

Coagulation Changes in Proteus Syndrome following Blunt Trauma

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Background	There are no prior reports that describe the management of a trauma patient with Proteus syndrome.
Summary	A 20-year old female with Proteus syndrome presented following motor vehicle accident with major blunt traumatic injuries. Previous anecdotal reports of this rare congenital disorder suggest a predisposition to a hypercoagulable state. Per protocol, routine serial thromboelastogram (TEG) assays were performed to assess coagulopathy and prophylactic low-molecular weight heparin (LMWH), 0.5mg/kg was administered subcutaneously twice daily (BID). To the authors' knowledge, this is the first report of coagulation changes in a patient with Proteus syndrome following major trauma.
Conclusion	A potentially hypercoagulable state must be considered when treating a trauma patient with Proteus syndrome; although, interventions should ultimately be prescribed on an individual basis. Serial TEGs can monitor coagulation changes and may help guide treatment of these patients.
Keywords	Proteus syndrome; trauma; hypercoagulability; venous thromboembolism (VTE); coagulation profile

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Case Description

A 20-year old African American female presented to Ryder Trauma Center (a Level I-certified trauma center) via ambulance following a motor vehicle crash. She was an unrestrained driver and denied loss of consciousness. The patient consented to release of all information; however, she did not consent to photographic documentation. On primary survey, the patient had a patent airway with bilateral breath sounds, Glasgow coma scale of 15, negative focused assessment with sonography in trauma (FAST), and the following vital signs: blood pressure 124/74mmHg, heart rate 83bpm, respiratory rate 18 breaths/min, temperature 37.0°C.

On secondary survey, there were noticeable deformities and edema to the bilateral lower extremities. The patient had only a great toe on her right foot and was missing her third toe on the left foot. Amputations had been performed early in the patient's life to resolve ambulation impairments secondary to extensive bony overgrowth.

Adjunct imaging via plain X ray and computed tomography (CT) confirmed fractures of the left tibia shaft (open, grade II), left femoral shaft (closed and displaced), and right distal tibia shaft (closed, displaced). Significant soft tissue stranding was noted in the right pelvic region. Incidental, nontraumatic findings included asymmetric enlargement of the left kidney, possible hemangioma of the liver, and soft tissues masses in the abdomen and pelvis, all consistent with Proteus syndrome.

The patient's admission laboratory values were as follows: body mass index: 24kg/m², hemoglobin and hematocrit (H/H) of 11.6/35, prothrombin time (PT) of 12.7 seconds, partial thromboplastin time (PTT) of 23.2 seconds, and international normalized ratio (INR) of 1.11 (all within the normal reference range). Prophylactic (0.5mg/kg BID) dosing of low-molecular weight heparin (LMWH) was instituted on hospital day (HD) 1.

The past medical history was significant for hypertension and Proteus syndrome and was diagnosed in early childhood. Past surgical history included caesarian section and 12 orthopedic procedures for surgical correction of the bilateral lower extremity deformities (the patient was born with congenitally fused lower limbs). Family history was significant for multiple first- and second- degree relatives with cancer, a sister who died from a myocardial infarction at age 36, and mother and grandmother who suffered multiple strokes, expiring from cerebral aneurysms. The patient denied any current medications and reported an allergy to penicillin.

Orthopedic surgery was consulted for the multiple skeletal injuries and elected to perform an irrigation and debridement of the left tibia fracture, followed by intramedullary nailing of the left tibia, retrograde intramedullary nailing of the left femur and closed reduction and splinting of the right tibia on HD 1. There were no complications and an estimated blood loss (EBL) of 300mL. Postoperatively, the patient was transferred to the trauma intensive care unit as a precautionary measure. An acute drop in H/H (from 11.6/35 to 5.1/15.4) was observed on HD 3 and was transfused two units (U) of packed red blood cells (PRBC). Her response was inappropriate, and she was transfused an additional 2U after which her H/H stabilized to 8.3/24.5. On HD 6, the patient underwent an uncomplicated definitive fixation of the right tibial fracture intramedullary nail (EBL 100mL). Postoperatively, the patient became anemic with a H/H of 6.4/19.5 and was transfused 2U PRBC (posttransfusion H/H: 9.3/28.0). Serial TEG was obtained on HD 3, 5, 6, 8 and 11 showing an initial hypercoagulable state (HD 3) then mild hypocoagulability (HD 5, 11) (Table 1). The patient was discharged on HD 13 in stable condition with one month of prophylactic of LMWH consistent with orthopedic practice at this institution. Follow-up clinic visits have been unremarkable.

