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BRIEF REPORT

Hemolytic uremic syndrome complicating *Mycoplasma pneumoniae* infection

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Abstract
Background *Mycoplasma pneumoniae* can cause various extrapulmonary manifestations but, to our knowledge, no case of *Mycoplasma pneumoniae* associated with hemolytic uremic syndrome (HUS) has been reported.
Case-Diagnosis/Treatment We describe a 1-year-old boy with *M. pneumoniae* respiratory tract infection and associated microangiopathic hemolytic anemia, slightly decreased platelet count and mild renal impairment, suggesting a diagnosis of HUS. Assuming *M. pneumoniae* infection was the cause of HUS in this case, the different possible mechanisms, including an atypical HUS due to preexisting complement dysregulation, an alternative complement pathway activation induced by *M. pneumoniae* infection at the acute phase, an autoimmune disorder, and a direct role of the bacteria in inducing endothelial injury, are discussed. The signs of HUS resolved with treatment of the *M. pneumoniae* infection.
Conclusions Hemolytic uremic syndrome may be an unusual complication of *M. pneumoniae* infection.

Keywords Mycoplasma pneumoniae · Thrombotic microangiopathy · Hemolytic uremic syndrome · Children

Introduction

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two syndromes which are both thrombotic microangiopathies characterized by hemolytic anemia, thrombocytopenia and other manifestations that may include renal and neurological impairment [1]. In its typical form in childhood, HUS is caused by Shiga toxin-producing bacteria, mainly enterohemorrhagic *Escherichia coli* [2], and in some regions *Shigella dysenteriae* type 1. HUS has also been associated with a variety of infectious agents, including *Streptococcus pneumoniae* [3] and viruses such as the Epstein–Barr virus (EBV) or more recently pandemic H1N1 influenza A virus [4].

Mycoplasma pneumoniae is a major causative agent of lower respiratory tract infections in all age groups that occurs worldwide [5]. Although pneumonia is a hallmark of *M. pneumoniae* infection, extrapulmonary manifestations involving almost all organs have been reported. Among these complications, neurological, skin, renal (interstitial nephritis, glomerulonephritis) and hematological (disseminated intravascular coagulation, immune thrombocytopenia, hemolytic anemia) disorders are common [6]. However, although some rare cases of TTP have been reported in adult patients [7, 8], to date *M. pneumoniae* infection has not been associated with childhood HUS.

Case report

A previously healthy 1-year-old boy presented at the pediatric emergency department with a 3-day history of cough and fever. Physical examination revealed a temperature of 39 °C, elevated blood pressure (115/74), normal consciousness, pallor and no purpura. Chest examination was normal. Blood tests the following day revealed a hemoglobin level of 6.6 g/dL, a reticulocyte count of 5 %, platelet count of 140×10^9/L, normal white blood cell count and normal renal function with a serum creatinine value of 25 μmol/L. Hemolytic markers showed a raised lactate dehydrogenase at 706 U/L, reduced

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haptoglobin at 0.15 mg/dL and the presence of 4.5 % schistocytes (Table 1). Coagulation tests were unremarkable, including fibrin degradation products and D-dimer. The direct Coombs test and cold agglutinin test were negative. Urinalysis was positive for blood and protein. The urine protein to creatinine ratio was 378 mg/mmol, and hematuria was confirmed on urine microscopy. Serum complement was normal (CH50 96 %, C3 1180 mg/L, C4381 mg/L). A chest radiograph revealed mild bilateral infiltrate. A renal ultrasonography showed unspecific increased cortical echogenicity. There was no personal or familial history of hematological disorders.

