



## Case report

## Influenza a H1N1 associated acute glomerulonephritis in an adolescent

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## ABSTRACT

Influenza virus primarily affects the respiratory system. It rarely causes extrapulmonary complications, with otitis media and febrile seizures being the most common in children. Acute glomerulonephritis as a complication of H1N1 influenza virus infection has been described only sporadically.

Herein we present a case of acute glomerulonephritis in a previously healthy adolescent, in the context of infection with influenza A H1N1 virus.

A 15-year old adolescent was admitted to our pediatric department due to fever, pharyngitis, cough, vomit, dizziness and fatigue. Based on his symptoms and the seasonal epidemiology, empiric treatment with oseltamivir was initiated while waiting for RT-PCR for influenza virus in pharyngeal swab, which was positive for A H1N1 influenza virus. In the first 24 h of admission, the patient presented macroscopic haematuria, which completely subsided in the following days, along with fever recession. The urine microscopic analysis showed findings compatible with acute glomerulonephritis. The patient remained normotensive while his biochemical profile including renal function, as well as further investigation of hematuria (immunoglobulins, C3, C4, ANA, anti-DNA, U/S) were all normal.

ASTO levels, which were initially above normal (562 IU/ml), did not increase significantly in the following days, and given the fact that C3 levels were constantly within normal limits and pharyngeal culture was negative for pyogenic streptococcus, they were not considered sufficient for poststreptococcal glomerulonephritis diagnosis.

Physicians should be suspicious and include influenza in the differential diagnosis when children present with uncommon symptoms such as hematuria along with even mild respiratory symptoms, during seasonal influenza period.

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## Introduction

Complicated influenza infection is often a cause of hospitalization and ICU admission and typically occurs in age extremes, immunocompromised patients and those with underlying medical conditions. However, previously healthy children are not excluded. In the USA the admission rate of non-high risk children due to influenza was estimated at 9 per 10,000 children aged <5 years before the implementation of influenza vaccination to the pediatric population [1].

Overall the most common complication in children is severe pneumonia, while the most common extrapulmonary complications are otitis media and febrile seizures [2]. Rarely renal manifestations including only 3 cases of acute glomerulonephritis

(AGN) have been described [3–6]. Most of the times, complications are associated with the acute phase of the viral infection and sometimes manifest as the presenting symptom, thus making the diagnosis of influenza tricky and delaying antiviral treatment. Herein we describe a case of influenza infection presenting with hematuria along with respiratory symptoms in a non-high risk adolescent.

## Case report

A 15-year-old adolescent was admitted to our clinic with a short history of fever, sore throat, cough, severe vomiting, headache and fatigue. His prior medical history was uneventful apart from admission to NICU due to *streptococcus agalactiae* early onset sepsis shortly after birth (GA 35<sup>+</sup>4 wks). He was fully immunized for his age. On examination he was in fair general condition, feverish up to 39.3 °C, with BP 135/80 mmHg, HR 120 bpm and SatO<sub>2</sub> 98% in air. Examination of his throat revealed inflamed tonsils but no

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exudates and lungs auscultation found any additional sounds. The rest of physical examination was also normal. Laboratory investigation showed WBC/6400/ml (N: 78%, L: 9.0%, M: 12.7%), Hb 12 g/dl, PLT 184000/ml, Ret 0.1, CRP 44.6 mg/L and biochemistry within normal limits, while his urine test revealed microscopic hematuria with no proteinuria. The blood, urine and pharyngeal cultures were sterile, coagulation screen within normal limits, while chest X-ray had no findings. Due to his respiratory symptoms and the fact that he was admitted in January, influenza was speculated and he was started on oseltamivir pos, while waiting for RT-PCR in pharyngeal swab which turned out positive for H1N1 influenza virus.

The second day in hospital he showed macroscopic hematuria and phase contrast microscopy revealed signs of AGN with 45% G1 forms, 90% dysmorphic red cells, 50% Hb void and 80% of wide variation in size. The laboratory investigation for AGN included antistreptolysin-O (ASTO): 562 IU/ml, C3: 95.3 mg/dl C4: 32.4 mg/dl, IgG 1050 mg/dl, IgA 173 mg/dl, IgM 108 mg/dl, urine Ca/Cr 0.0076, ANA, antiDNA, cANCA, pANCA that were all negative. Urinary tract US was normal.

In the course of the disease the boy presented intermittent mild proteinuria (1+ in urine analysis) with low urine protein/creatinine ratio, 24-h urine total protein below 200 mg and serum total protein and albumin within normal limits. The boy responded well to treatment and supportive measures, he was constantly normotensive and his hematuria progressively subsided. On 3-months follow up he showed no recurrence.

## Discussion

Influenza virus is mainly a respiratory pathogen, but other organs are occasionally severely affected. In adults rare extrapulmonary influenza complications include viral myocarditis, encephalitis, acute kidney injury and other renal manifestations in critically ill patients, hepatitis and diabetic ketoacidosis in patients with diabetes mellitus [2]. Most complications are associated with the acute phase of the viral infection while others appear time after, such as Guillain Barre Syndrome and exacerbations of underlying heart disease. In children otitis media is the most common extrapulmonary complication especially in toddlers <2 years old, followed by neurological manifestations namely febrile seizures, while occasionally myositis and myocarditis are encountered [2,3,7]. Renal manifestations are uncommon.

