Abstract:
A 7-day-old female infant presented to the emergency department with a chief complaint of bruises. She was found to have severe coagulopathy. Initial management focused on identifying and treating complications of the coagulopathy without causing harm to the patient. Further workup was performed with the assistance of hematology experts to determine the underlying cause. Ultimately, the patient's diagnosis was determined by a single laboratory test. This patient's presentation allows us to review the workup of neonatal coagulopathy with special attention to potential pitfalls one might encounter in the management of these patients.

Keywords:
neonatal coagulopathy; galactosemia; newborn screen

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A Baby With Bruises

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A 1-week-old former 37-week female infant presented to the emergency department (ED) with a chief complaint of bruising for 5 days. She was discharged home from the newborn nursery on day of life 2. The next day, the mother noted a "spot" on her left leg that resembled a bruise. As this first lesion was on her thigh, the mother attributed it to the hepatitis B and vitamin K intramuscular injections she received in the nursery. Over the following days, she began to develop similar lesions on her legs, feet, and buttocks. On the day of admission, she was referred to the ED for further evaluation by her pediatrician because of continued spread of the lesions.

The mother reported that the baby had otherwise seemed "normal." She had not measured her temperature since they left the hospital but had not noted the baby feeling warm or cool to touch. The baby had been breastfeeding well, approximately 8-10 times a day, making 6-8 wet diapers daily, and stooling after most feeds. Stools had transitioned and were yellow and seedy. She appeared jaundiced since day of life 2, although serum bilirubin levels in the newborn nursery were below the threshold for phototherapy. On review of systems, family denied irritability, abnormal movements, trauma, cough, rhinorrhea, congestion, shortness of breath, vomiting, or diarrhea.

The pregnancy was complicated by maternal hepatitis C with undetectable viral load, maternal hypertension, and an episode of maternal pneumonia in the third trimester that was treated with oral antibiotics as an outpatient. The patient was born via vaginal delivery at 37 weeks and 6 days after delivery was induced because of to maternal hypertension. Mother is now G1P1 and was group B *Streptococcus* negative. Apgars at birth were 8 and 9 at 1 and 5 minutes, respectively, and the birthweight was 3057 g. She received hepatitis B and vitamin K injections in the newborn nursery.

The family history was remarkable for a maternal great aunt with chronic idiopathic thrombocytopenia and a maternal grandmother with kidney disease of unknown etiology. Mother's medical history was also significant for precocious puberty and a small pituitary adenoma. The paternal family history was

unknown, and the father was not currently involved in the child's care. Both parents are white. The patient is currently living with her mother and maternal grandparents.

On examination, the patient was generally well appearing and breastfeeding vigorously with normal vital signs, including a heart rate of 163, blood pressure of 80/42 mm Hg, respiratory rate of 40, oxygen saturation of 100% on room air, temperature of 36.8°C, and a weight of 2700 g (11.7% down from birthweight). Her anterior fontanelle was soft and flat. Scleral icterus was present. Her cardiac and respiratory examinations were unremarkable with 2+ bilateral femoral pulses and normal peripheral perfusion without mottling. Her abdominal examination was normal without hepatosplenomegaly or masses. Her neurologic examination result was normal with appropriate strength and tone for age and a strong suck reflex. Her dermatologic examination result was notable for multiple nonblanching, ecchymotic patches on the bilateral legs, soles of feet, left middle toe, and right buttock ranging in size from 1 cm to 3-4 cm, and the lesion on left thigh showed a small, central eschar (Figure 1). She was jaundiced down to her midchest.

In the ED, it was confirmed she had received her vitamin K injection in the newborn nursery and that her newborn screen, obtained after 24 hours of life, was normal. A complete blood count (CBC), comprehensive metabolic panel, prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen levels were obtained. CBC revealed a white blood cell count of 15.9 × 10^3/μL, a hemoglobin of 19.2 g/dL, and platelet count of 166 × 10^3/μL with a differential of 53.8% neutrophils, 32.3% lymphocytes, 12.5% monocytes, 0.4% basophils, and 0.1% eosinophils. Comprehensive metabolic panel was notable for glucose of 47 mg/dL, total bilirubin of 16.9 mg/dL, conjugated bilirubin of 0.7 mg/dL, alkaline phosphate of 700 U/L, aspartate aminotransferase of 254 U/L, and alanine aminotransferase of 102 U/L. The PT was elevated at 65.4 seconds (reference: 11.8-14.5 seconds), INR was elevated at 8.1, PTT was elevated at 88.3 seconds (reference: 23-34 seconds), and fibrinogen was low at <60 mg/dL

