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CASE REPORT

Thrombotic microangiopathy after a invasive pneumococcal serotype 19A infection in a child vaccinated with 10-valent pneumococcal conjugate vaccine: case report

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Abstract

Objective: The pneumococcal disease is an important public health problem and the association with Hemolytic-Uremic Syndrome (HUS) is serious, but rare. The objective of the article is to report the case of a patient with this association and a complete vaccination schedule. **Case report:** Female infant, admitted with acute respiratory failure, secondary to pneumonia complicated with pleural effusion, presented positive fluid culture for *Streptococcus pneumoniae* serotype 19A. She developed anemia associated with schistocytes in peripheral blood, thrombocytopenia and acute kidney injury (AKI) requiring renal replacement therapy. **Discussion:** HUS associated with pneumococcus still presents high morbidity and mortality. In children with invasive pneumococcal infection associated with hematological and/or severe kidney disease, one must be aware of this complication. The following aspects related to the disease deserves attention: early identification and diagnosis to establish therapy, the ideal method of renal replacement and definition of long-term prognosis. The role of serotype 19A in increasing the rate of this complication is not yet well established. Work approved by the ethics committee, CAAE nº 77186223.9.0000.5129. There is no conflict of interest.

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INTRODUCTION

Thrombotic microangiopathy (TMA) results in occlusion of blood vessels by platelet-rich thrombi, leading to consumption thrombocytopenia and hemolytic anemia. These changes associated with fragmentation of red blood cells in the microvasculature, with formation of schistocytes, are essential for suspicion of the disease. Increased lactate dehydrogenase (LDH) levels, negative Coombs test, and normal coagulation profile may also be present.¹

One of the most important causes of TMA with consequent AKI in pediatrics is Hemolytic Uremic Syndrome (HUS), whose classic etiology is infection by *Escherichia coli* O157:H7 producing shiga toxin. HUS can also be triggered by infection with *Streptococcus pneumoniae* and it is therefore referred to as Atypical Hemolytic Uremic Syndrome due to *Streptococcus pneumoniae* (aHUS-Sp)¹⁻³.

Regarding pneumococcal disease, there is a broad spectrum of presentations in children and it is the most frequent cause of invasive bacterial disease in children under two years of age after the introduction of vaccines against *Haemophilus influenzae* type B and meningococcus. aHUS-Sp is a rare complication of invasive infection, but it has a high morbidity and mortality rate.^{3,4}

Since 2010, the National Immunization Program (PNI) calendar has recommended childhood vaccination with the 10-valent pneumococcal conjugate vaccine (PCV-10), with a three-dose schedule: two in the first year of life and a booster dose at 12 months of age. In 2013, the National Immunization Program incorporated the 13-valent pneumococcal conjugate vaccine (PCV-13) for specific patients⁵⁻⁷.

CASE REPORT

A 9-month-old female infant, previously healthy, with adequate vaccination according to the National Immunization Program (PCV10), was admitted with flu-like symptoms that evolved over three days and had progressively worsened. Complementary investigations revealed complicated pneumonia with pleural effusion (PE), leukocytosis, and increased inflammatory tests (CRP and LDH) (figure 1) (table 1). Antibiotic therapy with amoxicillin-sulbactam was initiated according to the institutional protocol, with noninvasive ventilatory support and chest drainage.

The patient developed respiratory failure, AKI KDIGO3, with oliguria and uremia; anemia, thrombocytopenia and comparative worsening of inflammatory tests. Antibiotic therapy was changed to Oxacillin+Ceftriaxone and she was referred to the intensive care unit under the hypothesis of aHUS-Sp with a pulmonary focus caused by *Streptococcus pneumoniae* subtype 19A, identified and typed in pleural fluid culture.

