Case report

Development of purpura fulminans by *Candida glabrata* and *Mucormycosis* infection post-surgery

Hussain Hussain [a,*], Aya Fadel [b], Efrain Garcia [a], Marco A. Ruiz [a], George Michel [a], Zahraa F. Saadoon [a], Rehan Sarfraz [a], Arumugam R. Jayakumar [c]

[a] *Larkin Community Hospital Department of Internal Medicine - Infectious Disease, Miami, FL, USA*
[b] *Hackensack Meridian Health Department of Internal Medicine at Ocean Medical Center, NJ, USA*
[c] *Department of Obstetrics, Gynecology and Reproductive Sciences, University of Miami Miller School of Medicine, Miami, FL, USA*

ARTICLE INFO

ABSTRACT

Purpura fulminans (PF) is a disorder with multifactorial causes that lead to acute localize skin microvasculature thrombosis. PF can be classified as one of the manifestations of disseminated vascular coagulation (DIC). Although, there are three types of PF including hereditary (autosomal dominant) due to mutations in single nucleotide polymorphisms (PROC and PROS1) and serpin family C member 1 (SERPINC1) genes. Idiopathic or acquired type of PF is complex and the pathophysiology is ambiguous, however, low levels of protein C and S were observed. The acute infectious form of PF occurs post-bacterial infection (e.g., *Neisseria*). The clinical presentation is limited to skin findings or systematic manifestation (shock, disseminated intravascular coagulation, or death). We are presenting two cases of PF sharing similar clinical manifestations developed within 12 h post-operatively with distinct micro-organisms infection. The first patient's wound culture grew fluffy mold, and the sequencing confirmed a *Mucormycosis, Absidia corymbifera* species, while the second patient was infected by cutaneous *Candida glabrata* which led to the development of PF. Our findings suggest that surgery can trigger local immunological responses in susceptible individuals such as concealed protein C and S deficiency or microorganism toxins that initiated the rapidly developing of PF in those patients.

Background

Purpura fulminans (PF) is a disorder with multifactorial causes lead to acute localize skin microvasculatures thrombosis, which evidences externally by purpuric rash of the skin [1,2]. PF was first discovered in 1884, since then the incidence of PF is relatively rare; in pediatrics PF is account for about 1:1,1000,000 live birth, which is occurs as a hereditary form (autosomal dominant) due to mutations in PROC and PROS1 genes [1–5]. These genes are responsible for encoding protein C and S, correspondingly [1,5,6]. Any deletion, insertion, missing or frame shift in these genes can lead to malfunction of these proteins and potentially hypercoagulability [5,6]. While in adults PF is account for about 10–20%, mostly related to infection and idiopathic [1].

PF can be classified as one of the manifestations of disseminated vascular coagulation (DIC). Therefore, it is considered to be one of the dermatological emergencies that requires instantaneous diagnosis and management. The clinical presentation may be limited to skin findings or it can be complicated by systemic evidences such as fever,

hemorrhage, shock, disseminated intravascular coagulation or death. The diagnosis is established through mainly clinical, serological, radiographical and biopsy aids in recognition of the disease [1–6].

Case presentations

We are presenting two cases of PF sharing similar clinical manifestations developed within 12 h post-operatively with different micro-organisms infection.

Case 1:. A 67-year-old male developed acute perforated small bowel due to an obstruction and underwent an uneventful laparotomy. The patient has a history of ulcerative colitis and cytomegalovirus colitis, both controlled with medications. The patient developed insidious cutaneous lesions within 12 h post-operatively (Fig. 1A and B). Laboratory investigation disclosed an elevation of D-dimer at 10.5 (< 0.4 μ/mL), fibrinogen at 451 (200–400 mg/dL), PTT at 40 (25–35 s), PT at 12 (10–13 s), BUN at 34 (20 mg/dL), and aspartate aminotransferase

(AST) as well as Alanine transaminase (ALT) are within normal range. Further, mild leukocytosis at 10.20 (4500–10000), anemia with a hemoglobin level at 7.3 (14–18 g/dl), increased erythrocyte sedimentation rate (ESR) at 96 (0–15 mm/hr), C-reactive protein at 60 (< 1.0 mg/dL), protein C was low at 47 (65–135 IU dL-1), while protein S was within normal level. The rest of the laboratory result was unremarkable. Therefore, we initiated broad-spectrum antibiotics (vancomycin 1 g q12h IV, and Zosyn 3.375 g q8h IV), and enoxaparin 40 mg subcutaneously. A skin biopsy was obtained, and the histopathological analysis confirmed PF (Fig. 1G). Moreover, deep wound culture grew a fluffy mold, and the sequencing of that mold confirmed a *Mucormycosis*, *Absidia corymbifera* (CNRMA 03.6611) species (Fig. 1F). Consequently, we modified the medications to liposomal amphotericin B 3 mg/kg/IV/ QD alone. The condition progressively deteriorated, the patient underwent emergency surgery on day 3 post-operatively due to wound dehiscence. Despite extensive management with anticoagulant, cryoprecipitate, antibiotics, antifungal and supportive care, the patient died on day eight post-operatively due to disseminated intravascular coagulation.