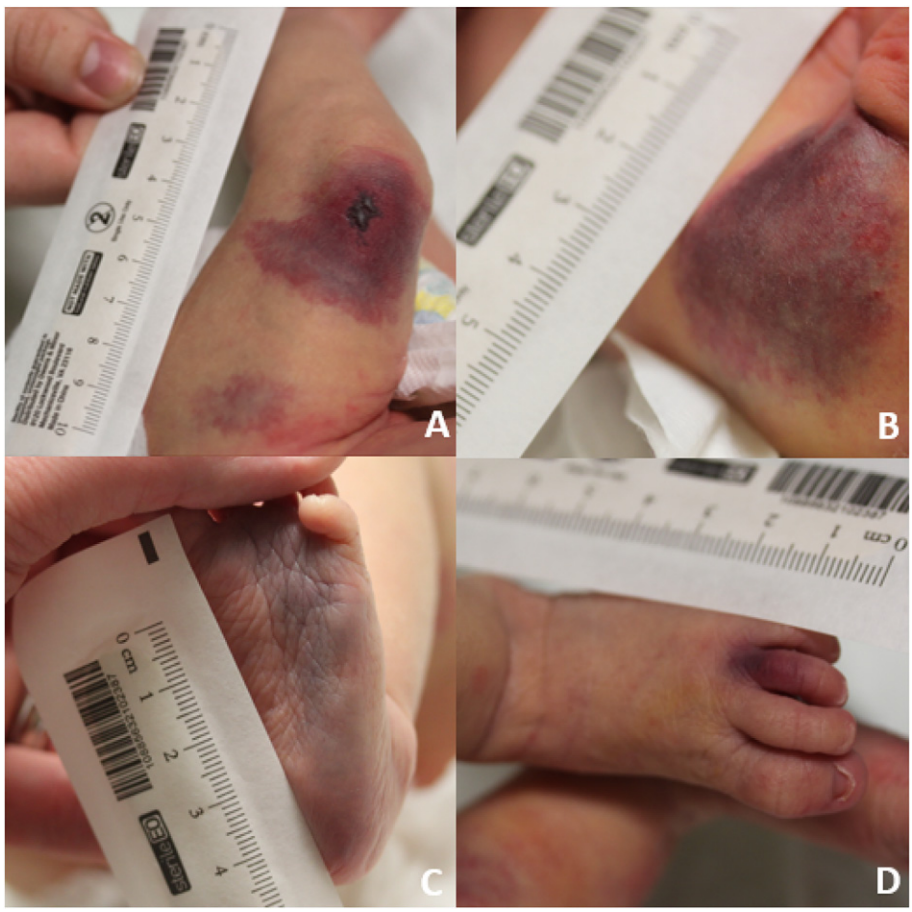

Figure 1. Photos of skin lesions: (A) left thigh, (B) right buttock, (C) bottom of left foot, and (D) top of left foot.

(reference: 188-450 mg/dL). A skeletal survey was completed and showed no evidence of healing or acute fractures.

Given the severity of her coagulopathy, vitamin K and fresh frozen plasma (FFP) were administered. A computed tomography scan of the head was obtained and was notable for a small subdural hemorrhage along the falx and tentorium, focal subarachnoid hemorrhage overlying the anterior left frontal lobe, and a hematoma overlying the right parietal bone. Neurosurgery was consulted and did not recommend surgical intervention. Because of concern for sepsis, a blood culture was obtained followed by initiation of ampicillin, gentamicin, and acyclovir. A lumbar puncture for cerebral spinal fluid and catheterization for urine specimen were deferred because of coagulopathy.

The hematology service was consulted and recommended additional factor testing, including protein C; protein S; antithrombin III; fibrinogen; D-dimer; and factors V, VII, and VII, which were sent on blood obtained prior to FFP administration. They encouraged continued supplementation with FFP until the coagulopathy was better defined and cryoprecipitate administration for hypofibrinogenemia. The patient did not show significant improvement in her coagulation panel despite repletion with FFP. She was ultimately admitted to the neonatal intensive care unit (NICU), where a previously completed study was repeated and revealed the final diagnosis.

