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Purpura fulminans due to *Streptococcus pneumoniae* bacteraemia in an unsplectomised immunocompetent adult without primary hypocomplementaemia

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SUMMARY

Invasive pneumococcal disease occurs in high-risk patient population which includes patients with asplenia and primary hypocomplementaemia. Pneumococcal sepsis can rarely cause disseminated intravascular coagulation (DIC) and intravascular thrombosis of small and medium sized vessels called purpura fulminans which is associated with a high mortality rate. We present the case of an immunocompetent woman in her 50s with an intact spleen who presented with septic shock from *Streptococcus pneumoniae* bacteraemia. Her hospital course rapidly progressed to multiorgan dysfunction, DIC and purpura fulminans. She was treated aggressively with broad spectrum antibiotics, coagulation factor replacement, multiple vasopressor support, renal replacement therapy and mechanical ventilator support. Despite aggressive measures, she succumbed to the multiorgan failure.

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 due for her seasonal influenza and pneumococcal polysaccharide vaccine 23 (PPSV23, indicated for her asthma) immunisations. She had received two doses of Pfizer-BioNTech (BNT162b2) COVID-19 vaccines (on 23/3/2021 and 13/4/2021). She denied recent travels or sick contacts.

Initial vital signs in the ED showed temperature of 40.4°C, heart rate of 131 beats per minute, blood pressure 64/39 mm Hg, respiratory rate 42 breaths per minute and an oxygen saturation of 80% on room air. Physical examination was most significant for a diffuse non-palpable, non-tender, purplish rash involving her face, trunk and extremities but sparing the periorbital area (figure 1). In the extremities, the rash had a lace-like reticular pattern (figures 2 and 3). She had bilaterally clear lung fields, regular first and second heart sounds without any murmurs. Neck was supple without any stiffness. Kernig's and Brudzinski's signs were negative. She had no focal neurological deficits. Abdomen was soft without any organomegaly.

INVESTIGATIONS

Imaging

Chest X-ray—No cardiomegaly, pulmonary infiltrates, pleural effusions or pneumothorax.

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.

Arterial and venous Dopplers—Negative for arterial and venous clots.

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

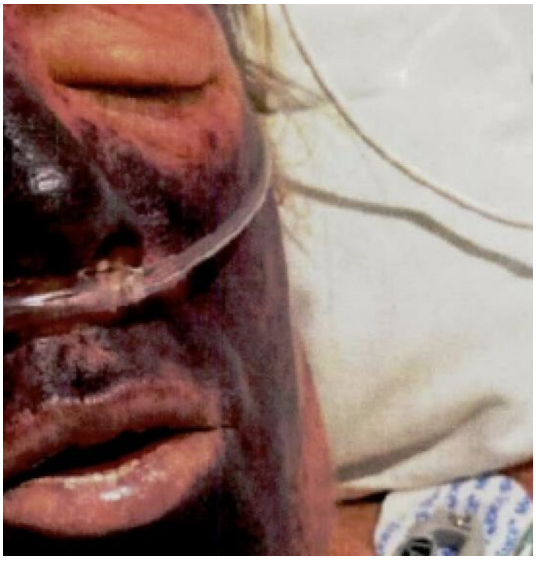

Figure 1 Non-blanching, non-palpable purpura over the face sparing the lips and periorbital areas.

(see table 1). 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.

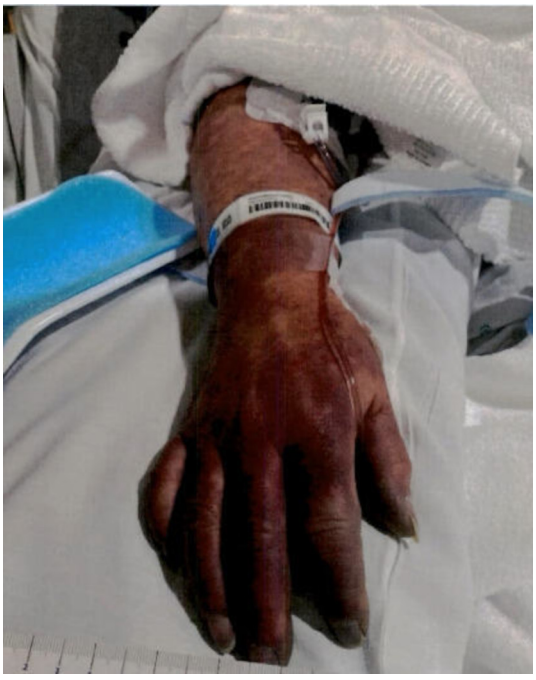

Figure 2 Mottling of skin over the dorsum of the hand with digit ischaemia.

