From purpura to idiopathic purpura fulminans: a guidance in diagnosis and therapy

Liselot De Cloedt [a], Inez Vanholder [b], Coskun Arkaz [c], Cynthia Lafaire [c], Filip Thiessen [c], Thierry Tondu [c], Marijke Traen [d], Elisabeth LIM Duval [e]

[a] AZ Monica, Department of Paediatrics, Deurne and University of Antwerp, Faculty of Medicine and Health Sciences, Wilrijk, Belgium
[b] University of Antwerp, Antwerp University Hospital, Department of Paediatrics, Edegem, Belgium
[c] University of Antwerp, Antwerp University Hospital, Department of Abdominal, Paediatric and Plastic Surgery, Edegem, Belgium
[d] AZ Monica, Department of Paediatrics, Deurne, Belgium
[e] University of Antwerp, Antwerp University Hospital, Paediatric Intensive Care Unit, Edegem, Belgium

els_duval@yahoo.com

Keywords

Varicella zoster virus ; chicken pox ; disseminated intravascular coagulation ; children : idiopathic purpura fulminans.

Abstract

Varicella is a common infection in children. Although benign in most cases, severe complications can occur, of which idiopathic purpura fulminans is one of the most devastating with high morbidity and mortality. It is a haematological emergency characterised clinically by well-demarcated erythematous maculae progressing rapidly to haemorrhagic necrosis. This form of purpura should be suspected in an otherwise healthy child with a history of varicella, no underlying sepsis, and coagulopathy with low protein S or C levels. Mimicking autoantibodies to anticoagulants, mainly against protein S, are thought to be aetiological factors. Therapy is based on the treatment of the underlying disease in combination with plasmapheresis and immunosuppression against the circulating autoantibodies. Depending on the degree of bleeding or hypercoagulability, plasma transfusion or anticoagulation may be considered.

We present a two-year-old girl with rapidly progressive purpura, leading to full-thickness skin necrosis requiring multiple surgeries and skin grafts. As early recognition and treatment is essential to reduce mortality and to prevent severe morbidity, awareness of this syndrome and its clinical evolution is important. We tried to establish a helpful guidance to facilitate diagnosis and treatment of idiopathic purpura fulminans.

Introduction

Varicella or chickenpox, caused by varicella-zoster virus, is a very common infection in children, characterized by vesiculo-papulous rash and fever. Although in most cases self-limiting, some rare but serious complications can occur, varicella-associated idiopathic purpura fulminans being one of them. Purpura fulminans (PF) is well known in paediatrics. It is an acute thrombotic disease that can occur during severe sepsis or in the context of protein C (PC) or S (PS) deficiency. In rare instances, PF can also occur after normally benign infections such as chickenpox or herpes. Autoantibodies to PC or PS, whether combined with diffuse intravascular coagulation (DIC) or not, are presumed to be the cause of this form of PF, called idiopathic PF (IPF) (1-3). Early clinical recognition appears to be difficult in practice and correct therapy also remains to be defined. Nevertheless, early identification and prompt treatment could reduce the mortality and often severe morbidity associated with this condition.

