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CASE REPORT

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Common pathway coagulopathy and hemorrhagic edema of infancy

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Key Clinical Message

When screening tests of haemostasis are abnormal, it is important to identify at which point in the coagulation cascade dysfunction may be occurring. This may assist to identify a specific deficiency/dysfunction, the type of bleeding to be anticipated, and replacement therapy if required. Unmasking of an inherited coagulopathy or the development of an acquired coagulopathy may occur in the setting of a second (febrile) illness. Differentiating between inherited and acquired coagulopathies will rely on clinicians taking a thorough personal and family bleeding history, and correlating these findings with the haemostasis screening results.

KEYWORDS

bleeding, dyscrasias, edema, microangiopathy, pediatrics

1 | CASE REPORT

A previously healthy 5-year-old girl of Middle Eastern heritage presented to the emergency department with spontaneous bruising and well demarcated purpura to her face, extremities, and trunk, sparing the mucus membranes. She had periorbital edema and swelling to her upper arms and thighs which had progressively increased over 2 days (Figures 1–4). The purpuric areas were warm and painful to touch. There had been a prodromal illness of mild cough and coryza without fever but low grade temperatures up to 37.5°C were recorded in hospital. She was born term at term after a nontraumatic delivery and had normal growth and development. She had no surgical history, although had her ears were pierced without complication. There was no personal or familial history of bleeding, however her parents and maternal grandparents were first cousins. She was a resident of a suburban area, and there was no history of ingestion of drugs (including anticoagulants) or other toxins. She was afebrile, normotensive, hemodynamically stable, and euvolemic with normal urinalysis. The remainder of the examination was unremarkable.

Full blood examination was largely unremarkable. Electrolytes, renal and liver function tests were normal, with a mildly raised C-reactive protein (CRP) of 26. Coagulation studies revealed prolonged coagulation studies (APTT and PT) with complete correction on mixing

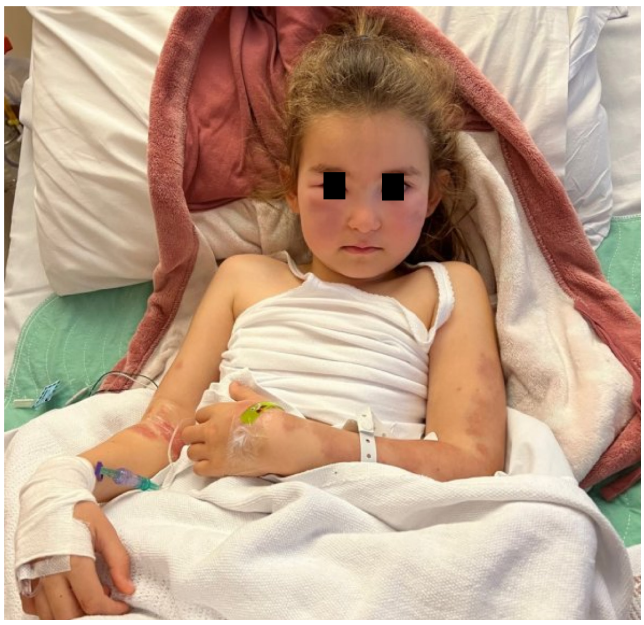

FIGURE 1 Facial and upper limb skin markings on presentation.

FIGURE 3 Right upper limb and right facial skin markings.

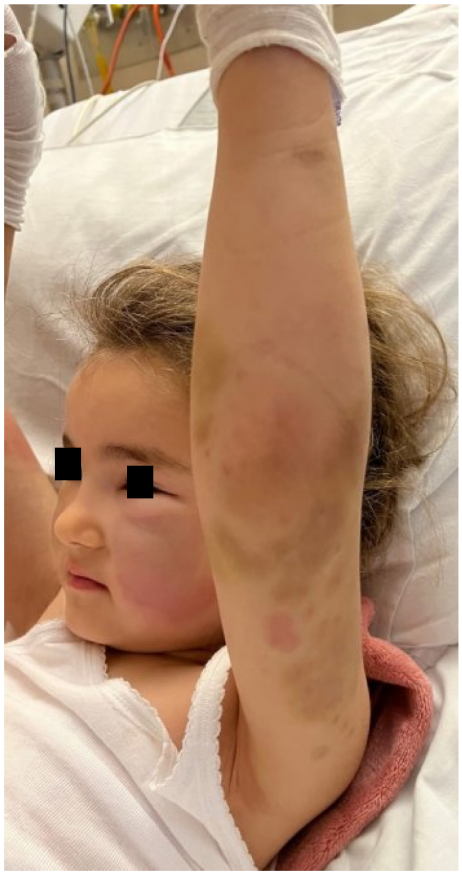

FIGURE 2 Limb and facial skin markings on presentation.