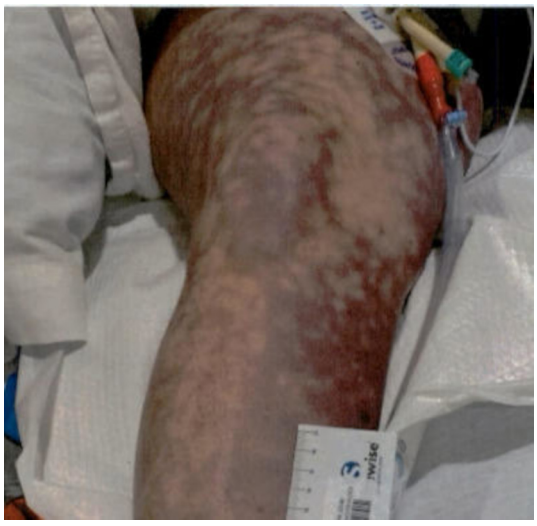

Figure 3 Livedo reticularis rash over the right lower extremity.

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 intra-aortic balloon pump in view of her abnormal coagulation labs

Table 1 Laboratory investigations

Complete blood count with differential count	**Day 1**	**Day 2**	**Day 3**	**Urinalysis**	**Day 1**	**Immunology**	Day 2
Haemoglobin (ref 120–140 g/L)	137	122	106	pH	5	IgG (ref 610–1616 mg/dL)	1174
Leucocyte count (ref 4.3–11 k/µL)	3.2	39.1	34.8	Protein	1+	IgA (ref 84–499 mg/dL)	334
Platelet count (ref 150– 450 k/µL)	62	27	23	Glucose	Negative	IgM (35–242 mg/dL)	67
Neutrophil (%)	77	95	95	Ketones	Negative	Complement C3 (ref 87–200 mg/dL)	65
Lymphocytes (%)	21	3	2	Nitrite	Negative	Complement C4 (19–52 mg/dL)	11
Eosinophils (%)	0	1	1	Leucocyte esterase	Negative	Free kappa light chain (ref 2.2–19.4 mg/dL)	59.8
Monocytes (%)	1	1	2	Erythrocytes	0–4	Free lambda chain (ref 5.71–26.3 mg/dL)	30.7
Basophils (%)	1	0	0	Leucocytes	0–4	Free kappa/lambda ratio (ref 0.26–1.65)	1.94
				Casts	None		
Chemistry panel	**Day 1**	**Day 2**	**Day 3**	**Arterial blood gases**	**Day 1**	**Infectious disease**	**Day 2**
Sodium (ref 136–145 mEq/L)	132	135	137	pH (ref 7.35–7.45)	7.24	Blood cultures	*Streptococcus pneumoniae*
Potassium (ref 4.5–5 mEq/L)	2.9	4.5	4.3	Pco_2 (ref 35–45 mm Hg)	23	Respiratory culture	Negative for bacterial, viral and fungal organisms
Chloride (ref 98–109 mEq/L)	101	105	96	Pao_2 (ref 75–100 mm Hg)	131	Urine streptococcal antigen	Positive
Bicarbonate (ref 24–28 mmol/L)	17	10	20	Fraction of inspired oxygen	45%	*Chlamydia pneumoniae* PCR	Not detected
Blood urea nitrogen (BUN) (ref 7–20 mg/dL)	23	30	15	**Autoimmune workup**	**Day 2**	Adenovirus PCR	Not detected
Creatinine (ref 0.6–1.1 mg/dL)	2.2	3	1.7	Antinuclear antibody titre (ref <1:40)	1:320	Bordetella pertussis and parapertussis PCR	Not detected
Total bilirubin (ref <1 mg/dL)	0.8	1.2	3.6	Antineutrophil cytoplasmic antibody titre (ref <1:20)	<1:20	MRSA PCR	Not detected
Aspartate aminotransferase (AST) (ref 13–39 U/L)	46	204	11 700	Antimyeloperoxidase (ref <1 AI)	<0.2	SARS-CoV-2 PCR	Not detected
Alanine aminotransferase (ALT) (ref 5–25 U/L)	15	53	2598	SS-A antibody (ref <1 AI)	>8	Human metapneumovirus PCR	Not detected
Alkaline phosphatase (ALP) (ref 34–104 U/L)	98	125	216	SS-B antibody (ref <1 AI)	<0.2	Influenza A and B PCR	Not detected
Total protein (ref 6.5–9 g/dL)	6.9	5.1	4.9	Smith antibody (ref <1 AI)	<0.2	Urine legionella antigen	Negative