DIFFERENTIAL DIAGNOSIS

When a neonate presents with bruising, nonaccidental trauma is a necessary item to include on the differential diagnosis. Bruising in this population can also be a clue to underlying hematologic abnormalities that should prompt laboratory investigation of the coagulation cascade. Specifically, large bruises and/or purpura can suggest an underlying platelet disorder or microvascular thrombotic condition.[1] This patient's findings of purpura, coagulopathy, and hypofibrinogenemia were consistent with neonatal purpura fulminans. Neonatal purpura fulminans is a clinical entity that consists of progressive dermal vascular skin necrosis in association with disseminated intravascular coagulation (DIC). Neonatal purpura fulminans is not in itself a definitive diagnosis and has multiple underlying etiologies. The root of all of these etiologies is a relative deficiency in protein C activity, either from increased consumption or decreased synthesis.[2] Protein C is a vitamin K–dependent anticoagulant protein that also has anti-inflammatory properties. Mild deficiency is typically associated with development of deep vein thromboses, but in neonatal purpura fulminans, severe deficiency causes microcirculatory thrombotic lesions that can result in inflammation and development of DIC. This causes a complicated clinical picture with prolonged PT and PTT from DIC and consumption of procoagulant proteins as well as increased risk of thrombosis formation from deficiency in protein C.[3]

As mentioned previously, there are multiple causes of neonatal purpura fulminans. These can be either congenital or acquired. Inherited disorders can result from any defect in the protein C pathway but are typically related to a defect resulting in severe protein C deficiency or protein S deficiency.[4] Protein S is a cofactor for protein C.[3] Purpura fulminans as a result of severe, inherited protein C deficiency typically results in lesions developing within a few hours to days after birth. There is a predisposition of lesions on the lower limbs or male genitalia as well as pressure points, such as heels and buttocks. Lesions can progress rapidly to full skin necrosis as well as digital or limb gangrene.[4] Although neonatal purpura fulminans is a classic manifestation of heritable protein C deficiency, it can be a diagnostic challenge because the presence of DIC from other causes, such as sepsis, can be associated with consumption and reduced plasma concentration of protein C and protein S. Therefore, findings of DIC with low protein C or protein S levels do not confirm a genetic defect in the protein C pathway.[4] Functional activity assays are recommended for initial testing but can also be affected by acute illness and require age-specific reference ranges for interpretation, as levels in healthy neonates are significantly below adult reference ranges. Testing on the parents of a patient with neonatal purpura fulminans may be helpful in determining the underlying etiology. Treatment of a heritable defect in the protein C pathway can include supportive care as well as the administration of protein C replacement therapy, which can take the form of protein C concentrate or FFP. Patients may also require anticoagulation given the increased risk for thrombotic events. A specialized pediatric hematologist should be involved in directing treatment.[2]

Other underlying conditions outside of heritable defects can also result in decreased synthesis of protein C or protein S.[2] This can include decreased synthesis from vitamin K deficiency, administration of vitamin K antagonists such as warfarin, or severe hepatic dysfunction.[2,5] As these are potential etiologies, maternal medication history and history of vitamin K administration should be identified.

Any cause of severe hepatic dysfunction could result in diminished protein C synthesis. Untreated galactosemia has also been reported as a cause of neonatal purpura fulminans, potentially due to underlying hepatic damage.[5]

Lastly, increased consumption of protein C or other proteins in the pathway can result in neonatal purpura fulminans. Examples of this include severe sepsis, acute venous thrombosis, or cardiac bypass.[2] Of these, sepsis is the most common etiology and has been associated with group B *Streptococcus* as well as *Neisseria meningitidis* infections most frequently.[2,4] In severe sepsis, systemic activation of coagulation and complement pathways with associated endothelial dysfunction results in DIC. Widespread activation results in consumption of circulating coagulation factors, which can include proteins C and S. Some organisms, such as *N meningitidis*, can also cause a local defect at the endothelium affecting protein C activation, worsening the loss of protein C activity.[4] Purpura fulminans as a result of sepsis can have a slightly different clinical presentation with lesions that develop distally and progress proximally or beginning as a diffuse rash.[4]