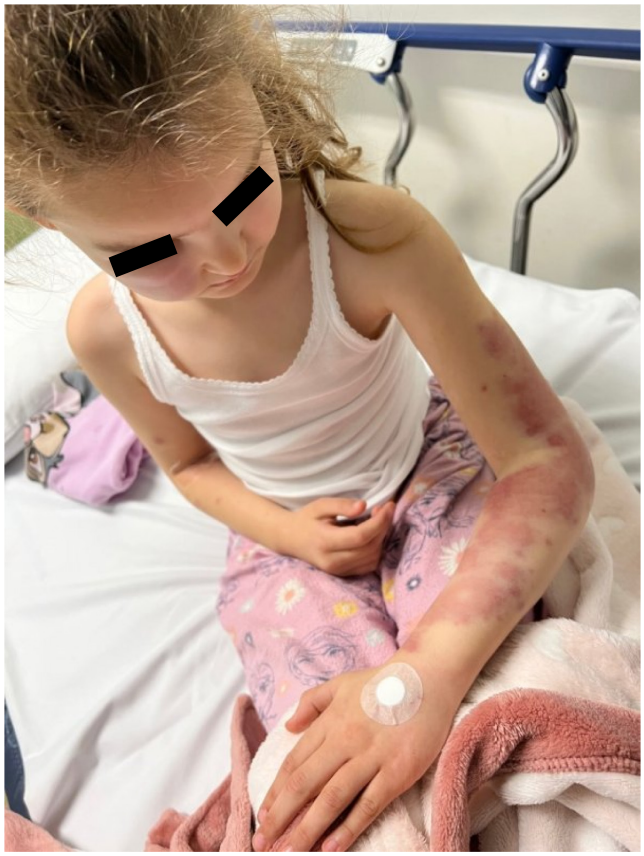

FIGURE 4 Left upper limb and facial skin marking.

studies, suggestive of a factor deficiency rather than an inhibitor. Her fibrinogen was normal, largely excluding a differential of DIC (Table 1).

Given concerns of potential sepsis (including meningococcal disease) due to the non-blanching nature of her rash, she was commenced on intravenous ceftriaxone

and clindamycin and flucloxacillin was later added. She received 5 mg of vitamin K intravenously and 30 IU/kg prothrombinex (3-factor), but her coagulation studies remained abnormal with an INR of 4.8 and aPTT of 77. She received a further 40 IU/kg prothrombinex and 10 mL/kg fresh frozen plasma, with correction of her INR (1.6) and aPTT (26). After 2 days of hospitalization, the rash and swelling improved with ongoing low-grade temperatures up to 37.5°C. An infective screen including blood and urine cultures, respiratory and stool viral PCRs was remarkable only for stool enterovirus PCR positivity.

Following transfer to a tertiary center, factor studies on pre-transfusion samples identified a congenital Factor V (FV) deficiency (Factor V levels <5%), unmasked in the context of illness. She was discharged home 2 days later, following marked improvement of her edema and rash. Repeat FV levels and genetic testing taken several weeks later confirmed a congenital FV deficiency.

This patient has a mild bleeding phenotype and hence no further active treatment has been required. She will be reviewed annually with a plan for coagulation factor support as required for dental or surgical interventions. Education for the family includes management of potentially heavy future menses, management of mucosal bleeding (e.g., epistaxis), and emergency planning in the event of a significant trauma or head strike. Recommendations have been made for testing her siblings.

2 | DISCUSSION

An understanding of the differential diagnosis of purpura in children is critical, as it may be a manifestation of relatively benign or life-threatening disease, and management must vary accordingly. Concerning features include rapid progression of symptoms, association with bleeding,

TABLE 1 Hematological and urine results at time of admission.

Full blood examination	Reference ranges	Coagulation studies	Reference ranges	Factor studies	Reference ranges
Hb 140 g/L	110–140	INR 5.7	<1.3	Factor V 5%	60–140
MCV 80	75–85	PT 57.1	10.0–14.0	Factor II 115%	70–110
MCH 28	24–34	aPTT 95	24–34	Factor VII 56%	70–150
Platelet count 252	150–140	Fibrinogen 3.2	1.50–4.0	Factor VIII 167%	35–180
Neutrophil count 8.2	2.0–9.0				
Lymphocyte count 1.3	2.0–7.5				
Film report: There is moderate lymphopenia		Correction on mixing with normal plasma. Suggestive of factor deficiency (INR 1.9, PT 25, aPTT 74)			
Urinanalysis		No red cells, white cells, protein, or bacteria seen on microscopy			

TABLE 2 Purpura differentials.