A presumptive diagnosis of thrombotic microangiopathy was made and a diagnostic workup of HUS and TTP was undertaken according to European guidelines [9]. Stool culture on sorbitol MacConkey agar detected no sorbitol-negative *E.coli*, and polymerase chain reaction (PCR) specific for the Shiga toxin genes (stx_1 and stx_2) and the *eae* gene were negative. Moreover, no antibody against lipopolysaccharide of enterohemorrhagic *E. coli* was detected in a serum sample collected on day 1. Hemocultures were negative, and no *S. pneumoniae* antigen was detected in the urine. ADAMTS13 activity was moderately reduced to 17 % of that in normal plasma, with no inhibitory autoantibody identified. Routine complement activation showed no evidence of complement alternative pathway activation (normal C3, C4 and complement factor B levels), mild transient decreased expression of membrane cofactor protein on peripheral leucocytes, no quantitative deficiency of complement factor H and complement factor I and no anti-factor H autoantibody (Table 1). In the meantime, *M. pneumoniae* had been detected in a nasopharyngeal aspirate using an in-house real-time PCR targeting the adhesin P1 gene [10], and a *M. pneumoniae* isolate had grown in Hayflick's modified broth medium from the nasopharyngeal specimen [11]. At the same time, *M. pneumoniae* serology was positive, with specific immunoglobulin M (IgM) detected in a serum sample using the *M. pneumoniae* IgM-ELISA assay (Medac, Hamburg, Germany). The positive PCR result, the positive culture and the presence of specific IgM confirmed an acute *M. pneumoniae* infection. The *M. pneumoniae* strain was examined for macrolide resistance-associated mutations in the 23S rRNA gene using real-time PCR and melting curve analysis [10]. A melting peak characteristic of the wild-type genotype was observed, showing that the strain was susceptible to macrolides. Two *M. pneumoniae* molecular typing methods were also applied on the *M. pneumoniae* isolate. It was categorized as subtype 2 based on the results of PCR–restriction fragment length polymorphism analysis of adhesin P1 and as MLVA type 33562 (alternative designation: MLVA type G) based on multi-locus variable-number tandem repeat analysis (MLVA) [10]. The serology for EBV and cytomegalovirus were also negative.

A diagnosis of acute *M. pneumoniae* infection with HUS was thus made, and the patient was treated with josamycin for 2 weeks. Respiratory symptoms disappeared within 2 days, and the hemoglobin level gradually normalized without red blood cell transfusion. The platelet count steadily increased, exceeding 400×10^9 on day 6. The glomerular filtration rate remained within the normal range, proteinuria normalized within 1 month, and hypertension resolved spontaneously on day 3. ADAMTS13 activity level was 34 % at 1 month post-treatment initiation and 74 % at 1 year. The child remained in clinical remission with normal laboratory evaluation after 12 months of follow-up.

Table 1 Laboratory features of a 1-year-old boy with *Mycoplasma pneumonia*-associated hemolytic uremic syndrome

Parameters	Day 1	Day 2	Day 8	Day 28	Normal range
Hemoglobin (g/dL)	8.1	6.6	8.2	11.9	11.5–14.0
Platelet count (x 10^9/L)	166	140	431	539	150–450
Schistocytes (%)	1.9	4.5	2.5	0	<1
Lactate dehydrogenase (UI/L)	608	706	567	432	180–430
Haptoglobin (mg/dL)	0.39	0.15	0.10	2.36	0.40–1.30
Creatinine (μmol/L)	24	25	21	15	15–32
Urine protein to creatinine ratio (mg/mmol)		378	122	29	0–50
C3 (mg/l)		1180			660–1,250
Membrane cofactor protein expression on peripheral leucocytes (%)		60		80	70–130
Complement factor B (mg/L)		181			90–320
Complement factor I (%)		109			70–130
Complement factor H (%)		119			65–140
Anti-factor H autoantibody		Negative			
ADAMTS13 activity (%)		17		34	<10

Discussion

Mycoplasma pneumoniae is the etiologic agent of approximately 15–20 % of community-acquired pneumoniae cases in children that require hospitalization. Up to 25 % of patients may experience extrapulmonary manifestations [5]. These complications may be diagnosed before, during or after pulmonary manifestations, or they can occur in the absence of any respiratory symptoms. The pathophysiology of extrapulmonary manifestations remains largely unclear. It has been suggested that extrapulmonary manifestations of *M. pneumoniae* infection could involve various possible mechanisms, including direct effects of pro-inflammatory cytokines induced by lipoproteins in the bacterial cell, autoimmunity through cross-reaction between the bacterial cell components and human cells and vascular occlusion due to vasculitis or thrombosis [6]. Our patient met the diagnostic criteria of HUS as established by the Centers for Disease Control and Prevention [12] and may be the first reported case of HUS complicating a *M. pneumoniae* respiratory tract infection. Diarrhea-negative HUS usually has a worse renal prognosis than HUS caused by a Shiga toxin. Our 1-year-old patient, however, had very mild renal impairment and did very well with minimal treatment.

