Sepsis due to *Streptococcus pneumoniae* associated with secondary hemophagocytic lymphohistiocytosis in a splenectomized patient for spherocytosis

A case report

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Abstract

**Rationale:** Hemophagocytic lymphohistiocytosis (HLH) is a syndrome that is characterized by an inappropriate hyperinflammatory immune response – primary, as a consequence of a genetic defect of NK cells and cytotoxic T lymphocytes or – secondary, in the progression of infections, rheumatic or autoimmune diseases, malignancies or metabolic diseases.

**Patient concerns:** We present the case of a secondary HLH due to *Streptococcus pneumoniae* infection in a splenectomized patient for spherocytosis, a 37-year-old patient who was splenectomised in childhood for spherocytosis, without immuneprophylaxis induced by antipneumococcal vaccine.

**Outcomes:** He developed a severe pneumococcal sepsis associated with secondary HLH, with unfavorable outcome and death.

**Lessons:** To our knowledge, just 2 similar cases had been published in the literature, none in which the secondary HLH was the consequence of an invasive pneumococcal infection in a splenectomized patient for spherocytosis, and the association of splenectomy with HLH is surprizin.

**Abbreviation:** HLH = hemophagocytic lymphohistiocytosis.

**Keywords:** hemophagocytic lymphohistiocytosis, HLH, splenectomized patient, *Streptococcus pneumoniae*

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome that is characterized by an inappropriate hyper-inflammatory immune response – primary, as a consequence of a genetic defect of NK cells and cytotoxic T lymphocytes or – secondary, in the progression of infections, rheumatic or autoimmune diseases, malignancies or metabolic diseases. Among HLH-related infections, the most common are the viral infections: Epstein–Barr virus, cytomegalovirus, other herpes viruses, the viruses of hepatitis B and C, etc., followed by bacterial, parasitic, or fungal infections. Association of secondary HLH to *Streptococcus pneumoniae* infection in a patient splenectomized for spherocytosis has not been described so far.

2. Case report

We present the case of a male Caucasian patient, aged 37 years, splenectomized for spherocytosis since the age of 4, with no prophylaxis of meningococcal, and pneumococcal infections through vaccination, that was brought to the emergency room for fever, diarrhea, vomiting, rash skin, myalgia, anuria, and marked alteration of his general condition. At the time of admission, on physical examination, the following changes were noticed: facial erythema, purpura on the legs (see Fig. 1), cyanosis of the extremities, jaundice, left basilar crackles, heart rate of 130 beats per minute, blood pressure of 140/100 mm Hg, hepatomegaly, and anuria. The laboratory investigations that were performed revealed the following alterations (at admission and in evolution) that are presented in Table 1.

Peripheral smear revealed normochromic normocytic red blood cells, as well as microspherocytes and spherocytes, frequent polychromatophilic macrocytes; erythrocytes with Howell–Jolly bodies (splenectomy), rare dacrocytes (teardrop cells), and schistocytes. Polymorphonuclears with vacuolated cytoplasm are present (toxic appearance), diplo-, encapsulated, and intra- and extracellular gram-positive cocci. Bone marrow sample was harvest and on hematoxylin-eosin stain an increased number of activated macrophages with prominent hemophagocytosis of hematopoietic elements was revealed. Blood cultures
Laboratory studies.

