PURPURA FULMINANS DUE TO *STREPTOCOCCUS PNEUMONIAE* BACTERAEMIA IN AN UNSPLECTOMISED IMMUNOCOMPETENT ADULT WITHOUT PRIMARY HYPOCOMPONENTAEMIA

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BACKGROUND

Purpura fulminans (PF) is a rare disorder associated with intravascular thrombosis and haemorrhagic infarction of the skin that progresses to vascular collapse and disseminated intravascular coagulation (DIC). The most common type of PF is acute infectious PF that complicates bacterial sepsis followed by neonatal PF due to protein C and protein S deficiency and idiopathic/postinfectious PF that manifests with rapidly progressive purpura.1

CASE PRESENTATION

A woman in her 50s presented to the emergency department (ED) with complaints of abdominal pain, vomiting, malaise and shortness of breath that started the day prior. Her medical history was notable for untreated Raynaud’s disease and moderate persistent asthma for which she was on a salmeterol-fluticasone inhaler daily and an as needed albuterol inhaler. She denied any recent changes in her medications nor did she report any new drug intake. She had undergone a left L3 to L5 laminectomy about 14 weeks prior to the visit for chronic back pain. She had no other surgical history. Her family history was unremarkable. She was an ex-smoker with a 10 pack-year smoking history but denied alcohol and illicit substance use. She was notable for untreated Raynaud’s disease and primary hypocomplementaemia.

INVESTIGATIONS

**Imaging**

*CT of the abdomen and pelvis*—Mild perinephric and periureteral fat standing on the left side. Other visceral organs including the spleen intact without any pathologies. Lung bases clear of obvious infiltrate, consolidation or effusion.

**Echocardiography**—Severe global hypokinesis of the left ventricle with an ejection fraction of 25%–30%, normal right ventricular function and no significant valvular abnormality.

DIFFERENTIAL DIAGNOSIS

Her very complex presentation of haemodynamic collapse with skin involvement raised concern for several differential diagnoses such as drug-related skin reactions—Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), cryoglobulinaemia’s, PF and DIC triggered by septic shock and autoimmune vasculitides.

Absence of recent drug intake and absence of features such as mucosal involvement, skin peeling and blistering made TEN/SJS less likely. For further evaluation of cryoglobulinaemia’s and autoimmune vasculitides, autoimmune, immunological and hepatitis/HIV labs were obtained. For further workup of septic shock, cultures and an extensive infectious disease workup was obtained.
For DIC, serial coagulation parameters, arterial and venous Dopplers were obtained. Her cultures and infectious disease workup resulted positive for *Streptococcus pneumoniae*. In the autoimmune panel, she tested positive for SS-A antibodies, rheumatoid factor and antinuclear antibodies (ANA) with titre of 1:320. However, review of her electronic medical records revealed that 12 years back she had a positive ANA with a titre 1:640 along with positive SS-A antibodies and rheumatoid factor. This was done as a part of her Raynaud’s disease workup. Additionally, although her complement levels were low (see table 1), 12 years back they were within normal limits with C3 of 119 mg/dL and C4 of 22 mg/dL, explaining that hypocomplementaemia was related to sepsis. Remainder of her autoimmune and immunological workup was unremarkable.

As other secondary causes of her skin abnormalities, haemodynamic collapse and critical illness were ruled out, the working diagnosis was PF secondary to *S. pneumoniae* bacteraemia.

**TREATMENT**

She was started on supplemental oxygen through nasal cannula and given aggressive intravenous fluid resuscitation. However, with persistent hypotension, she had to be started on intravenous vasopressors, hydrocortisone and broad-spectrum antibiotics with cefepime, vancomycin and metronidazole. She was transferred to the intensive care unit (ICU) for a higher level of management. Serial arterial blood gases (ABG) revealed worsening metabolic acidosis with poor respiratory compensation. Thus, she was initiated on a bicarbonate infusion. Cryoprecipitate was administered for laboratory evidence of DIC as noted by thrombocytopenia, elevated d-dimer, low fibrinogen, elevated activated partial thromboplastin time (aPTT) and an elevated international normalised ratio (INR) to target fibrinogen level >100 mg/dL.