M. pneumoniae has been mentioned in two other reports of HUS, but one of the patients described exhibited hemolytic anemia due to anti-P autoantibody [13] and a *M. pneumoniae* infection could not be confirmed in another patient with cold agglutinin disease [14]. A possible differential diagnosis of HUS is autoimmune hemolytic anemia, which has been described as a severe complication of *M. pneumoniae* infection and which occurs more often in children than in adults. The mechanism of intravascular hemolysis has been attributed to cold agglutinin disease characterized by the presence of circulating autoantibodies, usually IgM, directed against red blood cells. In our patient, however, the combination of hemolytic anemia, mild thrombocytopenia, nephrotic range proteinuria, with negative cold agglutinin blood test led us to rule out autoimmune hemolytic anemia and consider HUS. Moreover, normal coagulation tests and a modest decrease in the platelet count made other *M. pneumonia*-associated hematological disorders, like disseminated intravascular coagulation and immune thrombocytopenia, very unlikely.

The symptoms of this child led us to consider several etiological hypotheses: (1) an atypical HUS caused by preexisting complement dysregulation and triggered by *M. pneumoniae* infection, (2) a complement alternative pathway activation induced by *M. pneumoniae* infection at the acute phase, (3) an autoimmune mechanism and (4) a direct role of the bacteria in inducing endothelial injury.

Infectious triggers for atypical HUS due to disordered complement regulation have been postulated in the literature. In our case, atypical HUS triggered by *M. pneumoniae* infection was unlikely since adequate investigations of the complement system showed no underlying defect. However, although no abnormality could be detected, the role of complement dysregulation as a susceptibility factor for atypical HUS cannot be completely excluded.

Another hypothesis would be activation of the alternative complement pathway at the acute phase induced by *M. pneumoniae* itself, as documented in HUS caused by a Shiga toxin. The identification of some cases of acute postinfectious glomerulonephritis with transient hypocomplementemia (low C3) associated with *M. pneumoniae* suggests transient complement activation [15, 16]. However, screening for complement activation at admission was unremarkable in our patient.

As autoimmune disorders associated with *M. pneumoniae* infection have been reported, the immune mechanism has also been considered a justifiable target in investigations on TTP and anti-factor H autoantibody. Acute *M. pneumoniae* infection has been reported to be an initiating cause of TTP in adults [7, 8]. It has been suggested that TTP associated with *M. pneumoniae* infection may be the result of cross-reactive antibodies inactivating plasma von Willebrand factor-cleaving protease (ADAMTS13) [8]. In our patient, ADAMTS13 activity was reduced to 17 % of normal levels during acute disease, but it remained above the level which unequivocally establishes a diagnosis of TTP (<5 %), and no anti-ADAMTS13 autoantibody was detected. However, patients with acquired TTP may present with clinical and laboratory heterogeneity, and there are cases of TTP with moderate or mild ADAMTS13 deficiency (10–40 % of normal). These cases are usually those secondary to other diseases or conditions. It is also known that patients with thrombotic microangiopathies other than TTP may also present with moderately reduced levels of ADAMTS13. Moreover, the absence of anti-factor H autoantibody allowed ruled out an acquired atypical HUS triggered by *M. pneumoniae*.

Finally, one last hypothesis was a possible direct role of *M. pneumoniae* in inducing vascular endothelial cells lesions. We can speculate that a sialidase could play a role by unmasking Thomsen–Friedenreich antigen, as in pneumococcal HUS. However, no sialidase activity has been detected to date in isolates of *M. pneumoniae* from patients with community-acquired pneumonia [17]. A possible involvement of sialidase in extra-respiratory manifestations of *M. pneumoniae* remains to be investigated.