| Parameter                  | Values                                          |
|----------------------------|------------------------------------------------|
| **Parameter**              | **Day 1**                                      | **Day 2**                                      | **Day 7**                                      | **Day 15**                                     | **References value**                           |
| WBC                        | 5.0 x 10^9/mL                                  | 5.0 x 10^9/mL                                  | 3.6 x 10^9/mL                                  | 3.6 x 10^9/mL                                  | 4-10 x 10^9/mL                                 |
| Differential blood count   |                                                |                                                |                                                |                                                |                                                |
| Neutrophils                | 95%                                            | 95%                                            | 82%                                            | 82%                                            | 1-70%                                         |
| Lymphocytes                | 4%                                             | 4%                                             | 16%                                            | 16%                                            | 4-5%                                          |
| Monocytes                  | 4%                                             | 4%                                             | 1%                                             | 1%                                             | 0-10%                                         |
| Eosinophils                | 0%                                             | 0%                                             | 2%                                             | 2%                                             | 0-1.5%                                        |
| Hemoglobin                 | 12.8 g/dL                                      | 10.8 g/dL                                      | 8.5 g/dL                                       | 8.5 g/dL                                       | 13-17 g/dL                                    |
| Thrombocytes               | 56 x 10^9/mL                                   | 76 x 10^9/mL                                   | 48 x 10^9/mL                                   | 28 x 10^9/mL                                   | 150-400 x 10^9/mL                             |
| AST                        | 1419 U/L                                       | 1922 U/L                                       | 982 U/L                                        | 159 U/L                                        | 10-40 U/L                                     |
| ALT                        | 605 U/L                                        | 584 U/L                                        | 253 U/L                                        | 77 U/L                                         | 10-41 U/L                                     |
| Total bilirubin            | NA                                             | 7.39 mg/dL                                     | 2.25 mg/dL                                     | NA                                             | 0.2-1.2 mg/dL                                 |
| Direct bilirubin           | NA                                             | 4.45 mg/dL                                     | 2.00 mg/dL                                     | NA                                             | 0-0.3 mg/dL                                   |
| LDH                        | 2312 U/L                                       | 5488 U/L                                       | 150 U/L                                        | 380 U/L                                        | 136-145 U/L                                   |
| CPK                        | 2303 U/L                                       | 4072 U/L                                       | 16,417 U/L                                     | 15,731 U/L                                     | 39-308 U/L                                    |
| Fibrinogen                 | 107.8 mg/dL                                    | 71.1 mg/dL                                     | 86.9 mg/dL                                     | 85.2 mg/dL                                     | 180-380 mg/dL                                 |
| Ferritin                   | NA                                             | +                                              | +                                              | Neg                                            | Absent                                        |
| Glyceria                   | 35 mg/dL                                       | 96 mg/dL                                       | 150 mg/dL                                      | 380 mg/dL                                      | 74-106 mg/dL                                  |
| BUN                        | 90 mg/dL                                       | 131 mg/dL                                      | 309 mg/dL                                      | 433 mg/dL                                      | 16-48 mg/dL                                   |
| Creatinine                 | 5.58 mg/dL                                     | 6.66 mg/dL                                     | 9.65 mg/dL                                     | 10.25 mg/dL                                    | 0-7.1 mg/dL                                   |
| Cholesterol                | 117 mg/dL                                      | 102 mg/dL                                      | 102 mg/dL                                      | NA                                             | 109-202 mg/dL                                 |
| Triglycerides              | NA                                             | 267 mg/dL                                      | 288 mg/dL                                      | NA                                             | 50-160 mg/dL                                  |
| Total proteins             | 4.9 g/dL                                       | 6.3 g/dL                                       | 4.9 g/dL                                       | NA                                             | 6-8.3 g/dL                                    |
| PT                         | 31 sec                                         | 27 sec                                         | 19.4 sec                                       | 14.3 sec                                       | 9.8-12.2 sec                                  |
| INR                        | 2.57                                           | 2.04                                           | NA                                             | 2.39                                           | 0.86-1.1                                      |
| APPT                       | 100.2 sec                                      | 157 sec                                        | 70 sec                                         | 216 sec                                        | 24-36                                         |

ALT = aspartate aminotransferase, APPT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CPK = creatine phosphokinase, INR = international normalized ratio, LDH = lactate dehydrogenase, NA = not available, PT = prothrombin time, WBC = white blood cell.
biopsies taken during the anatomopathological examination revealed the following changes: massive infiltration of portal tract and sinusoids by mononuclear cells. The CD68 stain shows numerous large, irregularly shaped CD68+ cells as being macrophages, cells that are localized both in the portal tract and sinusoids, and with an increased phagocytic activity on lymphocytes, erythrocytes, and polymuclear cells. On CD8 stain, numerous CD8+ lymphocytes were revealed. The conclusion was: the described aspect is in concordance with the diagnosis of hemophagocytic lymphohistiocytosis. Autopsy examination also revealed bilateral renal papillae necrosis secondary to myoglobinuria, and the presence of hemophagocytosis in bone marrow, and lymph nodes Figs. 2–4.

3. Discussions

This case brings into question the risk of splenectomised patients to develop severe systemic infections with encapsulated bacteria, against which the vaccine prophylaxis is essential – for S. pneumoniae, H. influenzae, and Meningococcus. Lack of vaccination in this patient has enabled the development of severe infections with multidrug-resistant S. pneumoniae and the induction of secondary HLH, characterized by an uncontrolled inflammatory response, resulting in patient’s death.

Primary HLH has a family, autosomal recessive transmission, and is present in 50,000 new-borns annually. Secondary HLH may be induced by viral (29%), bacterial, or parasitic infections (20%), autoimmune or rheumatic diseases (7%), cancers (27%), and metabolic diseases or immunodeficiency syndromes (6%).

Among viral causes, the most common is associated with Epstein–Barr virus. There are also described associations with cytomegalovirus, herpes simplex,[2,3] varicella-zoster virus,[4] herpes virus 8, and associated with HIV infection.[5] There were also published associations with hepatitis B and C viruses,[6,7] influenza viruses,[8] enteroviruses,[9] rotavirus, severe acute respiratory syndrome virus,[10] hemorrhagic fevers,[11–15] HIV,[15–18] and so on. Among bacterial infections associated with HLH, there were published associations with Borrelia,[19], Babesia sp,[20] Bartonella sp,[21] Brucella sp,[22] Q fever,[23] Leptospira sp,[24] Listeria monocytogenes,[25] Mycoplasma pneumoniae,[26] and mycobacteria.[27–32] The most frequently described parasitic causes responsible for secondary HLH are: Leishmania sp,[33,34] malaria,[35–37] and Toxoplasma gondii.[38,39] Fungal infections are found to be associated with secondary HLH in HIV-infected patients such as Cryptococcus neoformans,[40] Candida spp,[41] or in patients with renal transplantation-association with disseminated histoplasmosis.[42]

