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Neonatal Purpura Fulminans with Pos Complicated by Hemophagocytic Lymphohistiocytosis: A Rare Presentation of Herpes Simplex Virus Infection

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ABSTRACT

Purpura Fulminans is a rare dermatological emergency characterized by purpuric lesions and skin necrosis, often as a result of disruptions in skin vasculature. Three forms of Purpura Fulminans exist: neonatal, idiopathic, and acute infectious, each with distinct characteristics and etiologies. We present a case of a 3-day-old female who was originally admitted to the neonatal intensive care unit (NICU) for respiratory failure, severe metabolic acidosis, and hypercarbia. On day 2, the patient was preparing for discharge, but developed tachypnea and perioral cyanosis. The sudden onset of Purpura Fulminans with cutaneous blisters and fever, lacked conventional triggers, posing diagnostic challenges. The infant's maternal history involved chlamydia infection during pregnancy. The absence of typical triggers such as Group B Streptococcus or Acinetobacter baumanni, along with a unique presentation of metabolic acidosis and hypercarbia, underscores the complex etiology of this case's Purpura Fulminans.While the association between Purpura Fulminans and Protein C deficiency is well documented in the literature, the exploration of diverse triggers and clinical presentations demands ongoing research.

BACKGROUND

Purpura Fulminans (PF) is a rare but acute dermatologic emergency characterized by purpuric lesions and skin necrosis resulting from the coagulation of microvasculature.[1] The 3 forms of this disease are neonatal, idiopathic, and acute infectious, all classified based on their triggering mechanism.[1] Protein C is a Vitamin K dependent cofactor synthesized in the liver and responsible for inhibiting the actions of thrombin.[1] In all 3 forms of PF, the end result is a deficiency and/or inactivation of protein C resulting in insufficient anticoagulation.[2] This pro-coagulatory state

occludes small cutaneous vessels appearing as petechial rashes and rapidly progresses to larger vessels leading to disseminated intravascular coagulopathy (DIC).[1] Though the mortality rate of this condition has been decreasing, survival often includes major amputation and lifelong disability.[2]

Neonatal PF is an inherited deficiency of protein C. Neonatal PF occurs in 1:1,000,000 live births.[1] 72 hours after birth a rapid onset purpuric rashes, cutaneous necrosis, and cerebral hemorrhage can be observed.[2]

Idiopathic PF is the rarest PF subtype with only several hundred cases ever reported. It follows around 7-10 days after an infectious disease that leads to the production of anti-protein S antibodies. The anti-protein S antibodies result in a transient deficiency and excretion of protein S, and a hypoactivation of the protein C pathway inducing a hypercoagulable state characteristic of PF.[1]

Acute infectious PF (AIPF) is the most common PF subtype and is associated with bacterial and viral triggers.[1] Bacteria such *Meningococcus* and *Streptococcus pneumoniae* produce endotoxins that inappropriately consume protein C, leading to a disruption in coagulation homeostasis.[1] Varicella is the most common viral trigger. In AIPF, thrombomodulin deficiency leads to impaired protein C inactivation, causing unchecked coagulation. AIPF is distinguishable from the neonatal and idiopathic forms by a perivascular neutrophilic infiltrate.[2]

CASE PRESENTATION

A 3-day-old female born at 38 weeks (APGAR score: 1, 5 minute: 9) was admitted to the NICU for respiratory failure associated with severe metabolic acidosis, hypercarbia and portopulmonary hypertension. The patient was born to a 20-year-old mother (G2P0) with a history of chlamydia during pregnancy but tested negative on admission. She recently discontinued oral prenatal vitamins and iron. The mother's blood work revealed A+ blood type with >10 IU/mLIgG to Rubella and negative IgG for HIV, Hepatitis B, and Syphilis.

The newborn patient appeared healthy and was prepared for discharge, but sudden tachypnea and perioral cyanosis developed. Subsequently, the patient developed a fever and malaise with formed clusters of blisters and pustules on her skin.

Following the observation of perioral cyanosis and tachypnea, the patient's oxygen was found to have desaturated to 80%. Subsequently the patient was started on continuous positive airway pressure then placed on high flow nasal cannula 100% oxygen; however, the patient's respiratory rate and work of breathing continued to climb. Blood culture was taken and following consultation with the infectious disease department, the patient was given vancomycin and cefotaxime.