TEG Parameters					
POST-OPERATIVE HOSPITAL DAY	ACTIVATED COAGULATION TIME (TEG-ACT) 86-118 sec	REACTION TIME (0-1 min)	KINETIC TIME (0.5-2.3 min)	ALPHA ANGLE (64-80°)	MAXIMUM AMPLITUDE (MA) MAXCLOT (52-71 mm)
HD 3	66 (L)	0.2	0.8	83.4° (H)	57
HD 5	160 (H)	1.2 (H)	1.3	71.9°	63.8
HD 6	97	0.5	0.8	77.7°	58.5
HD 8	113	0.7	0.8	79.5°	75.6 (H)
HD 11	167 (H)	1.2 (H)	1.0	76.7°	75.8 (H)

Table 1. Serial thromboelastograph. TEG= thromboelastography; HD= hospital day; normal reference ranges below column headings

Discussion

Proteus syndrome is a rare disorder characterized by progressive, asymmetric tissue overgrowth involving all three embryonic lineages.¹ Less than 200 cases of Proteus syndrome have been reported since its discovery in 1979 with an estimated prevalence of < 1:1 M.^{2,3} Proteus syndrome is caused by a random somatic mutation in the *AKT1* gene during early pregnancy that induces cellular proliferation in a mosaic distribution.⁴ Postnatal overgrowth varies significantly, but affected individuals commonly develop a range of tumors, skeletal malformations, pulmonary complications, and display a marked predisposition to venous thromboembolisms (VTE): deep vein thrombosis (DVT) and pulmonary embolism (PE).⁵ The cause of this hypercoagulable predisposition in this patient population has not been clearly defined. However, previous reports suggest the syndromic vascular malformations secondary to mosaic mutations in the AKT/PI3K pathway to be a significant risk factor for thromboembolism in these patients.⁶ Further, extensive genetic testing of 57 individuals with Proteus syndrome by Biesecker et al. did not identify significant associations with well-known prothrombotic conditions such as Factor V Leiden, prothrombin mutation, G20210A, AT III deficiency, or Protein C/S deficiencies.⁷ Instead, this study attributed the disproportionately high VTE risk to specific vascular and platelet dysfunctions caused by the AKT1 p.E17K mutation.⁷ Nevertheless, irrespective of the etiology of increased risk, individuals with Proteus syndrome clearly have unique coagulation abnormalities, thus clinicians must be cautious in their clinical management.

Clinical management of patients with Proteus syndrome is challenging because there is a wide spectrum of symptoms and potential clinical manifestations coupled with no definitive treatment protocols, especially in the setting of trauma. Although patients with Proteus syndrome are known to be hypercoagulable, there are no previous reports investigating the TEG results and other coagulation matrices in patients with Proteus syndrome, especially in the setting of trauma.⁵ Trauma patients, in general, are hypercoagulable due to significant endothelial damage, decreased venous blood flow, prolonged stasis, and the release of tissue factor, making trauma patients twice as likely to develop DVTs and PEs.⁸

In this report, the authors describe a patient with significant traumatic injuries and Proteus syndrome. Her initial TEG showed slight hypercoagulability, whereas routine coagulation parameters (PT, PTT, and INR) were within the normal range. She received prophylactic dosing of LMWH (0.5mg/kg BID) throughout the duration of her hospitalization. As her stay progressed, her TEG results varied between hypocoagulable and normal.

There are several points to emphasize. This patient nearly immediately received prophylactic dosing of LMWH that almost certainly changed her clotting dynamics. Secondly, this patient had a significant bleeding episode requiring multiple transfusions over several days and may have suffered from a mild consumptive coagulopathy. While the derangement in this patient's coagulation profile was likely multifactorial, this case report highlights the importance of analyzing patients with genetic predispositions on a case by case basis. The authors speculate that if therapeutic doses of anti-coagulants had been initiated due to this patient's predisposition for hypercoagulability, the effects might have been catastrophic. The utilization of serial TEGs in this case facilitated real-time surveillance of coagulation changes and helped guide clinical management in this complicated patient.

Conclusion

Patients with Proteus syndrome may develop dynamic changes in their coagulation profile based on injuries sustained and medications given. It is imperative that these sensitive patients be assessed on a case-by-case basis with routine high definition testing such as the TEG in combination with standard coagulation studies so that adjustments can be made to their prophylactic regimens. Further study is warranted to elucidate the association between Proteus syndrome, traumatic injury and coagulative states, but until such time clinicians must be cautious in managing these patients.

Lessons Learned

A potentially hypercoagulable state must be considered when treating a trauma patient with Proteus syndrome. Although most clinicians may never encounter Proteus syndrome, this case highlights the importance of increased surveillance when managing patients with rare genetic disorders.

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