CASE PROGRESSION AND DIAGNOSIS

After admission to the NICU, the baby remained stable despite persistent coagulopathy. Serial head imaging did not show progression in her intracranial bleed. An ophthalmology consult was completed and did not identify any intraocular bleeding. She mostly breastfed with formula supplementation but was intermittently made NPO due to emesis. Laboratory testing sent while in the ED was notable for protein C activity of <11% (normal 50-120%). Protein C concentrate was administered to the patient along with continued repletion with FFP. During the first days of hospitalization, despite this factor repletion, she remained coagulopathic with PT ranging from 31.1 to 58 seconds (normal: 11.8-14.5 seconds), PTT ranging from 39.9 to 133.5 seconds (normal: 23-34 seconds), and PT-INR ranging from 3.1 to 6.9, not showing a recognizable trend in any direction.

It was determined that her presentation was not consistent with protein C deficiency, as she was not responding to repletion and genetic testing for that disease returned negative. A repeat newborn screen had been sent at time of admission based on the recommendation of a geneticist. It resulted on hospital day 9 and was consistent with the diagnosis of galactosemia:

- Galactose: 115.59 mg/dL (normal <13, critical >26)
- Galactose-1-phosphate uridyltransferase (GALT) enzyme: 3.55 U/dL (normal >5.55, obtained after transfusion in the NICU)

Numeric results from her initial newborn screen were obtained from the Department of Health:

- Galactose: 12.82 mg/dL (normal <13)
- GALT enzyme: not run, as initial galactose value did not exceed the cutoff

On review of her coagulation laboratory values, which initially did not appear to have a trend, it was noted that her values improved during periods when she was not allowed to feed. Her coagulopathy resolved after she was transitioned to a soy-based formula. A repeat ophthalmology examination was performed and revealed development of mild bilateral cataracts when compared to her prior examination.

Her initial testing likely appeared similar to congenital protein C deficiency given her liver dysfunction and decreased synthesis from galactosemia in combination with neonatal coagulation immaturity, with low levels of protein C in infancy. Since her discharge from the hospital, she has been maintained on a soy formula diet and is doing well. She is currently 20 months old and appropriately meeting developmental milestones with minimal visual imparity from her cataracts.

DISCUSSION

Galactosemia is an inborn error of metabolism related to the galactose metabolism pathway. A variety of genetic mutations can result in deficiency in the enzyme GALT which results in the accumulation of galactose in the body.[6] Classic galactosemia is inherited in an autosomal recessive fashion and has a prevalence of 1:16 000-60 000 live births. Infants are typically asymptomatic at birth.[7] However, within a few days of ingestion of lactose, either within formula or breast milk, they may experience metabolic decompensation with poor feeding, poor weight gain, vomiting, lethargy, liver failure, jaundice, and coagulopathy. Other classically associated findings include *Escherichia coli* sepsis, cataracts, and pseudotumor cerebri with a bulging fontanel.[6,7] The standard of treatment is dietary galactose restriction, commonly with soy formula. Upon restriction of galactose intake, blood galactose levels fall quickly but always remain elevated, likely due to some endogenous galactose production.[7] Infants who survive the initial episode of decompensation

often develop long-term intellectual disability. Even when appropriately treated throughout their life, many patients with galactosemia still have learning disabilities and speech deficits. Most female patients will develop ovarian failure and require estrogen replacement therapy beginning in adolescence.[6]

As pediatric emergency care providers, we are unlikely to diagnose galactosemia in the ED but will encounter cases of neonatal coagulopathy, which deserves discussion as a broader category. There are many causes of neonatal coagulopathy, including vitamin K deficiency, inherited bleeding disorders (such as the hemophilias), maternal medication effect, liver failure, and sepsis resulting in DIC.[1] Therefore, the best step in the initial evaluation in the ED is a comprehensive and thorough history and physical examination.[8] Bleeding from puncture sites, the umbilical stump, gastrointestinal tract, or intraventricular or pulmonary hemorrhage can all suggest an underlying coagulation disorder. Purpura or bruising suggests a platelet disorder or microvascular thrombosis, as in this patient.[1] Important components of the history to elicit are maternal medication history (especially medications that affect vitamin K metabolism such as warfarin), previous administration of vitamin K, family history including history of siblings, and results and timing of the newborn screen.[1,6] It is important to remember, however, that patients can become ill before the newborn screen has resulted and a negative newborn screen does not rule out metabolic disease, given the possibility of false negatives and the inability to include all disorders on the newborn screen. Initial screening laboratory tests should include a CBC, peripheral blood smear, PT, PTT, and fibrinogen. These studies, in combination with the information above, should help direct further evaluation.[1]