On day 2 of hospitalisation, she had interval progression of the purpuric rashes with worsening hypotension requiring four vasopressor infusions—norepinephrine, vasopressin, epinephrine and phenylephrine. Dobutamine was attempted, but it caused worsening hypotension. Her mixed venous oxygen saturation was 75%. She was anuric and had to be started on continuous renal replacement therapy. Coagulation labs showed interval worsening of the platelet count, PT and INR. aPTT was stable and fibrinogen had improved to 62 mg/dL (table 1). Infectious disease, haematology and rheumatology opinions were obtained; further laboratory studies were ordered and antimicrobials were escalated to meropenem, vancomycin, levofloxacin, doxycycline, micafungin and acyclovir for a broad bacterial and fungal coverage. She was also initiated on empiric high dose pulse steroids—intravenous methylprednisolone 1 g daily to cover for autoimmune pathologies while the labs were pending. She continued to receive cryoprecipitate. Because of progressively worsening metabolic acidosis on ABG with poor respiratory compensation, she was intubated and started on mechanical ventilator support. Cardiology opinion was also sought to explore further options to support her haemodynamics; however, she was deemed to be a poor candidate for mechanical circulatory assist devices such as impella or an intraaortic balloon pump in view of her abnormal coagulation labs.

**Figure 1** Non-blanching, non-palpable purpura over the face sparing the lips and periorbital areas.

**Figure 2** Mottling of skin over the dorsum of the hand with digit ischaemia.

**Figure 3** Livedo reticularis rash over the right lower extremity.
Table 1

| Laboratory investigations | Day 1 | Day 2 | Day 3 | Day 4 |
|---------------------------|-------|-------|-------|-------|
| Complete blood count with differential count | | | | |
| Hemoglobin (ref 130–140 g/L) | 137 | 122 | 106 | 114 |
| Leucocyte count (ref 4.3–11.1 x10^9/L) | 6.2 | 21 | 69 | 67 |
| Platelet count (ref 150–450 x10^9/L) | 22 | 22 | 22 | 22 |
| Hematocrit (%) | 39.1 | 23 | 23 | 23 |
| Mean corpuscular volume (MCV) | 85 | 85 | 85 | 85 |
| Mean corpuscular hemoglobin (MCH) | 28 | 28 | 28 | 28 |
| Mean corpuscular hemoglobin concentration (MCHC) | 34.8 | 34.8 | 34.8 | 34.8 |
| Neutrophil (%) | 77 | 95 | 95 | 95 |
| Lymphocytes (%) | 21 | 3 | 3 | 3 |
| Monocytes (%) | 27 | 3 | 3 | 3 |
| Eosinophils (%) | 3 | 3 | 3 | 3 |
| Basophils (%) | 1 | 1 | 1 | 1 |
| C-reactive protein (CRP) | 0.4 | 0.4 | 0.4 | 0.4 |
| Procalcitonin (PCT) | <0.05 | <0.05 | <0.05 | <0.05 |
| Prothrombin time (PT) | >120 | >120 | >120 | >120 |
| International normalised ratio (INR) | >16 | >16 | >16 | >16 |
| Activated partial thromboplastin time (aPTT) | >20 | >20 | >20 | >20 |
| Fibrinogen (ref 192–257 mg/dL) | >60 | >60 | >60 | >60 |
| D-dimer (ref <0.5 FEU µg/mL) | >20 | >20 | >20 | >20 |
| Functional protein C (ref 83%–168%) | 15 | 15 | 15 | 15 |
| Factor VIII activity (ref 60%–150%) | 90 | 90 | 90 | 90 |
| Anti-beta-2-glycoprotein I IgM (ref <20 SMU) | <10 | <10 | <10 | <10 |
| Anti-RA (ref <20 SPU) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <14 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <12 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <11 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <10 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <9 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <8 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <7 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <6 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <5 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <4 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <3 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <2 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <1 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.5 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.2 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.1 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.05 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.02 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.01 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.0005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.0002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.0001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.00005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.00002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.00001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.000005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.000002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.000001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.0000005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.0000002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.0000001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.00000005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.00000002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.00000001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.000000005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.000000002 MPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgG antibodies (ref <0.000000001 GPL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgA antibodies (ref <0.0000000005 APL) | <10 | <10 | <10 | <10 |
| Anticardiolipin IgM antibodies (ref <0.0000000002 MPL) | <10 | <10 | <10 | <10 |
and very high risk of bleeding. She also started to become significantly volume overloaded.

On day 3 of hospitalisation, blood cultures were positive for S. pneumoniae and the S. pneumoniae urine antigen also returned positive. Despite cryoprecipitate administration, she continued to have abnormal coagulation labs (table 1). Antimicrobials were de-escalated to meropenem, vancomycin and clindamycin. High-dose methylprednisolone was stopped and switched back to stress dose hydrocortisone, appropriate for septic shock. She however continued to deteriorate progressively.