In conclusion, even if the precise mechanism by which HUS developed in our patient is unknown, our report suggests that *M. pneumoniae* is an unusual cause of HUS. The availability of a routine PCR-based assay for *M. pneumoniae* might be of help in the diagnostic work-up of HUS associated with lower respiratory tract infection.

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References

1. Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, Rizzoni G, Taylor CM, Van de Kar N, Zimmerhackl LB, European Paediatric Research Group for HUS (2006) A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int 70:423–431
2. Karmali MA, Petric M, Lim C, Fleming PC, Arbus GS, Lior H (1985) The association between idiopathic hemolytic uremic syndrome and infection by verotoxin-producing *Escherichia coli*. J Infect Dis 151:775–782
3. Copelovitch L, Kaplan BS (2010) Streptococcus pneumoniae-associated hemolytic uremic syndrome: classification and the emergence of serotype 19A. Pediatrics 125:e174–e182
4. Allen U, Licht C (2011) Pandemic H1N1 influenza A infection and (atypical) HUS: more than just another trigger? Pediatr Nephrol 26:3–5
5. Atkinson TP, Balish MF, Waites KB (2008) Epidemiology, clinical manifestations, pathogenesis and laboratory detection of *Mycoplasma pneumoniae* infections. FEMS Microbiol Rev 32:956–973
6. Narita M (2010) Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia. J Infect Chemother 16:162–169
7. Cameron D, Welsby P, Turner M (1992) Thrombotic thrombocytopenic purpura due to *Mycoplasma pneumoniae*. Postgrad Med J 68:393–394
8. Bar Meir E, Amital H, Levy Y, Kneller A, Bar-Dayan Y, Shoenfeld Y (2000) *Mycoplasma-pneumoniae*-induced thrombotic thrombocytopenic purpura. Acta Haematol 103:112–115
9. Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, Licht C, Loirat C, Pecoraro C, Taylor CM, Van de Kar N, Vandewalle J, Zimmerhackl LB, European Paediatric Study Group for HUS (2009) Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. Pediatr Nephrol 24:687–696
10. Pereyre S, Touati A, Petitjean-Lecherbonnier J, Charron A, Vabret A, Bébéar C (2013) The increased incidence of *Mycoplasma pneumoniae* in France in 2011 was polyclonal, mainly involving *M.pneumoniae* type 1 strains. Clin Microbiol Infect 19:E212–E217
11. Hayflick L, Stanbridge E (1967) Isolation and identification of mycoplasma from human clinical materials. Ann N Y Acad Sci 143:608–621
12. Centers for Disease Control and Prevention (1997) Case definitions for infectious conditions under public health surveillance. MMWR Recomm Rep 46:1–55
13. Fitzpatrick MM, Walters MD, Trompeter RS, Dillon MJ, Barratt TM (1993) Atypical (non-diarrhea-associated) hemolytic-uremic syndrome in childhood. J Pediatr 122:532–537
14. Bugajer-Gleitman HE, Balzar E, Lubec G, May L, Weissenbacher G (1976) The presence of cold agglutinins in hemolytic uremic syndrome. Padiatr Padol 11:245–253
15. Siomou E, Kollios KD, Papadimitriou P, Kostoula A, Papadopoulou ZL (2003) Acute nephritis and respiratory tract infection caused by *Mycoplasma pneumoniae*: case report and review of the literature. Pediatr Infect Dis J 22:1103–1106
16. Adra AL, Vigue MG, Dalla Vale F, Ichay L, Raynaud P, Mariani A, Morin D (2010) Favorable outcome in a case of *Mycoplasma pneumoniae*-associated crescentic glomerulonephritis. Pediatr Nephrol 25:1765–1969
17. May M, Brown DR (2011) Retrospective survey for sialidase activity in *Mycoplasma pneumoniae* isolates from cases of community-acquired pneumonia. BMC Res Notes 4:195