Of the defining HLH criteria established by the Histioocyte Society, respectively, fever, splenomegaly, cytopenia (on at least 2 lines in peripheral blood), hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, presence of hemophagocytosis in bone marrow or lymph node, reduction/absence of NK cells activity, and increase in the concentration of soluble IL-2 receptor, CD25,[43] the patient had 5 defining criteria for HLH. The presence of consumption coagulopathy evidenced by the presence of fibrin degradation products is associated with hypofibrinogenemia and thrombocytopenia in HLH, as well as the liver damage-elevated transaminases, hyperbilirubinemia, activated partial thromboplastin time prolongation. These changes are also

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Figure 2. Hematoxylin and eosin-stained sections of liver. Magnifications: ×40 (A) and ×100 (B).

Figure 3. Hematoxylin and eosin-stained sections of kidney. Magnifications: ×40 (A) and ×100 (B).
Table 2
Clinical and biological characteristics of the 3 cases with HLH due to S pneumoniae.

| #  | 1                              | 2                              | 3                              |
|----|--------------------------------|--------------------------------|--------------------------------|
| Author | Our case | Dalle et al[45] 1995 | Ondruschka et al[46] 2016 |
| Sex | M | M | M |
| Age, y | 37 | 8 | 25 |
| BMI/general and nutritional condition | 22.4 kg/m² | NA | 12.9 kg/m² Extremely poor general and nutritional condition |
| Fever | Yes | Yes | Yes |
| Organomegaly (liver, spleen) | Yes | Yes | Yes |
| Hemoglobin | Yes | NA | No |
| <9 g/dL | Yes | NA | |
| Platelets | Yes | NA | Yes |
| <100,000/μL | No | Yes | Yes |
| Neutrophils | <1000/μL | Yes | Yes |
| Hypertriglyceridemia ≥265 mg/dL | Yes | Yes | Yes |
| Ferritin ≥500 ng/mL | Yes | NA | NA |
| Hemophagocytosis, any involved organ | Yes | Yes | Yes |
| Natural killer cell activity, low or absent | NA | NA | NA |
| Soluble IL-2 receptor ≥2400 U/mL | NA | NA | NA |
| CRP reactive protein, normal range <5 mg/L | 117.74 | NA | 74.6 mg/L |
| HIV | Negative | Yes | Negative |
| Epstein–Barr nuclear antigen 1 antibody serology | Negative | NA | Positive |
| Epstein–Barr virus viral capsid antigen | Negative | NA | Negative |
| Cytomegalovirus IgG antibody | Negative | Negative | Negative |
| Herpes simplex virus 1/2 IgG antibody | Negative | Negative | Negative |
| Site of infection | Sepsis | Ears | Lungs |
| S pneumoniae | Multiresistant | Multiresistant | Multisensitive |
| Outcome | Death | Rapid improvement of his condition with adapted antibiotherapy | Death |

BMI = body mass index, HIV = human immunodeficiency virus, HLH = hemophagocytic lymphohistiocytosis, IgG = immunoglobulin G, M = male, NA = not available.

Figure 4. May–Grünewald Giemsa-stained sections of bone marrow. Magnifications: ×100 (A–D).
present within the septic context, their strict delimitation is not possible.

Although the diagnosis of HLH was early, the administration of dexamethasone, intravenous immunotherapy, and administration of etoposides have not improved prognosis, the patient’s death occurring on the 15th day of hospitalization. Renal insufficiency due to bilateral renal papillary necrosis has been associated with myoglobinuria as a result of septic myositis, demonstrated by high levels of creatine phosphokinase. There have been described situations in which S pneumoniae infections are responsible for the death of patients with primary HLH.[44] Two cases of HLH associated with a pneumococcal infection had been published (see Table 2). HLH association with hereditary spherocytosis is found in association with viral infections, such as parvovirus B19[47] or Epstein–Barr virus. Moreover, splenectomy is described as a therapeutic method in refractory HLH cases.[48–50]

3.1. Informed consent

Written informed consent was obtained from the patient’s next of kin (from his father) for publication of this case report and any accompanying images. The study was accepted by the Ethics Committee of the hospital and they encouraged publishing the article. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

4. Conclusion

The association of sepsis due to S pneumoniae with secondary HLH in a splenectomized patient for spherocytosis should be taken into consideration in similar cases like ours. To our knowledge, no similar cases had been published in the literature, in which the secondary HLH was the consequence of an invasive pneumococcal infection in a splenectomized patient for spherocytosis, and the association of splenectomy with HLH is surprising. Other similar observations are necessary in the future.

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