She remained in the pediatric intensive care unit for two months, on invasive ventilation for 26 days and renal replacement therapy. She required multiple transfusions of blood components, hemodynamic instability requiring vasoactive support, in addition to cholestatic jaundice with changes

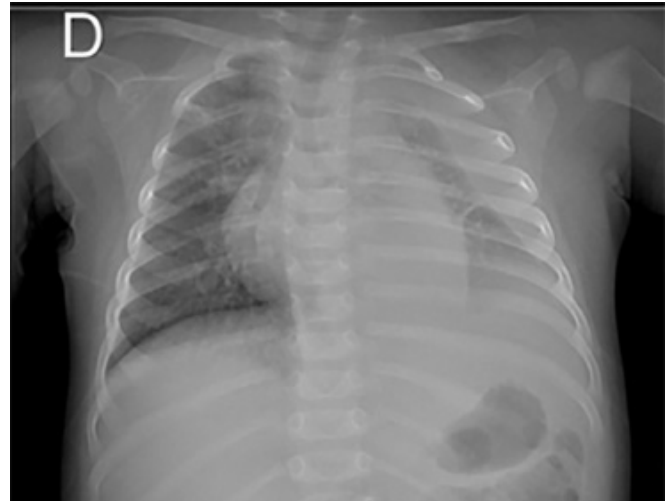


Figure 1. Chest radiograph showing hypotransparent lung parenchyma on the left, with opacity of the ipsilateral costophrenic sinus and deviation of the mediastinum and trachea to the contralateral side.

to her liver function and neurological manifestations, such as seizures and hypertonia. After stabilization, she evolved to chronic kidney disease (CKD) stage 3b.

DISCUSSION

The initial evaluation of a patient with suspected TMA should be careful to differentiate primary syndromes from other secondary systemic disorders. The most common primary causes are idiopathic thrombocytopenic purpura and HUS, and the importance of differentiation is justified by the difference in treatment.⁸

Sp-HUS occurs due to inadequate activation of the complement system through the stimulus generated by neuraminidase, an enzyme capable of cleaving n-acetyl-neuraminic acid, a constituent of the glycoproteins of the cell membranes of endothelial cells, platelets, red blood cells, and glomerular cells. The T-antigen is also present in hepatocytes, justifying the transient liver dysfunction in some patients^{3,6,8-10}.

All pneumococcal serotypes can produce neuraminidase, but the ones most associated with aHUS-Sp are 14, 6B, 9V, 19, 3, 8, 23F and 19A. Each serotype is capable of producing different amounts of this enzyme with different metabolic activity, and the risk of developing aHUS-Sp is greater the greater the bacterial load present.^{9,10}

Patients with aHUS-Sp frequently present pneumonia associated with empyema or PD. The average age is between 1-2 years and the initial disease presentation is severe. Oliguria is usually prolonged, requiring renal replacement therapy. Severe anemia and thrombocytopenia require frequent blood transfusions. Extrarenal complications include cholecystitis, pancreatitis, thrombosis, cardiac dysfunction, and hearing loss, as observed in this case.¹¹

The primary focus of pneumococcal infection should be treated with appropriate antibiotics. Intravenous ampicillin, penicillin G, or amoxicillin are the first choice for hospitalized

Table 1. Evolution of the most relevant laboratory tests during hospitalization.

Days of hospitalization	2nd	6th	15º	24º	30º	44º	48º
(HD onset)	15th	24th	30th	44th	48th	11,2	6,9
Hemoglobin (g/dL)	5.4	9.0	7.0	11.2	10.7	11.2	6.9
Hematocrit (%)	15.4	25.6	21.6	36.2	29.3	32.9	21.9
Leucocytes/mm ³	9080	23510	14360	25740	19940	21440	27500
Platelets/mm ³	30000	169000	26000	48000	785000	255000	492000
INR	x	1.36	1.03	2.36	1.02	1.00	1.18
Creatinine (mg/dL)	2.3	4.0	2.0	1.2	1.4	1.1	1.1
Urea (mg/dL)	169	213	137	105	195	122	130
Bilirubin total and direct (mg/dL)	x	x	x	2.8 1.8	6.5 5.2	5.9 4.2	x
AST ALT (U/L)	x	285 251	x	56 20	299 220	60 105	x
Alcaline phosphatase (U/L)	x	x	x	1972	3425	1864	x
Gama GT (U/L)	x	x	x	1033	12816	1477	x
C-Reactive protein (mg/dL)	151	92	103	x	57	x	x
Lactate dehydrogenase (U/L)	x	7630	x	x	1634	x	x

patients under five years of age. In complicated pneumonias with severe progression despite antibiotic use, with PD, empyema, necrotizing pneumonia, or lung abscess, treatment should be individualized. In cases of PD, it is necessary to quantify its volume and qualify its stage for the correct approach, whether expectant, chest drainage, video-assisted thoracoscopy, or fibrinolytics.¹²

