CASE REPORT

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Pneumococcal meningitis associated with glomerulonephritis: A case report

Pneumokokni meningitis udružen sa glomerulonefritisom

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Abstract

Introduction. *Streptococcus pneumoniae* is the second most common cause of meningitis in children, producing more serious complications than other bacteria. *Streptococcus pneumoniae* infections are a rare trigger of glomerulonephritis. We presented a case of glomerulonephritis developing concurrently with meningitis in a young male child. **Case report.** Gross haematuria, significant proteinuria, hypertension and decreased level of C3 alongside the signs of central nervous system involvement occurred in a male patient of 5 years and 3 months of age. Spontaneous resolution of renal affliction parameters followed the successful treatment of meningitis. The disease course was strongly suggestive of postinfectious glomerulonephritis, although it manifested at the same time as meningitis. The absence of the latent period might point to the development of IgA nephropathy, but since the renal function was stable, without any abnormalities in urine tests documented during follow-up, our opinion is that this was rather the case of postinfectious nephropathy. **Conclusion.** The presented case is a unique clinical form of postinfectious glomerulonephritis. An accurate diagnosis of this entity should ensure the adequate treatment and follow-up of these patients.

Keywords:
pneumococcal infections; streptococcus pneumoniae; child; meningitis; glomerulonephritis; diagnosis.

Apstrakt

Uvod. *Streptococcus pneumoniae* je drugi najčešći uzročnik meningitisa kod dece i izaziva značajno ozbiljnije komplikacije od drugih bakterija. Glomerulonefritis je retka posledica infekcije ovom bakterijom. Prikazali smo razvoj glomerulonefritisa istovremeno sa meningitisom kod dečaka. **Prikaz bolesnika.** Makrohematurija, značajna proteinurija, hipertenzija i snižen nivo C3 komponente javili su se uporedo sa znacima infekcije centralnog nervnog sistema kod dečaka u životnom dobu od 5 godina i 3 meseca. Spontana normalizacija parametara bubrežnog oštećenja usledila je nakon uspešnog izlečenja meningitisa. Tok bolesti je snažno ukazivao na razvoj postinfektivnog glomerulonefritisa, iako se manifestovao istovremeno sa meningitisom. Odsustvo latentnog perioda može sugerisati razvoj IgA nefropatije, ali s obzirom na stabilnu bubrežnu funkciju, bez ikakvih abnormalnosti u nalazu urina tokom perioda praćenja bolesnika, mišljenja smo da se u ovom slučaju radilo o postinfektivnom glomerulonefritisu. **Zaključak.** Predstavljeni slučaj pokazuje jedinstven klinički oblik postinfektivnog glomerulonefritisa. Tačna dijagnoza ovog entiteta trebalo bi da osigura adekvatno lečenje i praćenje obolelih.

Ključne reči:
infekcija, pneumococcus; streptococcus pneumoniae; deca; meningitis; glomerulonefritis; dijagnoza.

Introduction

Bacterial meningitis is a serious infection of the surface of the brain, affecting most commonly children and the elderly. *Streptococcus pneumoniae* (pneumococcus) is a commensal organism of the human upper respiratory tract [1], and the second most common cause of meningitis in children [2,3]. The risk of complications of bacterial meningitis is higher for *Streptococcus pneumoniae* than for other causative agents [4,5]. Glomerulonephritis is common in childhood. It represents an acute or chronic nonsuppurative inflammatory process in the glomeruli leading to impaired renal function. The pathogenesis is not fully understood, but it is suggested that glomerulonephritis is usually due to an immunologic response to a variety of etiologic agents. *Streptococcus pneumoniae* infections are a rare trigger of glomerulonephritis, and their exact contribution is unknown.

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We presented a case of glomerulonephritis developing concurrently with meningitis in a young male child.