OUTCOME AND FOLLOW-UP

Also, on day 3 of hospitalisation, she developed worsening hypoglycaemia with blood glucose levels persistently <50 mg/dL requiring escalation up to a 20% dextrose infusion. Her vasopressor requirements progressively increased and eventually she developed a pulseless electrical activity cardiac arrest. In spite of cardiopulmonary resuscitation, she could not be revived and she expired.

DISCUSSION

Our patient had a very complex initial presentation raising several possible differential diagnoses. She had a rapidly progressive clinical course complicated by multiorgan failure over the course of 48–72 hours eventually leading to death. Although the source of her S. pneumoniae bacteraemia remained elusive, it triggered a cascade of events from septic shock with multiple organ dysfunction to florid DIC and PF. This was all in the context of her being an unsplenectomised immunocompetent woman without primary hypocomplementaemia which is a rare phenomenon.

PF is a rapidly progressive life-threatening disorder characterised by thrombotic occlusion of several small and medium sized blood vessels leading to haemorrhagic infarction of the skin and DIC. It is predominantly seen in neonates and children and rarely occurs in the adult population. PF tends to be a complication of sepsis due to Neisseria meningitidis, S. pneumoniae, Group A and B streptococci and Haemophilus influenzae infections (accounting for >90% of PF cases). This results in the activation of the coagulation cascade and complement pathway, endothelial dysfunction and eventually DIC. PF can be the presenting feature of severe heritable deficiencies of protein C and protein S. It can also occur as a postinfectious complication occurring 7–10 days following certain viral infections such as varicella, rubella and rubeola.

The development of PF usually portends a high mortality rate of up to 60%.

The clinical features of sepsis-related PF include the signs and symptoms of the underlying sepsis itself along with a characteristic purpuric rash. Classically, the rash starts as erythematous macules which then rapidly expands, coalesces and becomes indurated and non-blanching. The rash can also appear mottled with a livedo reticularis pattern. As it progresses, central areas of necrosis develop with haemorrhage into the area causing bullae formation. The majority of patients also develop multiorgan dysfunction requiring supportive measures and DIC.

A multicentre retrospective study conducted in France compared the clinical characteristics of PF from Neisseria meningitidis and S. pneumoniae. It was found that patients with PF from S. pneumoniae had an overall higher ICU severity score, lower platelet counts, higher need for plasma and platelet transfusions, worse renal dysfunction, more frequent need for renal replacement therapy, more frequent need for mechanical ventilation, more vasopressor support and a higher ICU mortality.

In the USA, as of 2016 the incidence of pneumococcal infections was 9.14 per 100 000 with a mortality rate of 1 per 100 000. Invasive pneumococcal disease (IPD) is defined as isolation of S. pneumoniae from normally sterile sites. The burden of IPD is mainly determined by bacteraemia without a primary focus and without meningitis. Apart from asplenia, underlying haematological malignancies, hypocomplementaemia and alcohol abuse constitute the major risk factors for severe infections from S. pneumoniae.

The risk of IPD can be significantly reduced by vaccination. The Advisory Committee on Immunization Practices recommends the use of PPSV23 in adults from 19 to 64 years of age with medium risk of pneumococcal infections. Medium risk patients include those with a normal immunity but with certain comorbid conditions such as chronic lung diseases (including asthma), chronic heart disease, chronic liver disease, smoking, alcohol use disorder and diabetes mellitus. Unfortunately, the pneumococcal vaccination rate for those 19–64 years of age is significantly low at 24.5%.

Learning points

► Invasive pneumococcal disease (IPD) can result in fulminant sepsis leading to disseminated intravascular coagulation and purpura fulminans. This is associated with a very high mortality.

► Purpura fulminans caused by Streptococcus pneumoniae is associated with more complications and mortality in comparison to purpura fulminans due to Neisseria meningitidis.

► The Advisory Committee on Immunisation Practices recommends pneumococcal vaccines to people at increased risk of IPD; however, the vaccination rates are at a staggeringly low rate (24.5% for pneumococcal polysaccharide vaccine 23 in adults aged 19–64 years who are at medium risk).

► Patients at risk should be appropriately educated and emphasis should be given about pneumococcal vaccines as this can prevent lethal complications such as purpura fulminans.

Contributors SPS was involved in the conception, drafting, data acquisition and editing of the manuscript. MA was involved in the conception, editing and review of the manuscript. AH was involved in editing and final review of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from next of kin.

Provenance and peer review Not commissioned; externally peer reviewed.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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