Treatment of HUS includes clinical support to maintain patient stability. Renal replacement therapy, management of fluid overload, and hydroelectrolytic corrections are usually necessary. Anemia and thrombocytopenia should also be corrected with blood components.^{6,13}

Morbidity and mortality related to aHUS-Sp have decreased over the years with advances in supportive care and early diagnosis. The mortality rate is approximately 11-16% and is higher in the acute phase of the disease, especially in patients with invasive pneumococcal meningitis. Approximately 25-45% of patients develop CKD, and the most important risk factors for this sequela are the severity of AKI and the need for renal replacement therapy for more than 20 days in the acute phase.⁶

An important issue to be considered regarding invasive pneumococcal diseases is the decrease in their prevalence in several countries during the COVID-19 pandemic. Isolation and personal hygiene measures have led to a decrease in the transmission and contagion of respiratory viruses and bacteria in general, including pneumococcus. These measures to contain the spread of the coronavirus have led to a decrease in nasopharyngeal colonization by pneumococci, resulting in a decrease in innate immunity. As social distancing measures and encouragement of personal hygiene have been relaxed, children have returned to having contact with microorganisms

transmitted by the respiratory tract, but without the necessary natural immunity needed to prevent serious invasive diseases.⁵

Currently, in Brazil, two pneumococcal conjugate vaccines are available: PCV-10 and PCV-13. The first provides protection against bacterial serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, and the second provides protection against the same serotypes, plus 3, 6A and 19A. However, PCV-13 is available through the public healthcare system - SUS, but is restricted to immunosuppressed individuals. The immunobiological widely distributed as routine in childhood immunization is PCV10.^{5,6}

The PNI is one of the most comprehensive immunization programs in the world and ensures vaccination coverage for several diseases, including pneumococcal diseases. PCV-10 is available through the SUS, with an estimated 95% reduction in pneumococcal diseases caused by vaccine serotypes in the pediatric population under 5 years of age, compared to the pre-vaccination period. Widespread adherence to vaccination caused selective pressure and resulted in a change in the serotypes identified in invasive diseases, with an increase in those without coverage, mainly 3 and 19A.⁵

Correlating the literature with the reported case, the patient had received PCV-10 as recommended by the PNI, but the invasive pneumococcal disease was caused as a consequence of infection by serotype 19A, present only in PCV-13. The main consequence of this infection was aHUS-Sp with its classic complications.

FINAL CONSIDERATIONS

Although the pneumococcal serotype most frequently associated with aHUS-Sp is not reported in the literature, the

patient had a complete vaccination schedule according to the PNI, but with an unfavorable evolution caused by serotype 19A. This corroborates the importance of epidemiological surveillance that allows us to understand the behavior of circulating serotypes in the Brazilian population and the continuous incorporation of more comprehensive vaccines into the national calendar.

Additionally, the National Commission for the Incorporation of Technologies into the Brazilian Public Healthcare System – SUS (CONITEC) published a report in November 2022 regarding the critical analysis of the scientific evidence on PCV13 for the prevention of invasive pneumococcal disease in patients up to 5 years of age, aiming to evaluate its expanded use in the SUS. It was possible to observe that there is favorable evidence for the effect of PCV13 in comparison to PCV10, but it is still necessary to compare the effectiveness of the vaccines in relation to the population result of the global vaccination strategy so that there is complete replacement of PCV10 by PCV13.

