h for six weeks, then 40 mg/m^2/48h for another month). Prednisolone was tapered down slowly 5 mg per week over two months. Anemia was treated with packed red blood cell transfusions (for transfusions). The treatment resulted in a complete remission that maintained during two years of follow-up.

DISCUSSION

Primary tubulointerstitial nephritis (TIN) is a syndrome with a wide clinical spectrum characterized histologically by inflammation and damage of tubulointerstitial structures, with relative sparing of glomerular and vascular elements [4].

It is estimated that acute TIN accounts for 10–25% of reported cases of AKI in adults, and up to 7% of children [5]. However, both in children and adults acute TIN may be underreported as many patients with AKI recover spontaneously after removal of the suspected offending agent, and definitive diagnosis based on a renal biopsy is not routinely established [6].

Our patient presented with AKI two weeks after respiratory tract infection. She was treated with intravenous antibiotics (ceftriaxone, metronidazole). Also, the girl had an excessive bleeding due to hypermenorrhea, which led to hypovolemia and anemia. Medications, rather than infection, are now the leading cause of acute TIN in children [7]. Antimicrobials and nonsteroidal anti-inflammatory drugs are the most common drugs causing acute tubular necrosis (ATN) in children [8]. Drug-induced acute TIN is an idiosyncratic reaction, and as such it is difficult to predict which patients will be affected. No specific risk factors have been consistently identified.

Hypotension and hypovolemia are the two most important causes of decreased renal perfusion [9]. Renal ischemia and hypoxia can cause endothelial and epithelial cell dysfunction that becomes apparent once blood flow is restored. Both apoptotic and immune mechanisms are implicated in the renal dysfunction that follows ischemia and reperfusion [10]. This girl developed GIN with AKI, but there were no signs of rhabdomyolysis or evidence

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Table 1. Laboratory findings on admission to our hospital

Laboratory data	Results	Reference range
CBC		
HGB (g/l)	87	120–160
MCV (fl)	92	78–102
HCT (l/l)	0.27	0.36–0.46
Reticulocyte count (%)	2	<2
WBC (x 10^9/l) neutrophils (%) lymphocytes (%) monocytes (%) eosinophils (%) band neutrophils (%)	10.7 62 16 14 6 2	4.5–11.0 50–60 20–50 0–8 0–4 0–3
PLT (× 10^9/l)	276	150–450
Blood		
Creatinine (μmol/l)	349	40–100
Urea (mmol/l)	14.2	3.2–7.5
Uric acid (μmol/l)	388	178–351
Sodium (mmol/l)	130	135–145
Potassium (mmol/l)	3.5	4.1–5.1
Chloride (mmol/l)	96	98–107
Calcium (mmol/l)	2.01	2.25–2.67
Phosphate (mmol/l)	0.85	1.0–1.55
pH	7.42	7.35–7.45
HCO_3	25.3	26–32
Coagulation screen		
PT	15.8	11.8–15.1
aPTT	25.2	24–35
Urine		
RBC	200 acanthocytic RBC/hpf	≤3 RBC/hpf
casts	no evidence of casts	no evidence of casts
WBC	10 WBC/hpf	≤5 WBC/hpf
proteinuria	652 mg/d	<150 mg/d

CBC – complete blood count; HGB – hemoglobin; RBC – red blood cells; MCV– mean corpuscular volume; HCT – hematocrit; WBC – white blood cell; HCO_3 – bicarbonate; PLT – platelet count; PT – prothrombin time; aPTT – activated partial thromboplastin time; hpf – high-power field

of direct viral-induced AKI, suggesting that AKI may be mainly secondary to hemodynamic events.

Rapid reversibility and the absence of any systemic sings of autoimmunity render an underlying immune disorder (e.g. systemic lupus erythematosus, sarcoidosis, Wegener granulomatosis, Sjogren's syndrome) unlikely.

Numerous infectious agents have been implicated in the pathogenesis of acute TIN. Infections may induce acute TIN by two distinct processes. Organisms may directly invade the renal parenchyma, producing local renal infection and inflammation. This form of acute TIN may respond to treatment of the underlying infection. Alternatively, organisms may induce "reactive" intrarenal inflammation without evidence of renal infection. Mechanisms for the renal inflammatory reaction in the absence of renal infection are not clearly elucidated but are presumed to be immunologically mediated [11]. Since many viruses have been linked with TIN, we postulated a causal relationship between the proven influenza H1N1 infection and TIN. Nevertheless, we did not rule out other infections known to cause acute TIN, such as cytomegalovirus, Epstein–Barr virus, hepatitis C virus, human immunodeficiency virus, mycoplasma, or hantavirus.