Albumin (ref 3.5–5.7 g/dL)	3.3	2.3	2.5	Scl-70 antibody (ref <1 AI)	<0.2	Malaria thick and thin smears	No parasites seen
Troponin-I (ref <0.03 ng/dL)	0.05	0.67	4.8	Double stranded DNA antibody (ref <5 IU/mL)	2	*Mycoplasma pneumoniae* PCR	Not detected
Procalcitonin (ref <2 ng/mL)	213.63			Anticentromere antibody (ref <1 AI)	<0.2	Parainfluenza types 1, 2, 3 and 4 PCR	Not detected
Coagulation panel	**Day 1**	**Day 2**	**Day 3**	Anti-beta-2-glycoprotein I IgM (ref ≤20 SMU)	<10	Q fever phase 1 and 2 serologies (IgG and IgM)	Negative
Prothrombin time (PT) (ref 11.4–14.4 s)	65.1	>120	>120	Anti-beta-2-glycoprotein I IgG (ref ≤20 SGU)	<10	Enterovirus PCR	Not detected
International normalised ratio (INR) (ref 0.9–1.1)	7.6	>16	>16	Serine protease 3 Ab (ref <1 AI)	<0.2	Rhinovirus PCR	Not detected
Activated partial thromboplastin time (aPTT) (ref 24–36 s)	191	98	96	Anti-cardiolipin IgG antibodies (ref ≤14 GPL)	<10	Hepatitis A IgM antibodies	Non-reactive
Fibrinogen (ref 192–557 mg/dL)	<60	62	81	Anti-cardiolipin IgA antibodies (ref ≤11 APL)	<10	Hepatitis B antigen	Non-reactive
D-dimer (ref <0.5 FEU µg/mL)	>20	>20	>20	Anticardiolipin IgM antibodies (ref ≤12 MPL)	<10	Hepatitis B core IgM antibody	Non-reactive
Functional protein C (ref 83%–168%)		15		Rheumatoid factor (ref <14 units/mL)	20	Hepatitis C antibody	Non-reactive
Factor VIII activity (60%– 150%)		90		Anticyclic citrullinated peptide IgG (ref 0–19 units)	4	HIV 1 and 2 antigen and antibody	Non-reactive

AI, antibody index; APL, IgA phospholipid unit; FEU, fibrinogen equivalent units; GPL, IgG phospholipid unit; HIV, human immunodeficiency virus; IgA, immunoglobin A; IgG, immunoglobin G; IgM, immunoglobin M; MPL, IgM phospholipid unit; PCR, polymerase chain reaction; SGU, standard IgG beta-2 glycoprotein unit; SMU, standard IgM beta-2 glycoprotein unit.

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%.[2 3]

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.[3 4]

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.[5]

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.[6] 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.[7] Apart from asplenia, underlying haematological malignancies, hypocomplementaemia and alcohol abuse constitute the major risk factors for severe infections from *S. pneumoniae*.[8]

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%.[9 10]

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.

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