

Case report

Acute cholecystitis associated with pneumococcal bacteremia and purpura fulminans

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SUMMARY

The case of a previously healthy 47-year-old woman who was admitted to our hospital with symptoms of acute abdomen, septic shock and cutaneous rash is presented. The U.S. revealed cholelithiasis, cholecystitis and pericholecystitis and the patient was immediately treated by surgical removal of the gall bladder. In the blood culture a penicillin-susceptible strain of *Streptococcus pneumoniae* (*Pneumococcus*) was isolated. After surgery the patient was transferred to I.C.U. where she presented M.O.D.S. (Multiple Organs Failure Syndrome) and D.I.C. (Disseminated Intravascular Coagulation). She died two days later despite pharmacologic therapy and mechanical support, of respiratory and renal failure.

To our knowledge, this is a very rare case of acute cholecystitis associated with pneumococcal bacteremia (we found only five similar cases in the literature). Pneumococcal septic shock is usually associated with immunosuppression or asplenism (surgical or functional). In our patient functional hyposplenism was diagnosed by identification of Howell-Jolly bodies in the peripheral blood smear.

Key words: Pneumococcal bacteremia, *S. pneumoniae* bacteremia, purpura fulminans, acute cholecystitis.

INTRODUCTION

S. pneumoniae (*Pneumococcus*) is a common etiologic agent of community acquired pneumonia, bacteremia, meningitis, sinusitis and otitis media.

Invasive pneumococcal infection is a serious disease that usually occurs at the extremes of age (children and elderly population) and is associated with some predisposing illnesses. Alcoholism, HIV infection, splenectomy, connective tissue diseases, steroid use, diabetes mellitus and intravenous drug use, remain the most common risk factors for invasive pneumococcal infection.¹ Other conditions such as agammaglobulinemia, hematological malignancies and sickle cell disease are correlated with this severe infection. The morbidity and mortality of invasive pneumococcal infection are still high despite antibiotic therapy and advances in medical technology.

The incidence of invasive pneumococcal infection has increased during recent years because of the emergence of antibiotic-resistant pneumococcus and the increased numbers of patients with HIV infection. Worldwide an alarming number of infections by pneumococcal strains resistant to penicillin, cephalosporins and other antibiotics, has appeared.¹ The risk factors for penicillin-resistant *S. pneumoniae* include recent administration of antimicrobial agents, patients with HIV infection who have received Cotrimoxazole prophylaxis, hospitalized patients with serious coexisting illness and patients who acquire *S. pneumoniae* in the hospital or nursing home.

Invasive pneumococcal disease is rarely correlated with gastrointestinal infections like peritonitis, colitis or intra-abdominal abscess. Acute cholecystitis is exceptionally associated with pneumococcal bacteremia. We present a case of a 47-old-woman with functional asplen-

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ism who presented pneumococcal bacteremia and acute cholecystitis.

Case report

A previously healthy 47-years- old woman with a mild mental retardation was admitted to the emergency department of our Hospital after she was found fainted in her house. No other information was obtained because she was living alone. The results of the clinical examination showed that she suffered from hypotension (80mmHg over 50mmHg), sinus tachycardia (120 b/min), fever (38°C), reticulated peliosis, and diffuse abdominal pain mostly in the right upper quadrant with hypoactive bowel sounds. At neurological examination she was found to be in great mental confusion (Glasgow Coma Scale =11). Respiratory and cardiac function appeared to be normal. On admission to hospital her WBC count was 13.600 cells/mm, with 86.2% polymorphonuclear leucocytes, 11.3% lymphocytes and 2.5% monocytes. The serum enzymes were SGOT 154 U/L, SGPT 102 U/L, CPK 237 U/l, ALP 300 U/l, LDH 728 U/L and total bilirubin 0.76 U/L. Serum glucose, bun, creatinine, electrolytes, amylase, hemoglobin, and platelet counts were normal. Protein electrophoresis was practically normal. Thyroid hormones were T3 0.11ng/dl, T4 1.0µg/dl and TSH 5.0µIU/ml. HIV test was negative. Coagulation abnormalities were found consisting of a markedly prolonged PT (25'') and APTT (87''), with normal plasma fibrinogen concentration (360 mg%). A high level of fibrin degradation products (D dimer >10), a very low protein C (PC) and antithrombin III (ATIII) concentration were also found (18% and 19% respectively).

A severe metabolic acidosis was observed at the blood gases analysis. The cerebrospinal fluid was clear with protein concentration 92mg/l and negative gram stain. Cerebrospinal fluid, urine and blood cultures were obtained before and right after antimicrobial therapy began. The U/S of the liver-biliary tract-pancreas revealed cholelithiasis and gall bladder hydrops, cholecystitis and pericholecystitis. The patient was treated surgically by removal of the gall bladder. After surgery she was transferred intubated and under mechanical ventilation to ICU. In ICU the patient developed septic shock. High doses of fluids for volume resuscitation, vasopressor agents and glucocorticoid were administrated without significant results. The cutaneous rash was diagnosed as purpura fulminans due to septic shock (Figure 1).

Cerebrospinal fluid, sputum and urine cultures were negative. In the blood culture a penicillin-susceptible strain of *S. pneumoniae* was isolated. Clinical and labo-



Fig. 1. Purpura fulminans due to septic shock

ratory findings were negative for immunodepression and there was on appearance no risk for invasive pneumococcal infection (alcoholism, HIV infection, connective tissue diseases, steroid use, diabetes mellitus and intravenous drug use). Her spleen was morphologically normal but Howell-Jolly bodies were found in blood examination and then functional asplenia was diagnosed. Despite appropriated antibiotic therapy and supporting measure such as mechanical ventilation, continuous venous-venous hemofiltration (CVVHF), vasopressor support and administration of blood, FFP (Fresh Frozen Plasma), Protein C and Antithrombin III, the patient died two days after her admission in ICU by irreversible septic shock, disseminated intravascular coagulation and multiple organ failure.