Influenza H1N1 virus infection may present with impairment of renal function ranging from mild disease to the severe form with need for renal replacement therapy [12]. Before the influenza A:H1N1 pandemic, direct kidney involvement in children with influenza A virus infection had been rarely reported [13]. Recently, Ghiggeri et al. [14] reported two children with influenza A:H1N1 infection who presented with hematuria 48 hours before the start of classic pulmonary signs of influenza. These patients did not develop acute glomerulonephritis and AKI, but it was suggested that macroscopic hematuria may be the first sign of an influenza A:H1N1 infection.

There are several reports of clinical findings of H1N1 infection in children, but few reporting AKI, with a wide range in incidences [15]. Some authors think that the pathophysiologic mechanism of AKI in H1N1-infected patients is multifactorial ATN, mainly because of a combination of hypoperfusion, renal vasoconstriction, and rhabdomyolysis in the setting of severe systemic inflammatory response syndrome [15]. Conversely, in a case series of patients with H1N1 infection, mild to moderate ATN was present in all patients, but myoglobin pigments and thrombotic angiopathy were present only in some patients [12]. Hypotension as well as rhabdomyolysis where found to be significantly correlated with AKI [11].

The initial treatment of acute TIN is primarily supportive, with dialysis therapy as indicated. In infection-related acute TIN, specific treatment of the underlying infection is indicated [11]. Prognosis for the recovery of renal function in children with acute TIN is excellent [5, 11]. Most affected patients recover renal function completely.

The use of corticosteroid therapy for acute TIN remains controversial. Anecdotal case reports and uncontrolled trials with small number of patients suggest a therapeutic benefit [5, 11]. However, prospective controlled studies of corticosteroids or other cytotoxic agents in acute TIN are lacking. In the absence of therapeutic trials, our case report suggest that treatment with oseltamivir phosphate and moderate dosage of prednisolone is associated with good prognosis in patients who develop AKI due to GIN associated with influenza A:H1N1 infection.

In summary, we presented a severe but reversible case of acute GIN and AKI associated with influenza A:H1N1 infection. Although a causal effect cannot be confirmed, this case suggests that influenza A:H1N1 should be considered in the differential diagnosis of acute GIN manifested with AKI in children.

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Грануломатозни интерстицијумски нефритис удружен са инфекцијом инфлуенцом *A: H1N1* – приказ случаја

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КРАТАК САДРЖАЈ

Увод Узроци акутног тубулоинтерстицијумског нефритиса могу се поделити у четири велике категорије: лекови, инфекције, имунолошке болести или идиопатски процеси. Приказујемо адолесценткињу узраста 17 година која је развила акутно бубрежно оштећење (АБО) као последицу грануломатозног интерстицијумског нефритиса (ГИН) удруженог са инфекцијом инфлуенцом *A: H1N1*.

Приказ случаја Болести су претходили акутна респираторна инфекција, која је почела две недеље раније, промене по кожи и метрорагија. На пријему је адолесценткиња била фебрилна, са присутним претибијалним тестастим едемима, макулозном оспом по кожи екстремитета и аускултаторним налазом на плућима који је могао одговарати бронхопнеумонији. У лабораторијским анализама: нормоцитна анемија, азотемија, хематурија и протеинурија. Ехосонографски преглед уротракта је био уредног налаза. Антинуклеусна антитела, антитела на цитоплазму неутрофила, лупус антикоагуланс, антифосфолипидна антитела – негативна. Комплемент нормалан. Уринокултура и урин на *Löwenstein* негативни. Серологија на инфлуенцу *A: H1N1* позитивна. Перкутана биопсија бубрега је показала туболоинтерстицијумски нефритис са формираним перитубуларним грануломима и без лезије гломерула. Налаз имунофлоресценце (*Ig A*, *M*, *G* и *E*) негативан. Девојчица је лечена *Tamiflu*-ом (*oseltamivir phosphate*) током пет дана уз терапију преднисоном, током шест недеља 2 *mg/kg*, а након тога алтернативна терапија преднисоном (1 *mg/kg*/48×) током четири недеље уз постепено укидање лека. Лечење је резултирало комплетном ремисијом која је трајала током две године праћења.

Закључак Приказали смо тежак али реверзибилни случај ГИН и АБО удружене са инфекцијом вирусом инфлуенце *A: H1N1*. Иако се узрочна веза не може потврдити, овај приказ случаја сугерише да инфекцију вирусом инфлуенце *A: H1N1* треба диференцијално дијагностички размотрити у случају ГИН које се манифестује са АБО код деце.

Кључне речи: акутно бубрежно оштећење; грануломатозни интерстицијумски нефритис; инфекција инфлуенцом *A: H1N1*.

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