ECAT Newsletter

Case Report

Acquired protein S deficiency with purpura fulminans presentation in the aftermath of varicella zoster in a child

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Case description

A 4-year-old girl was referred to the paediatric intensive care unit (PICU) in our hospital because of purpura fulminans. A week earlier, she had suffered an acute varicella zoster virus (VZV) infection with the appearance of characteristic vesicular lesions and fever. On the day of admission, the girl suddenly experienced pain in both legs and massive, well-delineated purpuric lesions appeared. Upon admission to the ICU, her vital functions were preserved and some remaining, crusted varicella zoster lesions were noticed. The purpuric lesions started to resolve within hours of hospitalisation.

Coagulation tests indicated a serious coagulopathy with a prothrombin time (PT) of 36% (reference interval (RI): 70-120%), an undetectably low fibrinogen level, i.e. <40 mg/dL (RI: 200-400 mg/dL), and an activated partial thromboplastin time (aPTT) of 44.7 seconds (s) (RI: 28.9-38.1 s). Thrombocytopenia was observed with a platelet count of 167 000/µL (RI: 229 000-533 000/µL).

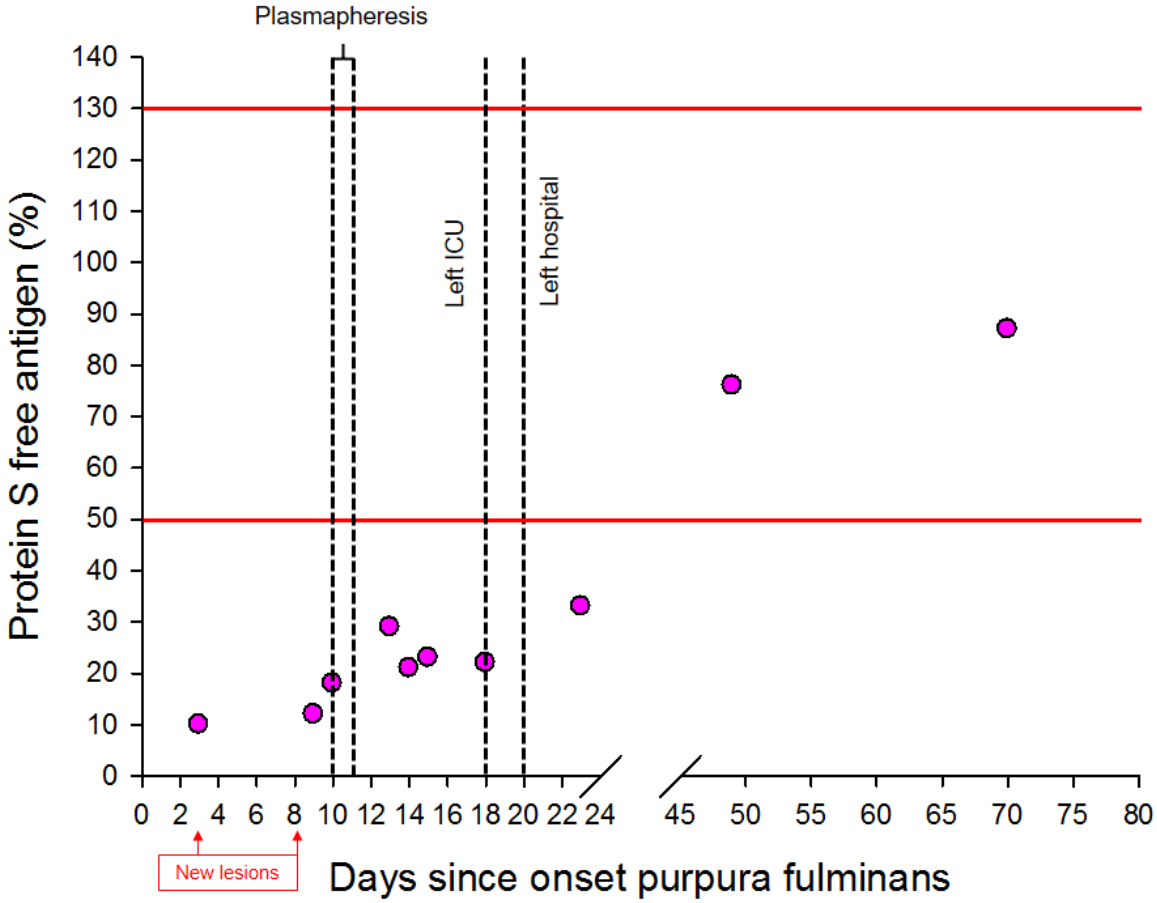
Fresh frozen plasma (FFP) was administered, resulting in the normalisation of PT to 71%, an increase in fibrinogen level to 101 mg/dL, the platelet count remaining unchanged at 159 000/µL, and a decrease of aPTT to 39.2 s. That day she was transferred to the paediatric ward for further monitoring. The following night, her general condition deteriorated and she experienced intense abdominal pain with vomitus. The next morning (i.e. day 3), lab coagulation parameters were determined and showed PT 56%, fibrinogen level 64 mg/dL, platelet count 212 000/µL, and aPTT 45.5 s. These laboratory parameters preceded the clinical deterioration later that day, with the recurrence of new very extensive gluteal purpuric lesions for which she was readmitted to the PICU. FFP was administered again (slow infusion 10 mL/kg), failing to improve coagulation parameters: PT 51%, fibrinogen level 52 mg/dL, and aPTT 41.3 s, with the platelet count remaining stable at 209 000/µL.