Following dermatology consultation, the baby had worsening multiorgan system dysfunction that led to sepsis. DIC was observed along with decreased renal and liver function. Further testing revealed elevated ferritin levels which were treated with continuous renal and blood product replacement therapy. Skin eruptions suspicious for PF were observed, with DIC and distal purpura including the vulva. These findings elicited a workup for possible HSV induced hemophagocytic lymphohistiocytosis. Workup revealed a white blood cell count of 5.4 k/mL (low), red blood cell count of 3.29 mil/mcl , Hct of 29.7%, hgb of 9.9 g/dl, and a platelet count of 52 k/mcl .

Figure 1: *Purpura Fulminans and DIC on Upper Extremity and Trunk*

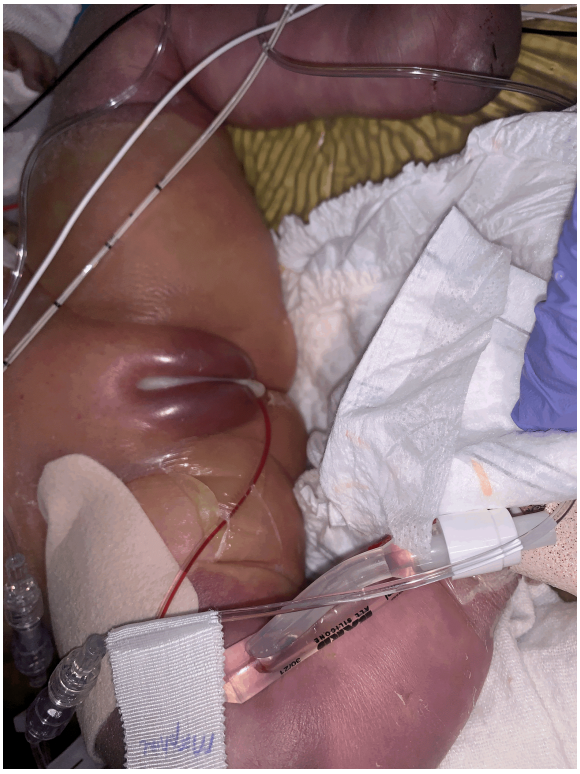

Figure 2: *Distal Purpura on Vulva with Discharge*

DISCUSSION

The case presented above demonstrates a unique case of PF developing in a 3-day-old female who was originally admitted to the neonatal intensive care unit (NICU) for respiratory failure, severe metabolic acidosis, and hypercarbia. The mother's history of *Chlamydia sp.* during pregnancy and work up for HSV-induced hemophagocytic histiocytosis raise concerns about the etiology and pathogenesis of PF in this case.

PF is a life-threatening acute disorder characterized erythema followed by irregular central areas of cutaneous hemorrhage and necrosis.[5] With DIC and dermal vascular thrombosis often developing as a sequelae.[5] Vesicles and bullae may also form and affected areas are painful and indurated. Although the condition is initially sterile, it can progress to secondary infection by gangrenous tissue, which contributes to increased mortality and morbidity. The formation of vascular coagulation is pathognomonic for PF. [5] The pathogenesis of PF differs from similar conditions such as Henoch-Schönlein purpura and drug-induced purpura due to its mild inflammatory component.

Laboratory investigations including CBC, PT, PTT, fibrinogen, and fibrin products should be conducted.[5] PF treatment begins with supportive care and hydration to impede the thrombosis that can take place in multiple organs.[1] The neonatal form is treated with hydration and platelet transfusion administration, along with a workup of protein C and S levels. If a deficiency of protein C or S is found, heparin, antithrombin III, and protein C concentrate can be administered.[1] Idiopathic PF is treated similarly with the addition of corticosteroid to modulate immune response.

Heparin binds to antithrombin III inhibiting thrombus formation and consumption of

coagulation factors. [5] Heparin can be administered with fresh frozen plasma or antithrombin III to help reverse the development of skin necrosis. Clinical and laboratory monitoring of heparin can be difficult when values are abnormal, leading to the development of arbitrary schemes such as a bolus of 4-10 000 units i.v followed by an infusion.[5] Acute phase proteins such as vitronectin bind inactivated heparin and thus can be used to assess heparin levels and achieve optimal therapeutic results.[6] However, without clearly defined approaches, heparin resistance can occur, resulting in relapse and increased difficulty in further management. A meta analysis of patients with sepsis, septic shock, and infection-associated DIC found treatment with heparin compared to placebo or reduced relative mortality rate by 12%.[6]

Protein C is a vitamin K-dependent glycoprotein that has anticoagulant and anti-inflammatory properties.[5] Early Protein C correction is crucial in restoring skin perfusion and treating PF. It is recommended to monitor daily protein C concentrations and administer it via i.v infusion as per necessary. Carefully tapering the concentrations over several days to allow the body to stabilize. Currently, optimal duration, dosages, and blood concentration of Protein C have not been defined.[5]

Patients with PF are thought to be different enough to benefit from a PC zymogen. THe market withdrawal of rhAPC has limited PC treatment to only PC concentrate, available in the US as Ceprotin. PC concentrate therapy has been shown to reduce markers of DIC, which is integral to PF, however the studies showing this have small patient populations and differing medication doses.