Case 2:. A 35-year-old female underwent an elective abdominoplasty, which was complicated by sudden purpuric (purple-dark blue discoloration of the skin) at the surgical site (Fig. 1C and D). Broad spectrum antibiotics started (Vancomycin 1 g q12h IV and cefepime 2 g q8h IV), and laboratory investigation showed leukocytosis (17, 000, 4500–10000), anemia (8.7, 12–17 g/dl), thrombocytosis (599,000, 150−450), elevated ESR and C-reactive protein levels at 68 mm/hr and 29, respectively. Further, the blood smear showed toxic neutrophils and acanthocytes. The coagulation study showed an elevated D-dimer at 8.1 (< 0.4 μ/mL), PT at 18 (10–13 s), and PTT at 39 (25–35 s). However,

protein C and S levels were low, 43 (65–135 IU dL) and 51 (60–150%), respectively. The skin biopsy confirmed PF (histopathology not showing). We initiated Enoxaparin (40 mg q12h subcutaneously). The wound cultures grew *Candida glabrata* (Fig. 1E), the culture has been repeated and has confirmed the existence of the microorganism*, and* the antibiotics were swapped to Micafungin 100 mg IV qd alone. The condition resolved 13 days post-operation.

Discussion

Purpura fulminans (PF) is a distinctive and devastating acute thrombotic disorder [1]. It is manifested clinically as large irregular areas of insidious purple-black skin discoloration that quickly progress to necrosis/gangrene of the dermal and epidermal as well as deep soft tissue. Although rare, PF can evolve to cause various complications and multiorgan failure. It is frequently associated with disseminated intravascular coagulation (DIC); therefore, it can be classified as a subtype of DIC [1].

The histopathology of PF revealed significant distortion of the cutaneous architecture, including thinning of the stratum corneum (Fig. 1G, red arrows), the presence of subepidermal bullae, and extensive dermal thinning (Fig. 1G, black arrows). These changes likely resulted from vascular microthrombi and ischemia, leading to tissue apoptosis. Additionally, there was congestion and accumulation of red blood cells (Fig. 1G, white arrowheads), indicative of microthrombi formation, along with dermal thinning (Fig. 1G, white arrows). The tissue exhibited acute inflammation with the infiltration of various immune cells. Furthermore, there was a notable increase in dense pink collagens, fibrotic stroma, and scattered fibroblasts (Fig. 1G, yellow arrows).
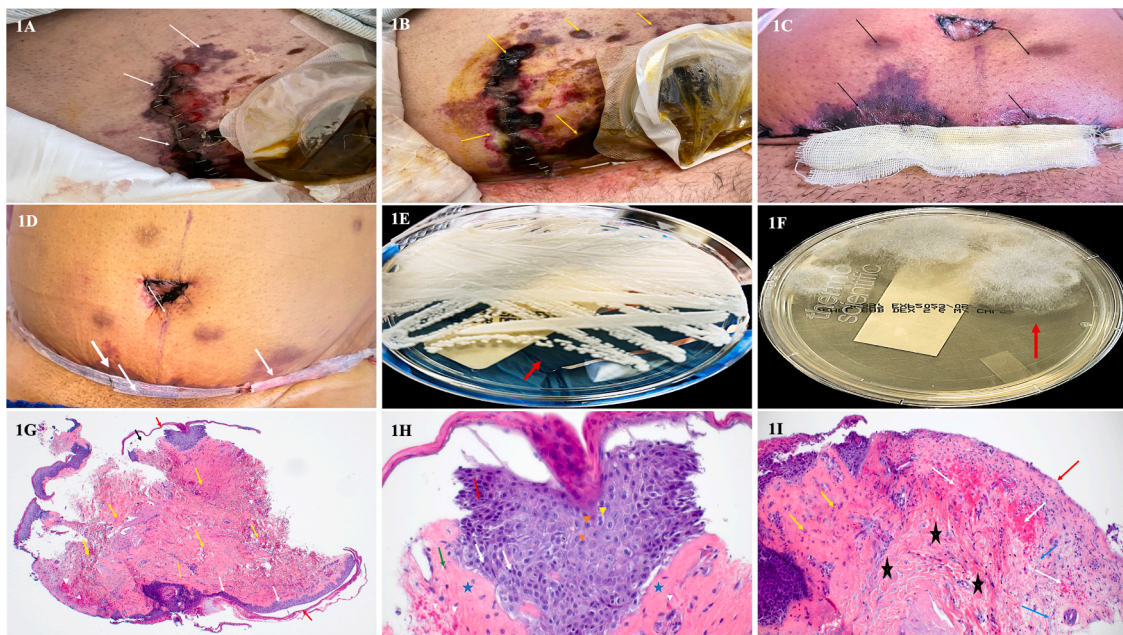
Fig. 1. **A** is the first case with non-palpable purpuric rash scatters around the surgical site (white arrows), colostomy bag is observed adjacent to the lesions. **1B** is the worsening of Case 1 lesions, more black discoloration observed (yellow arrows). **1C** is the second case with non-palpable purpura demonstrated alongside the surgical wound (black arrows). **1D** is improving Case 2 lesions. **1E** is showing an agar with fungal growth (red arrow). **1F** is the fluffy appearance of fungus on the culture plate (red arrow). **1G** is showing entire cutaneous histopathological changes of Case 1. Thinning of the epidermis (stratum corneum) (**1G**, red arrow), sub-epidermal bullae (**1G**, black arrow). Thinning of the dermis (**1G**, white arrows). Multiple areas of red blood cell accumulation and thrombosis within the inner dermis (**1G**, white arrowheads). Architecture destruction is obviously seen with various fibrosis and collagen deposits. Acute skin inflammation is characterized by the infiltration of neutrophils, eosinophils, macrophages, lymphocytes, mast cells, and plasma cells. Dense pink collagens, fibrotic stroma, and fibroblast are scattered in the tissue (**1G**, yellow arrows). **1H** is showing severe accumulation of melanocytes (**1G**, white arrows), stratum spinosum is condensed (**1G**, red arrow), fibroblast (**1G**, green arrow), fibrosis and collagen (**1G**, star), Neutrophils (**1G**, orange arrowhead), intracellular edema (**1G**, yellow arrowhead), microthrombi (**1G**, white arrowheads). **1I** is showing severe red blood cell accumulation/microthrombi (**1I**, white arrows). Various stages of fibroblasts (**1I**, yellow arrows), scatters of fibrotic stroma and collagens (**1I**, black stars), and inflammatory cells are found in the tissue. Blue arrows (**1I**) are pointing to the hyphae. The red arrow (**1I**) is showing an obliteration of the epidermis.