Here we present a case of H1N1 infection associated AGN. The diagnosis was based on clinical and laboratory findings, on the ground of microscopic hematuria which coincided with his respiratory symptoms. From his medical history no constant use of non-steroidal anti-inflammatory medication, which is referred as a cause of AGN, was reported. In addition there was no history of abdominal pain, dysuria or trauma connected to his gross hematuria neither a history of respiratory infection in the preceding month. Rapid reversibility and the absence of any systemic signs of autoimmunity rendered an underlying immune disorder (eg systemic lupus erythematosus) unlikely.

In children AGN most commonly follows a streptococcal throat infection or less frequently, a skin infection. In addition viruses such as hepatitis A, B and HIV are well known pathogens, but infection with the H1N1 subtype of influenza A has been less commonly reported in the literature. In the diagnosis of post-streptococcal AGN throat culture and serologic tests such as ASTO are both used. In our case ASTO was over the normal limits, but it did not increase significantly in the following weeks, and there was neither a prior history of pharyngitis, nor a positive throat culture or a low C3 which coincides with post-streptococcal AGN. In addition the combination of symptoms and the remission of

hematuria along with his recovery from flu is in favour of an influenza associated AGN. There is always the possibility of a recurrence of post-streptococcal AGN during a respiratory infection; however there was no history of prior hematuria in our case. In terms of other viral causes we did not proceed to further investigation, based on the child's normal biochemistry profile, the fact that he was fully immunized for his age and the short course of the disease which lasted as long as his flu symptoms.

In adults with severe influenza cared for in ICU settings, there is an increased likelihood, up to 66%, to develop acute kidney injury [2]. In children influenza associated renal complications are mostly described in hospitalized patients with underlying kidney disease or in PICU patients with multiorgan dysfunction syndrome [8]. In addition large case series are missing making the incidence of influenza related renal injury in the non-high risk population difficult to determine.

Influenza associated renal complications include acute kidney injury, acute tubular necrosis (ATN), rhabdomyolysis, AGN, Good-pasture syndrome and hemolytic uremic syndrome (HHS) [3,7]. A recent review describes in total 25 thrombotic microangiopathy cases such as HHS and thrombotic thrombocytopenic purpura associated with influenza infection. Most of them were noted during 2009 pandemic [6].

As for glomerulonephritis, influenza infection seems to be connected with several types such as acute immune complex GN, membranoproliferative GN, minimal change nephrotic syndrome and focal segmental glomerulosclerosis; however no case series are reported [8]. There are only 3 case reports published so far presenting AGN as one of the first manifestations of influenza infection within pediatric population. All three were associated with 2009 A H1N1 subtype and were noted during the last pandemic [4,6].

Pandemic H1N1 seems to be more commonly associated with extrapulmonary complications. In a prospective study by Lee et al significantly more hospitalized adult patients had extrapulmonary complications during the 2009–2010 pandemic compared to those in a seasonal influenza cohort (23% vs 16%; P = .004), with 5.8% of the former presenting with renal manifestations [9].

Several pathological studies have demonstrated that H1N1 virus is not confined only to the lungs. The virus was found in glomerular macrophages, epithelial cells in the capsule of Bowman and distal tubular cells in fatal 2009 pandemic cases [10]. Using molecular methods pandemic H1N1 2009 influenza A virus was also detected in 1/14 hospitalized influenza patients by To et al [11]. Unfortunately we did not have the chance to search for the presence of H1N1 in the urine of our patient.

It seems that direct viral injury to the kidney is not the only pathogenetic mechanism following influenza A virus infection. Pathogenesis is not yet thoroughly illustrated but it seems that in severe cases of renal manifestations, rhabdomyolysis, renal hypoperfusion secondary to hypovolemia, glomerular microthrombosis due to disseminated intravascular coagulation, and an altered immune response with systemic mononuclear cell activation might be implicated [2].

In conclusion, paediatric patient with renal systems and respiratory complaints might have active influenza, but also other viral pathogens [12]. We believe that there is need for including influenza in differential diagnosis when children present with uncommon symptoms such as hematuria along with even mild respiratory symptoms, during seasonal influenza period. Thus, delay in diagnosis and treatment and unjustified antibiotic use on the ground of other postulated diagnoses would be avoided. Further studies are also imperative to estimate the risk of renal complications in influenza paediatric patients in total and not only in the PICU cases.

### Author statement

Ioannis Drikos & Garyfallia Syridou carried out and participates at the clinical procedure and the manuscript demonstration. Artemis Vintila, Antigoni Pegkou, Loukia Zografou & Panagiotis Rongas participate at the follow up of the patient. Eleni Papa, Dimitris Kyriazopoulos, Olga Savelieva, Eleni Antonopoulou participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

### Declaration of Competing Interest

The authors have no conflicts of interest or funding to disclose.

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