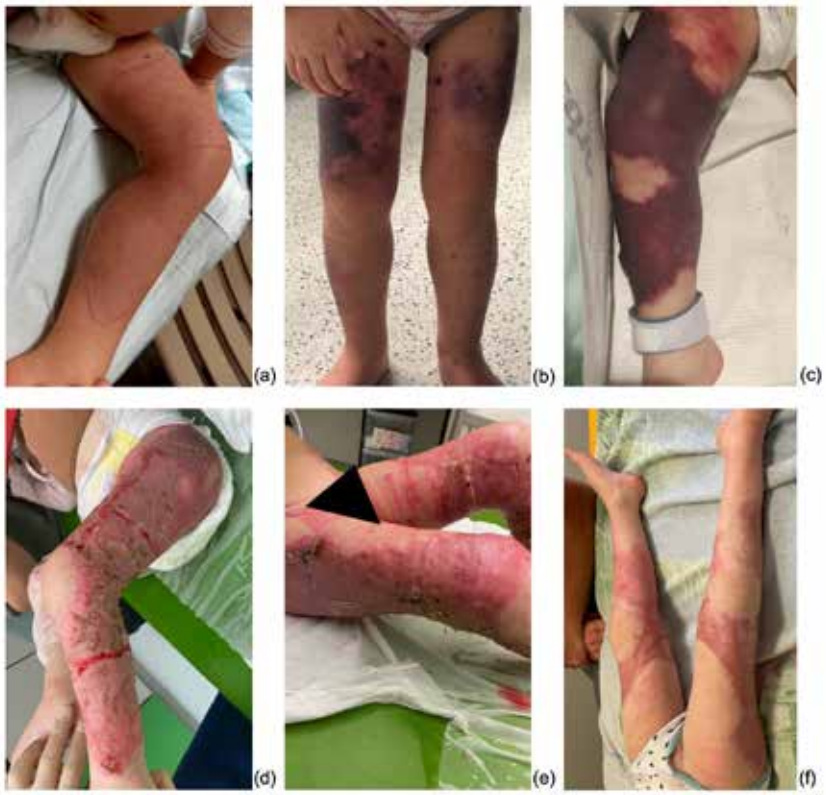
We present a case of a previously healthy two-year-old girl with IPF four days after the onset of a varicella infection. She developed full thickness skin necrosis which needed surgical debridement and skin grafting of both legs. This case demonstrates that the clinical picture might be misleading with delayed therapy as a result. English literature was reviewed to obtain a helpful guidance for the clinician in diagnosing and treating this pathology.

Case report

A two-year-old girl presented at the emergency department with what appeared to be ecchymoses on both legs (Figure 1a). She had developed mild varicella four days ago, with low-grade fever and general malaise, but appeared otherwise well. Further anamnesis revealed that she had been born prematurely at 33 weeks; there were no previous hospitalisations or history of bleeding diathesis. On suspicion of cellulitis, although not typical, she was admitted and started on intravenous antibiotics (penicillin and clindamycin). Laboratory evaluation showed a slightly prolonged activated partial thromboplastin time (APTT) and a slightly elevated C-reactive protein. Leukocytes were normal, as were thrombocytes, PTT, INR and D-dimers.

Within 24 hours, the lesions rapidly progressed to purpura and became painful with oedema of both legs (Figure 1b). Laboratory follow-up revealed evidence of disseminated intravascular coagulation (DIC) with prolonged plasma clotting time (INR of 2,95, normal range 0,8-1,2), thrombocytopenia (46x1000/µL, normal range 166-396x1000/µL), high D-dimers (>80 mcg/mL, normal range <0.65 mcg/mL) and reduced plasma fibrinogen (<30 mg/dL, normal range 170-350 mg/dL). Suspecting ongoing sepsis despite broad-spectrum antibiotics, she was transferred to the paediatric intensive care unit (PICU). Penicillin was changed to ceftriaxone and acyclovir was added. Post-varicella IPF was clinically suspected and treatment with fresh frozen plasma (FFP, 20 ml/kg/d), immunoglobulins (Ig, 0.8 g/kg) and methylprednisolone (2 mg/kg/d) was started and continued for three days. Both PC and PS activity came indeed back low (41% (71-125%) and <3% (70-130%, respectively)), supporting the working hypothesis. Low molecular weight heparin (LMWH) was started subcutaneously aiming at an anti-Factor Xa level between 0.5 and 1 U/ml. Clindamycin was stopped after three days, acyclovir was given for seven days.

Figure 1: Clinical presentation at the emergency department (a) and 24 hours (b) and 48 hours (c) after onset. Lesions after surgical debridement and grafting (d), at discharge (e) and two months later (f).



Despite treatment, the purpura progressed to bullae and necrosis (Figure 1c). In collaboration with the Department of Plastic Surgery the wounds were treated on a daily base under procedural analgesia with ketamine to await further demarcation. On day six, she developed fever and inflammatory parameters increased. The antibiotics were changed to piperacillin-tazobactam, and skin culture revealed a *Moraxella* species. Meanwhile, both platelet count and PC level normalised, but PS level remained very low (< 3%). Lupus anticoagulant was negative and antithrombin activity and active protein C resistance were normal. Despite adequate anti-Factor Xa levels, the child developed a small thrombus at the tip of a central catheter in the right subclavian vein. The line was removed. Anticoagulation therapy was changed to rivaroxaban, a novel oral anticoagulant (NOAC).