In Fig. 1H, we noted melanocyte accumulation (white arrows), stratum spinosum alterations (red arrow), inflammatory cell infiltration (orange arrowheads), and intracellular edema (yellow arrowheads). The normal skin architecture was replaced by severe fibrotic stroma and collagen deposition (blue stars) due to widespread apoptosis caused by microthrombi (white arrowheads). In Fig. 1I, we observed significant accumulation of red blood cells/microthrombi (white arrows). There were various stages of fibroblasts (yellow arrows), scattered fibrotic stroma and collagen deposition (black stars), and inflammatory cells in the tissue. Non-septate hyphae were also observed in Fig. 1I (blue arrows). These complex skin pathology changes rapidly developed, primarily attributed to extensive histamine release compared to other coagulation factors, leading to progressive skin necrosis.

There are three different types of PF; neonatal PF (type I), which is inherited as an autosomal dominant due to mutations in single nucleotide polymorphisms (PROC and PROS1), and serpin family C member 1 (SERPINC1) genes [1–4]. Further, those genes are responsible for protein C, S, and antithrombin III, respectively [1,2]. A defect of those genes can be homozygous, which produces severe PF, or a heterozygous manifestation of PF that is less severe [1–4]. Proteins C and S are considered to be vitamin K-dependent cofactors, which are considered pro-fibrinolytic [5]. Additionally, protein C is one of the important inhibitors of the coagulation system that inhibits factor Va and VIIIa, consequently down-regulate thrombin manufacture [5,6]. Therefore, patients with defective functions of proteins C and S develop PF.

Idiopathic or acquired PF (type II) is commonly developed post-infection or post-drug (i.e., cocaine) [3]. This type is associated with acquired protein C and S deficiency, which results in the development of acute PF [3,5,6]. The pathophysiology is ambiguous, however, anti-protein S antibodies developed 10–14 days post-infection [6]. Consequently, there is a hypoactivation of the protein C pathway as well as a decreased protein S level that ultimately leads to thrombogenesis [5].

The acute infectious form of PF (type III) is considered the third type that develops in the presence of acute microorganism infection [3]. The most common etiologies are bacterial infection with *Neisseria* Meningitidis*, Haemophilus influenzae, Clostridium, Klebsiella,* cocaine*, rickettsia, and Streptococcus* or viruses such as SARS-CoV-2 [3–9]. The pathophysiology begins with the production of mostly endotoxin and/or less likely exotoxin [3,10]. In the presence of endotoxin, there is an overwhelming inflammatory response leading to the surging of cytokines and chemokines [11]. Mechanistically, the bacteria and its derivatives as well as the severe inflammatory response are responsible for the development of PF through; an elevation of procoagulants (tissue factor), which is released from macrophages and monocytes [10–13]. Further, alteration of the level of antithrombin III, protein C and S due to endothelial dysfunction [13–15]. Also, the level of plasminogen activator inhibitor-1 is increased from endothelial cells, which inhibit fibrinolysis [13–15]. All these in addition to the cytokines along with the extracellular histones propagate extensive inflammation, cell apoptosis, and necrosis [2,13–15].