REFERENCES

1. Thompson GL, Kavanagh D. Diagnosis and treatment of thrombotic microangiopathy. *Int J Lab Hematol* [Internet]. 2022[citado 16 de novembro de 2023];44(S1):101–13. Disponível em: <http://dx.doi.org/10.1111/ijlh.13954>
2. Vilardouro AS, Cachão J, Rodrigues M, Durão F, Costa-Reis P, Sandes AR, et al. Hemolytic-uremic syndrome: 24 years' experience of a pediatric nephrology unit. *J Bras Nefrol* [Internet]. 2022 [citado 16 de novembro de 2023];45(1):51–9. Disponível em: <https://encr.pw/N9Lge>
3. Cestari AL de O, Vilela R, Kunisawa J, Lopes CE. Síndrome hemolítico-urêmica relacionada à infecção invasiva pelo *Streptococcus pneumoniae*. *Rev Paul Pediatr* [Internet]. 2008 [citado 16 de novembro de 2023];26(1):88–92. Disponível em: <https://www.scielo.br/j/rpp/a/VgYkXxJmNVHzR55DTPvKpRt/>
4. Ferreira M, Oliveira H, Silva NC e., Januário L, Rodrigues F. Doença Invasiva Pneumocócica Pediátrica Antes da Vacinação Universal: 1995 - 2015. *Acta Med Port* [Internet]. 2017 [citado 16 de novembro de 2023];30(6):457–62. Disponível em: <https://estudogeral.uc.pt/handle/10316/102202>
5. Vieira LMN. Pneumonia em crianças: novo desafio no ano de 2022. *Rev Médica Minas Gerais* [Internet]. 2022 [citado 16 de novembro de 2023];32(Supl 11):29–33. Disponível em: <https://rmmg.org/artigo/detalhes/3962>
6. Agarwal HS, Latifi SQ. Streptococcus Pneumoniae-Associated Hemolytic Uremic Syndrome in the Era of Pneumococcal Vaccine. *Pathogens* [Internet]. 2021 Jun 9[citado 20 de dezembro de 2023];10(6):727. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8227211/>
7. Sociedade Brasileira de Imunizações. Calendário Nacional de Vacinação da Criança [Internet]. Agosto/2023[citado em 20 de dezembro 2023]. Disponível em: <https://sbim.org.br/calendarios-de-vacinacao>
8. George JN, Nester CM. Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA). Em: UpToDate [Internet]. Julho/2023[citado em 20 de dezembro 2023]. Disponível em: <https://encr.pw/mR4gu>
9. Copelovitch L, Kaplan BS. Streptococcus pneumoniae-associated hemolytic uremic syndrome. *Pediatr Nephrol* [Internet]. 2008 [citado 16 de novembro de 2023];23(11):1951–6. Disponível em: <http://dx.doi.org/10.1007/s00467-007-0518-y>
10. Battista M, Hoffmann B, Bachelot Y, Zimmermann L, Teuber L, Jost A, et al. The role of pneumococcal extracellular vesicles on the pathophysiology of the kidney disease hemolytic uremic syndrome. *mSphere* [Internet]. 2023[citado em 20 de dezembro 2023];8(4). Disponível em: <http://dx.doi.org/10.1128/msphere.00142-23>
11. Niaudet P, Boyer OG. Overview of hemolytic uremic syndrome in children [Internet]. UpToDate. Outubro/2023 [citado 05 de janeiro de 2024]. Disponível em: <https://acesse.dev/SmMgS>
12. Nascimento-Carvalho CM. Community-acquired pneumonia among children: the latest evidence for an updated management. *J Pediatr (Rio J)* [Internet]. 2020 [citado 05 de janeiro de 2024];96(Supl 1):29–38. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/31518547/>
13. Polito MG, Kirsztajn GM. Microangiopatias trombóticas: púrpura trombocitopênica trombótica e síndrome hemolítico-urêmica. *J Bras Nefrol* [Internet]. 2010 [citado em 5 de janeiro de 2024];32(3):303–15. Disponível em: <https://www.scielo.br/j/jbn/a/zP9NxG6NfB5fRDjSL9SbQvM/?lang=pt>