Case report

A 5-year and 3 months old male patient was admitted to our intensive care unit due to fever, somnolence and dark urine. His illness developed over the course of 3 days. His condition was initially manifested with a slight fever. On the evening of the next day, he developed a high fever, reaching 39.6°C which continued through the night. The following morning he vomited repeatedly and passed odd smelling and dark urine. Prior to hospitalization, he received an antipyretic for fever and diazepam for seizure prophylaxis. From his personal history, we learned that he had 3 episodes of febrile seizures during the previous year, and was suffering from unrecognized nocturnal enuresis. Also, skin prick test was positive for house dust. He was fully vaccinated according to the Serbian vaccination calendar which did not include the antipneumococcal vaccine. Family history did not reveal any information about renal diseases. On admission his body temperature was 39.4°C, he was vitally stable, conscious but somnolent, moderately dehydrated, a systolic murmur was noted, his blood pressure was increased and meningeal signs were negative. Blood tests had shown elevated count of white blood cells (WBC) 23.7×10^9/L [normal range (NR) 4.8–10.8 10^9/L], polymorphonuclear cells (PMNs) 92.6% NR 40–74%), C-reactive protein (CRP) 243.7 mg/L (NR 0–5 mg/L) and procalcitonin (Pct) 9.210 ng/mL (NR 0.5–2.0 ng/mL), and increased erythrocyte sedimentation rate (ESR) 50 mm/h (NR 0–5 mm/h). Urine was dusky and morning urine sample test demonstrated pyuria (25–30 WBCs) [normal value is less than 5 WBCs per high-powered field (HPF)], hematuria (40–50 red blood cells (RBC)/HPF, NR 3–5 RBC/HPF) and proteinuria (+++) – normal finding is negative, with hyaline and erythrocyte cylinders. Arterial blood gas analysis revealed a mild acidosis and hypokalemia. Upon admission, a lumbar puncture was performed and a cloudy cerebrospinal fluid (CSF) was attained, with a high count of WBC dominated by PMNs cells 3,925/mm^3 (normal count < 5 WBCs/mm^3). CSF biochemistry demonstrated elevated proteins [3.0 g/L (NR 0.15–0.3 g/L)] and decreased glucose level (CSF glucose ratio 0.37 mmol/L, normal ratio 0.6 mol/L). Based on these results he was treated under the diagnosis of bacterial meningitis with third generation cephalosporins and vancomycin, dexamethasone and phenobarbitone. Further tests were ordered to evaluate the renal function. The day after admission we received the result of the latex particle agglutination (LPA) test which indicated a pneumococcal infection that was later confirmed by CSF culture detection of penicillin-resistant *Streptococcus pneumoniae*. According to the pneumococcus susceptibility, antimicrobial treatment was continued with vancomycin and meropenem for 14 days and additional 7 days with cefotaxime. Nasal and throat swab cultures were both positive exclusively with *Staphylococcus aureus*. Urine culture result demonstrated *Klebsiella-Enterobacter*, 5,000 colony forming units (CFU) *per* mL (CFU/mL). Since the first hospital day his blood pressure levels were frequently above the 95th percentile for age, gender and height. Because of significant proteinuria and hypertension, a diuretic and enalapril were added to his treatment. Our patient's general condition improved, his neurological status was normal since the 8th day at the Clinic, but he continued with multiple daily spikes of fever for the total of 14 consecutive days. Gross haematuria also continued while the coagulation status was normal and there were no other signs of the haemorrhagic syndrome. Testing the relatives for haematuria was negative. The initial elevation of urea [10.2 mmol/L (NR 3–8 mmol/L)] and creatinine [94 μmol/L (NR 49–106 μmol/L)] in the serum were normalized after carefully balanced hydration. Antistreptolysin O titer (ASOT) was in NR (< 250 U/mL), C3 level was decreased [0.25 g/L) (NR 0.9–1.8 g/L)], while C4 was increased [0.51 g/L (NR 0.1–0.4 g/L)]. His 24-hour urine collection test had shown normal creatinine clearance ranging from 0.82 to 2.07 mL/s (NR 1.47–2.28 mL/s; Reference values have not been established for the age < 18 years) but revealed significant proteinuria reaching 2.03 g/day (NR < 0.14 g/day) which continued until gross haematuria subsided during the fourth week of illness. By that point, the levels of C3 and C4 were beginning to normalize along with blood pressure levels. Specific therapy for the renal disorder was not introduced. The findings of the control lumbar puncture, performed 7 days after the initial, were normal including the culture, with the exception of microscopic examination that revealed 48 PMNs and 32 lymphocytes. The results of the brain magnetic resonance examination were normal. Electrocardiographic (ECG), cardiac and abdominal ultrasound examination findings were also normal. During the second week of illness the patient developed anaemia, with normal peripheral blood smear findings and normal reticulocyte count. After CRP level normalized, he was discharged with stable renal function after spending 26 days at our clinic. Two months after disease onset C3 and C4 levels were normal, but microscopic haematuria and mild proteinuria could still be registered in the morning urine samples. In the 24-hour urine collection test proteinuria was still present but reduced. By that time enalapril was discontinued and his blood pressure was normal in all measurements. After four months of further follow-up proteinuria and microscopic haematuria disappeared, blood pressure, complement levels and overall renal function remained normal, and neurological sequelae did not develop.