It is important to note that the neonatal coagulation system is dynamic and differs significantly from adults. Normal factor levels in neonates are typically much lower when compared to those in adults, with most of them at 50% of adult levels, but reaching adult levels by 6 months of age. Levels can also vary with gestational age. Therefore, it is essential that providers consult appropriate reference ranges when interpreting coagulation results.[9]

Once coagulopathy is identified, there are several treatment options. If available, treatment should be directed at the underlying cause, such as dietary restriction of galactose in galactosemia or antimicrobials for a patient in sepsis.[10] Other supportive care measures include administration of products such as FFP or cryoprecipitate. FFP is human donor plasma that is frozen soon after collection. It contains all of the clotting factors present in the initial collected unit.[9] Cryoprecipitate is the cold-insoluble portion of FFP collected after FFP is thawed. It is specifically rich in fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin; it is often used in the setting of hypofibrinogenemia.[11] Vitamin K should be administered because it can be helpful for both vitamin K deficiency or liver failure.[12]

After initiating treatment, infants should also be evaluated for potential sites of blood loss. Neonates with coagulopathy can present with bleeding in their gastrointestinal tract, as well as intracranial, pulmonary, or mucocutaneous sites.[1] Coagulopathy can be associated with spontaneous intracranial hemorrhage without preceding trauma. Patients with spontaneous bleeding from coagulopathy as opposed to a traumatic bleed tend to have a better neurologic recovery when comparing similar bleeds. Although there are case series available describing intracranial hemorrhage due to coagulopathy, the degree of coagulopathy required to cause spontaneous hemorrhage is not known.[13]

Health care providers should be thoughtful when caring for coagulopathic patients, as interventions and treatment methods may cause harm. Lumbar puncture in patients with bleeding disorders can increase the risk of subdural, epidural, or subarachnoid hematoma formation.[14] There has also been a case report of life-threatening urethral hemorrhage after complicated urinary catheterization in adult with DIC.[15] Abnormal coagulation paramaters have been observed more frequently in adults with bleeding complications after central line placement.[16] Our patient ultimately developed a large liver hematoma after difficult placement of an umbilical line while coagulopathic. In addition, the decision to let this baby feed resulted in worsening coagulopathy, development of cataracts, and a prolonged hospital stay. Inborn errors of metabolism can be a cause of coagulopathy, and a normal newborn screen does not rule out an underlying metabolic condition.[6]

It is important to discuss how the results of this patient's original newborn screen affected her care. At this time, all states in the United States screen for galactosemia, but there is a wide variety in their screening methods.[17] At the time of this patient's birth, the state of Tennessee screened for galactosemia with a galactose level. A GALT enzyme activity assay was obtained if galactose was elevated above the upper limit of 13 mg/dL and no second newborn screen was obtained later in the patient's life. This patient's initial galactose level was 12.82 mg/dL at 25 hours of life, just below the cutoff

of 13. Therefore, a GALT enzyme was not run and the diagnosis of galactosemia was missed. As a result of this patient's presentation, the newborn screening protocols were changed in the state of Tennessee to include GALT enzyme assessment on all newborns, regardless of initial galactose values.

SUMMARY

This patient's presentation leaves us with several important learning points to consider when caring for coagulopathic neonates. A thorough history and physical examination can help direct the workup of neonatal coagulopathy.[8] There are also several potential pitfalls in laboratory testing to be aware of in this patient population. First, normal coagulation parameters vary based on patient's gestational and chronologic age, so it is essential to consult appropriate reference ranges.[9] Second, as important as the newborn screening program is in helping identify inborn errors of metabolism, it is equally important to consider the possibility of an inborn error of metabolism even in the setting of a negative newborn screen and adjust the patient's diet accordingly.[6] Ultimately, neonates presenting with coagulopathy are a delicate population that require a thoughtful approach to their workup and management.

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