After three and a half weeks the injuries were well demarcated. Initial surgical debridement revealed full thickness skin necrosis with areas of fat necrosis; vacuum assisted closure (VAC) was used postoperatively. The patient underwent two additional surgical debridements and VAC modifications to obtain well vascularised tissue for skin grafts (Figure 1d). Due to the large skin defects compared to the body surface, the Meek micrografting technique was used: skin grafts were cut into micrografts and expanded at a ratio of 1:3 to obtain sufficient coverage. One week after successful skin grafting, donor skin was placed over the grafts for temporary covering and protection. The donor skin could be removed one week later (Figure 1e). The girl was discharged after sufficient wound healing and continued to receive ambulatory and rehabilitation care (Figure 1f).

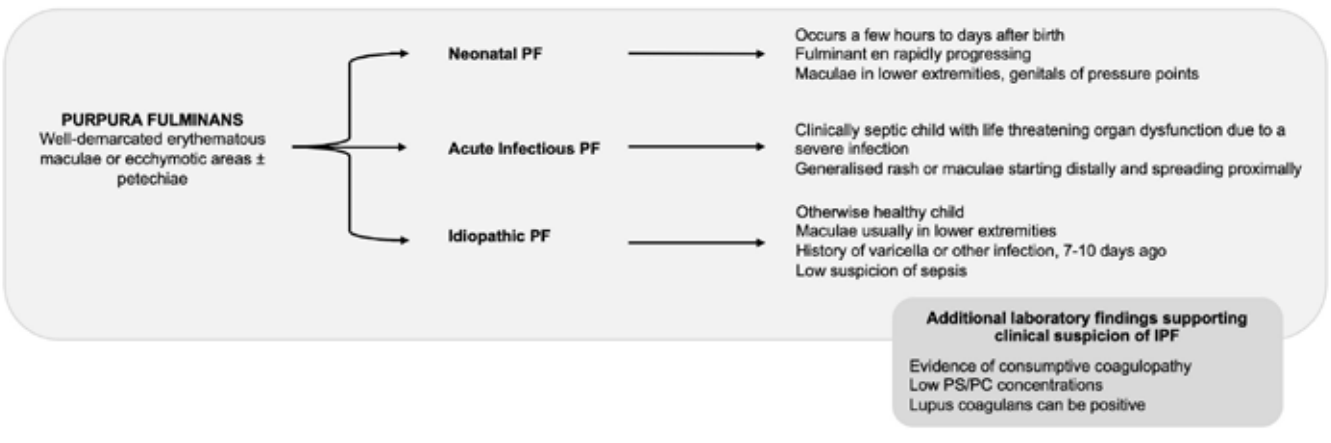
NOAC was continued for 2.5 months, at which time PS levels normalised (78%). One year after the onset of symptoms, she still wears her pressure garments and receives intensive physiotherapy. She can walk and bend her knees independently.

Discussion

Purpura fulminans is characterised by overwhelming endothrombosis in the both dermal and systemic microcirculation, resulting in rapidly progressive haemorrhagic skin necrosis, gangrene and multiple organ failure. Mortality is high, up to 50%, and those who survive often experience long-term morbidity due to contractures, amputation or severe scarring (1–4). Several mechanisms may underlie PF, most involving to the PS and/or PC anticoagulation pathway (Figure 2) (1,3–7).

In *neonatal PF*, there is a congenital deficiency of PC or PS, resulting in severe PF within hours to days after birth. This form of PF is caused by a homozygous or compound heterozygous pathogenic variant in the *PROC* or *PROS* gene and manifests mainly at the level of the lower limbs, male genitals and pressure points such as the heels and buttocks (3,4,6,7). Deficiency of anticoagulant factors can also be acquired, for example in severe sepsis, where systemic activation of coagulation causes consumption of anticoagulants. This *leads to acute infectious PF* with streptococcal disease accounting for the majority of cases. The clinical picture manifests as a septic-appearing child, with organ failure and a skin pattern that typically develops in the distal extremities

Figure 2: Types of purpura fulminans and how to differentiate.