Discussion

A young boy was diagnosed with pneumococcal meningitis at our clinic during late September 2014. The diagnosis was made quickly after admission based on clinical presentation and CSF findings. He was accordingly treated with antibiotics adhering to recommendations for bacterial meningitis. Initial antimicrobial therapy was the combination of ceftriaxone and vancomycin. Isolated *Streptococcus pneumoniae* was penicillin resistant and sensitive to third generation cephalosporins, meropenem, and vancomycin. The minimal inhibitory concentration (MIC) for cephalosporins

was higher than for meropenem. Having in mind the patient's general condition, the treatment choice for pneumococcal meningitis was the combination of meropenem and vancomycin, since both of them were suggested to be effective by the The National Institute for Health and Care Excellence (NICE) clinical guidelines [2]. The rationale for this decision was that the pneumococcal infection was the main reason for the clinical presentation, including the renal disorder. Meropenem was chosen over cephalosporins due to better MIC. The dose of vancomycin was 15 mg/kg/6h, adjusted for achieving the target trough level recommended for pneumococcal CNS infections [6] which is in fact around the demonstrated threshold for nephrotoxicity [7]. However, in the setting of an acute renal failure, manifesting during a serious infection, we maintained the recommended dose as it is usually done in cases of acute renal impairment secondary to sepsis. Frequent 24-hour urine collection tests demonstrated normal creatinine clearance, and therefore no dosage correction was needed.

Pneumococcal meningitis is one of the clinical manifestations of invasive pneumococcal disease (IPD). IPD is usually seen in the very young (under the age of 2 years) and the elderly (older than 50) patients, also in patients with chronic diseases such as chronic liver or kidney diseases, diabetics, patients with primary and secondary immunological deficits, then in cases of meningeal membrane damage due to trauma, and in children with cochlear implants [8–13]. The human nasopharynx is the main reservoir for *Streptococcus pneumoniae*, where it commonly leads to only asymptomatic colonization. We found in available reports that carriage rates of *Streptococcus pneumoniae* go as high as 53% among young children, especially those attending day care centres [14]. Clinical examination and visualisation studies in the presented case did not determine the entry point for *Streptococcus pneumoniae* in the upper respiratory tract nor elsewhere. Common colonizers of the upper respiratory tract, such as *Haemophilus influenzae* and *Staphylococcus aureus* antagonise *Streptococcus pneumoniae* colonization [15]. Demonstrated overgrowth of *Staphylococcus aureus* in our patients' respiratory mucosa might imply that there was some other point of entry for pneumococci, but since those two microorganisms share the same nishe and resources [16] it is possible that the same preexisting disorder created favourable conditions for *Streptococcus pneumoniae* invasion and *Staphylococcus aureus* overgrowth. Our patient had prior confirmation of house dust hypersensitivity although was not diagnosed for a particular allergic disease, but subclinical damage to the naso- and oropharyngeal mucosae by allergy might have led to pneumococcal adherence and migration through the respiratory epithelium and later development of invasive disease [17]. Pneumococcus was not detected in the blood culture of our patient, but haematogenous dissemination could not be excluded since 75% of pneumococcal meningitis patients have a positive result [8, 18]. It is important to note that *Streptococcus pneumoniae* is capable for an unmitigated invasion of endothelium and epithelium, *via* its surface antigens binding to receptors on host cells, which facilitate epithelial cell transcytosis [19–21]. The development of IPD is greatly dependent on host's ability to defend itself, thus any state that impairs necessary defence mechanism increases the chance of serious illness caused by *Streptococcus pneumoniae*. There have been discovered rare forms of primary immunodeficiencies that predispose to pneumococcal infections [22–26]. Investigation in a Swedish cohort of 40 patients with a homozygous C2 deficiency, revealed 23 (58%) cases with invasive, mainly pneumococcal infections [27] implying that an inborn impairment of the complement system might predispose to IPD.

The incubation period for this type of infection can be as short as 1–3 day sand the onset of IPD is usually sudden as it was in the presented case. It is estimated that in the case of intact meningeal membranes a significant bacteriaemia during 12–24 hours is necessary before the breach of the blood-brain barrier.