DISCUSSION

Sepsis due to pneumococcal infection is a lethal condition with high mortality rates that is correlated with the pneumococcal serotypes and patient's comorbidity such as sickle cell disease or asplenia. The capsular serotype of *Streptococcus pneumoniae* is the most important subclassification of the species because of its strong influence on human immunity. Susceptibility to invasive disease is determined by the inability of the host to generate specific opsonizing antibodies against capsular antigens.^{2,3} About the role of surgical asplenia or functional hyposplenism in the development of invasive pneumococcal disease, it's useful to remark that asplenic or hyposplenic individuals are susceptible to overwhelming infection, particularly by the encapsulated organisms such as pneumococcus, meningococcus and haemophilus influenzae.

Functional hyposplenism is usually unknown and may be diagnosed by identification of Howell-Jolly bodies in the peripheral blood smear. Associated diseases include gastrointestinal disorders, hemoglobinopathies, autoimmune disorders, amyloidosis, neoplasm, circulatory disturbances and other diseases.⁴

Gastrointestinal manifestations of invasive pneumococcal disease are not frequent. The most common is primary peritonitis.¹ Primary or spontaneous peritonitis is the peritoneal inflammation that originates outside the peritoneal cavity or in the absence of an intra-abdominal source of infection. Once pneumococcus was the most common cause of primary peritonitis but in recent years it became a significantly less common etiologic agent. Pneumococcal peritonitis occurs more frequently in children, in whom it is usually associated with nephrotic syndrome or cirrhosis.⁵ Some other sites of gastrointestinal infections are reported in the literature associated with pneumococcal bacteremia: appendicitis, colitis, phlegmonous gastritis/enteritis, typhlitis, retroperitoneal or ileopsoas muscle abscess, intra-abdominal, splenic, pancreatic or liver abscess and terminal ileitis.¹ Various theories had been advanced to explain the pathogenesis of this rare and potentially life-threatening form of pneumococcal infection, but the mechanism by which pneumococcus causes gastrointestinal disease still remains unknown. Primary peritonitis in women in the absence of underlying disease probably results from an upper genital tract infection with pneumococcus.⁶

Our patient presented clinical signs of acute abdomen with ultrasound relevance of cholelithiasis, hydrops and cholecystitis. The intraoperative findings confirmed the diagnosis. The presence of cholecystitis must be correlated in our patient with pneumococcal infection because any other site of infection was excluded (lungs, CNS, urinary tract) and pneumococcal bacteremia was documented in the first hours of her hospitalization. Cholecystitis could be considered the source of infection in this case. In fact the possibility of hematogenic infection of gallbladder is improbable because the incidence of pneumococcal bacteremia is high worldwide but the recognition of infection in gastrointestinal tract is rare. We found in literature only five reports of acute cholecystitis associated with pneumococcal bacteremia.⁷⁻⁹

At the time of admission at the hospital the patient presented purpura fulminans with progressive hemorrhagic skin necrosis. Purpura fulminans is also referred as "symmetric peripheral gangrene"¹⁰ and it is caused by dermal vascular thrombosis in the setting of DIC, thus have suggested that it should be considered a cutaneous

marker for DIC.¹¹ This syndrome has been observed in three clinical situations: severe infections, hereditary or acquired Protein C pathway disorders, and idiopathic form. Acute infectious purpura fulminans is most commonly caused by *Neisseria meningitidis*, *Hemophilus influenzae* and *Pneumococcus*. The overall mortality rate of this severe syndrome is very high: 43% in a recent retrospective study.¹² It is characterized by thrombocytopenia, petechiae and ecchymosis with disseminated thrombosis of small vessels, resulting in tissue hypoperfusion and imminent peripheral gangrenes and almost invariably acute renal failure.¹³

Pneumococcal septic shock and purpura fulminans is well described in asplenic or immunocompromised patients in many studies over the last three decades. This clinical setting occurs with or without Waterhouse-Friedrichsen syndrome (hemorrhagic necrosis of the adrenals that leads to profound, often irreversible shock). Recently sporadic cases of pneumococcal septic shock and hemorrhage in previously healthy adults and children were reported.

Protein C is a natural anticoagulant with anti-inflammatory properties that inactivates coagulation factors Va and VIIa limiting coagulation and enhancing fibrinolysis.¹³ Antithrombin, another well known natural anticoagulant, is a broad-spectrum plasma serine protease inhibitor, affecting the intrinsic, extrinsic, and common coagulation pathways. During septic shock and DIC the levels of PC and AT III in plasma decrease, reflecting the consumption of coagulation factors. In patients dying by sepsis lower levels of plasma PC and ATIII than in survived patients are detected. These results have led to the assumption that administration of activated PC and AT III in early stages of DIC could help to maintain the regulatory control of coagulation.¹⁴ Recently a large multicenter randomized controlled trial showed a significant reduction of mortality by treatment with activated protein C in patients with sepsis-induced organ dysfunction.¹⁵ Concerning AT III the results of a large clinical trial in septic patients indicates that high-dose Antithrombin, at least when combined with heparin therapy, is not beneficial in patients with severe sepsis and septic shock but it may be beneficial without concomitant heparine administration.¹⁶ In the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock recombinant human Activated Protein C (rhAPC) is recommended in patients at high risk of death (APACHE II =25, sepsis-induced multiple organ failure or sepsis-induced Acute Respiratory Distress Syndrome) and with no absolute contraindication related to

bleeding risk or relative contraindication that outweighs the potential benefit of rhAPC.¹⁷

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