Protein C activity, measured on a plasma sample obtained prior to first FFP administration, was 46% (RI: 59-168%), antithrombin was above 145% (RI: 75-145%), and free protein S antigen was far below RI at 10% (RI 50-134%). Additionally she was diagnosed as a heterozygote carrier of Factor V Leiden and homozygous normal for the Factor II G20210 mutation. The course of the free protein S antigen levels is depicted in Figure 1.

Her lesions did not show necrosis, so a conservative approach regarding the purpura was adopted. The next 24 hours (i.e. day 4), blistering of the lesions was observed and they were aseptically incised. Severe anaemia occurred, with the haemoglobin level dropping from 12.3 g/dL on admission to 5.8 g/dL on day 5.(RI: 11.0-14.0 g/dL). The coagulation parameters remained normal for the next 48 hours, with aPTT 34.4 s, PT 77%, and the fibrinogen level 422 g/dL on day 5.

Nevertheless, on day 8 a second clinical relapse happened with the reoccurrence of purpuric lesions. FFP was since then continuously administered at 20 mL/hour. On day 10, plasmapheresis was initiated and repeated on day 11. On day 18 she was transferred to the paediatric ward where she stayed for another 48 hours, without any new lesions occurring. The patient left the hospital on day 20 and remained symptom-free during further clinical follow-up. She stayed on enoxaparin treatment until the normalisation of protein S levels, which was observed at the second follow-up consultation.

Figure 1. Course of protein S free antigen of a 4-year-old girl with post-varicella zoster purpura fulminans. Red lines indicate upper and lower normal values (i.e. 50 and 130% respectively).'New lesions' indicate new purpura fulminans lesions and milestones are indicated with dotted lines.



Discussion

Protein S is one of the components of the anticoagulant system, and together with protein C, it forms a complex that inactivates activated factor V, part of the prothrombase complex, and activated factor VIII, part of the tenase complex [1]. Protein S deficiency can be either inherited or acquired.

First discovered in 1984, congenital protein S deficiency has been associated with more than 300 mutations in the PROS1 gene [2], with the majority being missense and nonsense mutations. Congenital protein S deficiency is an autosomal dominant disease with a prevalence ranging from 0.03 to 0.13% in the general population.

In individuals with thrombosis, the prevalence of protein S deficiency rises to 1 to 5% [3]. The relative risk of developing a first venous thromboembolism with protein S deficiency can be as high as a factor 10, compared to the general population, and the relative risk of recurrent venous thromboembolism ranges from 1.0 to 1.4. Comparable numbers are observed for protein C deficiency (relative risk 1.4-1.8) [4]. The prevalence of factor V Leiden ranges from 3 to 7% in the general population and occurs in up to 20% of patients with recurrent venous thromboembolism. The relative risk of developing a first venous thromboembolism is up to 5 times higher than in the general population [4].

A combination of both protein S deficiency and activated protein C-resistance via factor V Leiden has already been reported [5]. Zöller et al. observed that 72% of individuals with a combination of both inherited protein S deficiency and factor V Leiden suffered from at least 1 venous thromboembolism during their lifetime [6].