During multiplication, pneumococci concurrently undergo autolysis [28], also the application of effective antibiotics induces massive destruction of microorganisms and release of bacterial products that are highly immunogenic and may lead to an increased inflammatory response in the host [29, 30], which was manifested in our patient with prolonged high fever and elevated levels of inflammatory markers. The clinical course was complicated by haematuria, almost from the very beginning. Haematuria has long been accepted as a sign that should prompt the investigation of bacterial endocarditis [31] because of possible infarctions in the urinary tract that cause loin pain and haematuria. Bacterial endocarditis has so far been described as a complication of pneumococcal infections [32]. Other than haematuria and fever, our patient's findings did not support the diagnosis of bacterial endocarditis according to Duke criteria [33], since the blood culture was negative and there was no evidence for endocardial involvement. One of the possible complications of IPD is disseminated intravascular coagulation (DIC) [34]. It is well known that the regulation of thrombin formation is disrupted during inflammation [35]. Diagnosis of DIC in our patient was made unlikely by normal coagulation status and fibrinogen level. Thus, in this setting, without any other bleeding site and normal coagulation screen, it would be reasonable to infer that a local damage in the urinary tract was the cause of haematuria, rather than a systemic impairment of the coagulation cascade. Elevation of serum urea and creatinine associated with haematuria raised suspicion of hemolytic uremic syndrome (HUS). IPD may be complicated by HUS and pneumococcal-associated cases account for 14% of all HUS diagnosed in the United Kingdom [36]. Although our patient had developed anaemia by the second week of illness, normal levels of liver enzymes, the normal erythrocyte and thrombocyte count, along with normal peripheral blood smear findings and the presence of erythrocyte casts and later normally shaped erythrocytes in urinalysis, made the diagnosis of HUS unlikely, according to the Center for Disease Control's definition of HUS [37] and the Canadian Paediatric Society's *Streptococcus pneumoniae* associated haemolytic uremic syndrome case definitions [38].

Intensive immune response elicits immune complex deposition which may result in glomerulonephritis. Haematu-

ria, proteinuria, and elevated blood pressure indicated the development of nephritic syndrome in our patient. Cases of adults and children developing a clinically apparent pneumococcal disease and subsequently acute glomerulonephritis, have been previously described [39–42]. *Streptococcus pneumoniae* is now a recognized cause of postinfectious glomerulonephritis (PIGN). Acute poststreptococcal glomerulonephritis is the classic example of PIGN. The pathogenesis remains unknown, and there is still no definitive insight into the nature of the main causative antigen[43]. Unfortunately, we were unable to test for serotype of the pneumococcus. So far pneumococcus types 5, 6C, 7, 9, 14, 15 and 17F have been isolated from patients who developed a glomerulonephritis following a pneumococcal infection, and those serotypes have been suggested to be nephritogenic strains [40, 44–48]. Although, in one of these patients, a 4-year-old girl described by Hyman et al. [48], type 14 pneumococcal antigen was detected in the kidney [48] implying that the pneumococcal antigens may play a role in the local activation of the immune response, we could not find any evidence supporting significance of particular serotypes in the development of nephritis from the available literature. This was also the only case describing the histology of a mesangial proliferative glomerulonephritis. The other available reported case in which a renal biopsy was performed describes a membranoproliferative glomerulonephritis after pneumococcal pneumonia [49]. These findings correlate with acute PIGN histology, particularly in the early stages [43]. Complete resolution of all parameters of renal function deterred us from performing a kidney biopsy in our patient.

The disease course of PIGN is usually mild with spontaneous resolution of clinical parameters. The clinical course, resolution of haematuria, hypertension and transient decrease of C3 level in the presented case were in line with the typical presentation of PIGN with a significant exception of the time that passed from infection to glomerulonephritis onset. The similar disease course was described by other authors, demonstrating an acute glomerulonephritis following the pneumococcal infection within 24–48 hours [41, 45, 47]. Those cases also presented with a decrease of C3, but unlike in previous reports, the elevation of ASOT was not demonstrated in our patient. Renal function normalised in all, with various periods needed, spanning from 5 days to 8 weeks. A usual latent period of 1–3 weeks is seen in PIGN, however, the nephritis of IgA nephropathy (IgAN) may occur either at the same time or just 12–72 hours after precipitating event [50]. It was demonstrated that antibody levels specific for various streptococci antigens, including those of the pneumococcus, are increased in patients with IgAN [51, 52] which suggests that pneumococcal antigens are pathogenic in this disease. IgAN commonly occurs in patients older than 15 years of age, the duration of gross haematuria is usually less than 3 days in IgAN, the degree of proteinuria is low, and the episodes of haematuria and proteinuria recur [50]. Although IgAN can manifest itself as nephrotic syndrome or as an acute nephritic syndrome, overall disease course of our patient was rather in favour of PIGN.

Conclusion

Pneumococcal meningitis is a rare cause of glomerulonephritis. It is important for clinicians to be aware of possible clinical presentations and the development of glomerulonephritis following a pneumococcal infection. Considering that only a few cases of PIGN caused by pneumococcal infections have been reported in children, and the early onset of glomerulonephritis, the presented case is a unique clinical form of PIGN. PIGN should be considered in any child who presents with an acute form of glomerulonephritis, regardless that non-typical infectious agents are detected. Most patients recover full renal function and are not biopsied, but an accurate clinical diagnosis of this entity is nonetheless possible and should ensure the adequate treatment and follow-up of such patients.

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