Acute infectious PF should primarily be treated with antibiotics such as carbapenem or vancomycin and beta-lactams to cover *Neisseria meningitidis*, *Streptococcus sp.*, *Staphylococcus sp.*, and *Clostridia sp.* Clindamycin and intravenous Ig therapy is beneficial to inhibit toxins central to disease progression. Similarly to other PF forms, protein C administration can reduce the inflammatory cascade and coagulation that leads to cutaneous purpura. Indication of anticoagulation therapy for acute infectious PF is based on concurrent DIC.[1]

One of the first areas of potential PF treatment involved exploring activated protein C therapy in Sepsis. In the early 1990s, there was interest in the benefits of antithrombin, protein c (PC), or activated protein C (APC) in patients with sepsis since these were proteins associated with a larger proportion of sepsis patients and a increased risk of death. Animal studies have demonstrated antithrombin and protein C supplementation reduced coagulopathic and lethal effects of E. Coli infection. One subsquent study, the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study found that patients who received rhAPC (drotrecogin alfa) received a significant mortality benefit. But follow-up studies to PROWESS did not reproduce similar results and rhAPC ended up being withdrawn from the market.

A review of case report literature demonstrated multiple noteworthy presentations of PF. A case report by Singal and Dhir documented three noteworthy cases of neonatal PF caused by *Acinetobacter baumannii.* Three full-term neonates, all born within twelve hours of each other at a tertiary care facility located in Delhi, India developed hemorrhagic blisters and ecchymoses over acral areas and thighs 12-36 hours after birth.[3] All three neonates were managed in the neonatal intensive care unit and were treated with intravenous fluid, parenteral antibiotics, and fresh frozen plasma. In the first neonate, the acral bullous lesions turned hemorrhagic and necrotic by day one and gangrenous by day three. The lesions spread rapidly to the thighs and toes and were

associated with sepsis. By day 5, acute respiratory distress was observed and the patient expired due to septicemia by day 7. The other two neonates showed improvement with skin lesion healing by day 7. Blood cultures obtained from the neonates all yielded *Acinetobacter baumannii*, which is a far less likely etiology of PF than traditional causes such as *Meningococcus* and *Streptococcus pneumoniae.* D-dimer measurements for neonates 1, 2, and 3 were 1943, 783, and 2249 ng/L (normal range <250 ng/L), respectively. Swabs from the healthcare workers, instruments, and labor room surfaces failed to yield pathogens. Detailed evaluation of the mothers failed to reveal any infection focus.[3]

In another case report by AlBarrak and Al-Matary, a full-term male neonate presented with PF secondary to early-onset group B-streptococcal (GBS) infection.[4] The 43-hour-old infant was admitted to the emergency department with fever (39.5°C) and lethargy. He was immediately started on intravenous ampicillin and gentamicin. His initial workup revealed DIC. On observation he had cutaneous necrosis involving the tip of the fingers, nails, scrotum, and foot. Blood and CSF cultures grew GBS and he had normal levels of protein C and S for his age. The infant died 48 hours later due to multi-organ system failure despite maximum intensive care support.

CONCLUSION

As a potentially fatal syndrome with rare occurrence, Purpura Fulminans remains a condition that requires further dermatological research. To the greatest depth of current understanding, all three forms of PF (neonatal, idiopathic, and acute infectious) are linked to a deficiency and/or inactivation of Protein C, which leads to a state of hypercoagulability in patients. This can have fatal consequences, as it predisposes patients to DIC and can lead to manifestations such as purpuric lesions and skin necrosis. However, a comprehensive understanding of the mechanisms and etiologies behind the different forms of PF has yet to be found. As discussed earlier in this paper, Albarrak and Al-Mattary's case report documents a typical presentation of AIPF while Singal and Dhir's case documents unusual etiologic agents of PF including *Acinetobacter baumanii*; and the patient in our case report had metabolic acidosis, hypercarbia, and no maternal history of pertinent infections, which are not stereotypically associated with PF. Therefore, PF seems to have a range of etiologic agents and clinical manifestations that remains unclear in their association with each other. Research in PF should continue in effort to find solutions for patients who present with such a medical emergency.

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