In our patients; we found a unique type of PF, which developed within 12 h post-operatively. This can be considered type III with idiopathic observation or a new immunological phenomenon needs further investigation. We noticed that the PF developed only on the surgical sites (Fig. 1). The exact pathophysiology is still ambiguous, but we have concluded two plausible explanations; the surgery may induce an initial immunological response by releasing various cytokines, chemokines, and procoagulants to recruit more inflammatory cells. This process may be exacerbated by microorganism toxins that potentially lead to the development of PF according to the pathophysiology described earlier. However, our patients may have a history of protein C or S deficiency (genetic or acquired) in addition to the microorganisms, the PF is more likely to develop.

References

[1] Perera TB, Murphy-Lavoie HM. Purpura Fulminans. StatPearls. Treasure Island (FL). StatPearls; 2023.
[2] Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis-associated disseminated intravascular coagulation and thromboembolic disease. Mediterr J Hematol Infect Dis 2010 13;2(3):e2010024. https://doi.org/10.4084/MJHID.2010.024.
[3] Martinez-Cabriales S, Ocampo-Garza J, Barbosa-Moreno L, Chavez-Alvarez S, Ocampo-Candiani J. Purpura fulminans 10 years after contaminated cocaine use. Lancet 2015;386(10004):e21. https://doi.org/10.1016/S0140-6736(15)60069-1.
[4] Takayanagi K, Grochwska E, Al-Bader M, Doresowamy N, Freeman NV. Purpura fulminans in neonates and childhood. Z Kinder 1985;40(3):182–7. https://doi.org/10.1055/s-2008-1059741.
[5] Cahill M. Protein-C concentrate for meningococcal purpura fulminans. Lancet 1998;351(9107):987–8. https://doi.org/10.1016/S0140-6736(05)60655-1.
[6] Colling ME, Bendapudi PK. Purpura fulminans: mechanism and management of dysregulated hemostasis. Transfus Med Rev 2018;32(2):69–76. https://doi.org/10.1016/j.tmrv.2017.10.001.
[7] Dalugama C, Gawarammana IB. Rare presentation of rickettsial infection as purpura fulminans: a case report. J Med Case Rep 2018;12(1):145. https://doi.org/10.1186/s13256-018-1672-5.
[8] Nasrullah A, Javed A, Tariq U, Young M, Moeen Z, Balaan M. Purpura Fulminans: a Rare but Fierce Presentation of Pneumococcal Sepsis. Eur J Case Rep Intern Med 2019;7(1):001373. https://doi.org/10.12890/2019_001373.
[9] Pangburn J, Gibbs J. Two cases of COVID-19 patients with associated purpura fulminans. J Burn Care Res 2023;44(2):485–6. https://doi.org/10.1093/jbcr/irac176.
[10] Jones E, Stair-Buchmann M, Kotliar S, Haith L. Purpura fulminans in toxic epidermal necrolysis: case report and review. J Burn Care Res 2015;36(6):e274–82. https://doi.org/10.1097/BCR.0000000000000195.
[11] Betrosian AP, Berlet T, Agarwal B. Purpura fulminans in sepsis. Am J Med Sci 2006; 332(6):339–45. https://doi.org/10.1097/00000441-200612000-00006.
[12] Branson HE, Katz J, Marble R, Griffin JH. Inherited protein C deficiency and coumarin-responsive chronic relapsing purpura fulminans in a newborn infant. Lancet 1983;2(8360):1165–8. https://doi.org/10.1016/s0140-6736(83)91216-3.
[13] Smith OP, White B, Vaughan D, Rafferty M, Claffey L, Lyons B, et al. Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura

fulminans. Lancet 1997;350(9091):1590–3. https://doi.org/10.1016/s0140-6736 (97)06356-3.

[14] Powars D, Larsen R, Johnson J, Hulbert T, Sun T, Patch MJ, et al. Epidemic meningococcemia and purpura fulminans with induced protein C deficiency. Clin Infect Dis 1993;17(2):254–61. https://doi.org/10.1093/clinids/17.2.254.

[15] White B, Livingstone W, Murphy C, Hodgson A, Rafferty M, Smith OP. An open-label study of the role of adjuvant hemostatic support with protein C replacement therapy in purpura fulminans-associated meningococcemia. Blood 2000;96(12): 3719–24.