Acquired protein S deficiency can be caused by pregnancy, liver disease, sepsis, acute thrombosis, disseminated intravascular coagulation (DIC), nephrotic syndrome, ulcerative colitis, multiple myeloma, and can be induced by certain drugs (for example coumarin derivatives, L-asparaginase, and oestrogens). Another cause of acquired protein S deficiency has been linked to varicella zoster, with in extreme cases a presentation with purpura fulminans.

Purpura fulminans is a DIC-subtype, characterised by skin necrosis [7], and is mainly confined to children [8]. Post-varicella zoster thrombotic sequelae have already been reported [7, 9-12]. According to Cameron et al., hospitalisation due to post-varicella zoster coagulopathy is 0.04/100 000 per year in the United Kingdom and Ireland (95% confidence interval 0.02-0.09/100 000 per year) [13]. Children stay for a median of 9 days in hospital (inter-quartile range: 1.0-23.75 days) and have a median age of 4 years at presentation (inter-quartile range: 2.0-7.0 years) [13].

Purpura fulminans linked to protein C and/or protein S deficiencies can be seen in three clinical situations: congenital homozygous protein C or protein S deficiency (mainly observed in neonates or young children), during acute bacterial or viral infection due to acquired protein C deficiency, and VZV infection can cause post-infection acquired protein S deficiency [8]. VZV-associated purpura fulminans typically occurs one week after onset of the acute infection [8, 9], as is also illustrated in our case report. The pathophysiology of acquired protein S deficiency following varicella zoster has been observed to be associated with protein S-neutralising antibodies [9, 14], and tends to be self-limiting within weeks [9]. These antibodies cause increased protein S plasma clearance, resulting in acquired protein S deficiency. The patient we describe received on multiple occasions FFP not resulting in any increase of free protein S antigen levels (Figure 1). FFP, although frequently administered, is not capable of adequately restoring the protein S levels in VZV-associated purpura fulminans [9]. However, the existence of protein S-neutralising antibodies could not been proven in this case. Additionally, anti-cardiolipin antibodies and transient lupus anticoagulant can also be observed in some cases [12, 15]. In our patient, the presence of lupus anticoagulant could not be demonstrated and anti-cardiolipin antibodies were not investigated.

The characteristics of 12 children who suffered from post-varicella zoster protein S deficiency have been summarised by De Geyer et al. [9]. The course of purpura fulminans can have unfavourable consequences, for example leg amputation [9], cerebral infarction [10], and most frequently lead to (sometimes very extensive) necrosectomy. Our patient did not show these serious complications, despite the increased risk of developing post-VZV thrombotic sequelae associated with factor V Leiden, as was the case in this patient [16]. Purpura fulminans is not solely observed in children, as illustrated for example by the case of a 42-year-old woman who developed purpura fulminans following a co-infection with VZV and cytomegalovirus [8].

The laboratory work-up of protein S deficiency has several potential pit-falls [17]. Functional protein S assays are sensitive to activated protein C complex-resistance [29]. As this girl was also carrier of a heterozygous factor V Leiden, these clotting-based assays would have resulted in erroneous results due to the activated protein C resistance. Protein S is largely bound in the plasma and this has consequences for the dosage of protein S via antibody-based assays. Depending on the design of the assay, only free (i.e. biologically active) protein S or total protein S is measured. The assessment of free protein S is considered the golden standard and was also used to monitor this patient. Several drugs either influence the protein S levels or can interfere with the assays. Purpura fulminans is a thrombotic coagulopathy and anticoagulants are thus a mandatory part of the treatment. As a consequence of the anti-vitamin K activity of coumarin derivatives, protein S levels and other vitamin K-dependent coagulation factors cannot be assessed during anti-vitamin K treatment. Direct thrombin inhibitors and anti-Xa drugs falsely decrease the result of activity-based protein S assays whereas these drugs do not influence the antibody-based assays for free and total protein S levels [19].

In conclusion, this case report demonstrates that VZV infection is not always an innocent disease of childhood. The symptoms of this girl were swiftly recognised by the paediatricians and linked to the varicella zoster infection. During hospitalisation, she experienced two relapses of purpuric lesions. The first relapse was preceded by the disturbance of routine coagulation parameters, and could thus be considered to raise the alarm regarding the upcoming new purpura. In the follow-up, free protein S antigen values normalised and the girl recovered without major sequelae.

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