Viral	Enterovirus	Adenovirus	Influenza		
Bacterial	*Neisseria meningitides*	*Streptococcus pneumoniae*	*Haemophilus influenza*	Group A Streptococcus	*Staphylococcus aureus*
Mechanical	Vomiting or coughing (in distribution of superior vena cava)	Local physical pressure (e.g., tourniquet)	Non-accidental or accidental injury		
Hematological	Immune thrombocytopenia	Malignancy (e.g., leukemia)	Aplastic anemia	Disseminated intravascular coagulation	Hemolytic uremic syndrome or (TTP) thrombotic thrombocytopenia purpura
Other	Henoch–Schönlein purpura	Other vasculitis	Drug-induced thrombocytopenia		

abdominal or joint pain, features of shock, lethargy, or hepatosplenomegaly.[1] Important differentials are listed in Table 2.

This case provides an interesting illustration of a rare inherited coagulopathy, presenting in the context of a viral illness with a similar phenotype to acute hemorrhagic edema of infancy (AHOI), although atypical in light of her age and markedly deranged coagulation studies. AHOI is an immune-mediated small vessel vasculitis that typically presents with purpura, edema, and fever in children from 4 months to 2 years, although cases have been described up to 5 years of age.[2] Viral upper respiratory infections are the most common trigger, but bacterial infections, medications, and immunizations have been associated. Although sharing features with Henoch–Schönlein purpura, systemic involvement is less frequent, it is not associated with renal disease[2] and usually follows a benign self-limiting course.[3]

Factor V (FV) deficiency is a rare bleeding disorder that does not typically present with spontaneous nontraumatic bruising and purpura, and is not associated with AHOI, although we hypothesize our patient's underlying deficiency may have influenced the severity of her presentation. There is an estimated incidence of 1/1,000,000 in the general population although higher prevalence is reported where there is parental consanguinity.[4] Congenital deficiency has an autosomal recessive inheritance with more than 150 mutations including missense, nonsense, frameshift, and splice mutations identified.[4] The manifestation of FV deficiency is varied, but most commonly presents with mucosal bleeding, or bleeding with invasive procedures. Rarer manifestations include recurrent miscarriages, intracranial hemorrhage in the newborn, gastrointestinal bleeding, and/or hemarthrosis.[4] There is significant phenotypic variability observed with the same measured level of FV, which is poorly understood.[5]

FV is a glycoprotein that plays an essential role in the formation of the prothrombinase complex, which is critical for clot formation. Deficiency will present with prolongation of both aPTT and PT, suggestive of a deficiency in the common pathway of the coagulation cascade. Common pathway deficiencies include Factors II, V, X, or fibrinogen and may be inherited or acquired in the context of inhibitor formation, liver dysfunction or vitamin K deficiency.[5] Confirming FV deficiency requires testing with a FV assay. Combined FV/VIII deficiency can occur and should be excluded via a Factor VIII assay. The mainstay of treatment for severe bleeding is fresh frozen plasma as there is no commercially available FV concentrate, although a novel plasma derived FV concentrate has been successful "in vitro."[6] For more severe bleeding platelet transfusion may also be required as Factor V is stored within platelets (suggest consult with hematologist as risk of alloimmunization). Minor bleeding events may be successfully treated with local measures (e.g., compression) or antifibrinolytic agents (e.g., tranexamic acid).[7] Where FV deficiency is identified, referral to a tertiary bleeding disorder service is recommended to organize appropriate counseling and follow-up.

In summary, when patients present with purpura a wide array of differentials must be considered, with a high index of suspicion maintained for acquired coagulopathies that may be unmasked by coexisting illness. When abnormal coagulation studies are found, specific testing is required to identify the underlying factor deficiency and thus target appropriate treatment.

AUTHOR CONTRIBUTIONS

Jye Gard: Conceptualization; data curation; formal analysis; investigation; project administration; supervision; writing – original draft; writing – review and editing. **Raffaela Armiento:** Conceptualization; investigation; writing – original draft; writing – review and editing. **Anna Cartwright:** Writing – original draft; writing – review and editing. **Shelley Bell:** Writing – original draft; writing – review and editing. **Anthea Greenway:** Investigation; supervision; validation; writing – review and editing. **Erin O'Reilly:** Investigation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

CONSENT

Written informed consent was obtained from the patient's parent to publish this report in accordance with the journal's patient consent policy.

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