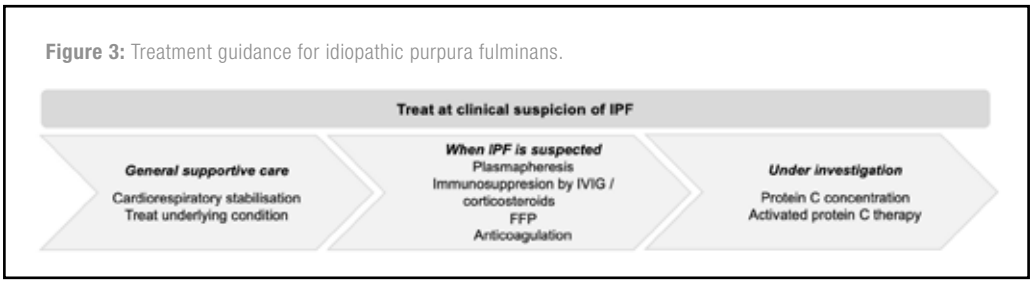


Figure 3: Treatment guidance for idiopathic purpura fulminans.

rapidly progressing proximally or a generalised diffuse rash affecting the whole body surface (3,4,7). Finally, PF can occur post-infectiously as an autoimmune response to otherwise benign childhood diseases such as varicella. This postinfectious PF, also known as *idiopathic PF*, typically occurs seven to ten days after the primary infection (1,5,6). The incidence post-varicella PF is rare, only 0.05 to 0.16%, but it is one of the most devastating complications. The viral infection probably induces the production of IgG-mediated autoantibodies against PS (mainly) or PC or anti-thrombin III (3,7–11). Although the exact mechanism has not been fully elucidated yet, the most likely pathophysiology of IPF appears to be cross-reactivity against the virus and PS via molecular mimicry (9,11,12).

IPF should be suspected clinically by the appearance of well-demarcated erythematous maculae or ecchymosis, with or without petechiae, a few days after a varicella infection. Lesions usually appear first and primarily on the extremities, particularly the thighs and lower legs, while distal lower extremities and upper limbs often appear to be spared (1,3,4,8,9). They rapidly increase in size and intensity and develop into painful blue-black, non-blanchable haemorrhagic necrosis. Bullae may form, culminating in gangrene and full-thickness necrosis within 24 to 48 h. The clinical picture may eventually deteriorate to multi-organ failure due to large-vessel venous thrombosis and systemic microvascular thrombosis (3,5,6). If this clinical picture is observed in an otherwise healthy child, a recent (less than 15 days ago) varicella or other infection is anamnestically reported, and no other signs of sepsis are identified, IPF should be strongly suspected and treatment should be initiated (1,3,6,9).

Although the typical presentation of IPF is a laboratory picture of DIC without a clinically severely ill/septic looking child, there is no simple test to confirm the diagnosis. Laboratory tests often show prolonged plasma clotting times, thrombocytopenia, decreased plasma fibrinogen concentration or increased plasma fibrin degradation products, but these findings are aspecific and can occur in DIC of any cause (3,7,8). As IPF is caused by an autoantibody-mediated decrease in the plasma concentration of PS (or less often PC), concentrations of these antithrombotic agents should be measured. A plasma concentration of PS or PC below 30% makes the diagnosis of IPF likely (3,4,9).

In addition, autoantibodies against anticoagulant proteins such as PS or PC, but also against lupus anticoagulant, anticardiolipin or prothrombin fragment 1+2, may be found during or after varicella infection. The correlation between the levels of these autoantibodies and the incidence of complications of varicella infection, such as IPF, is still under debate. However, the presence of lupus anticoagulant has been frequently reported in IPF (3,10,13,14).

The diagnosis of IPF should be made by careful consideration of clinical and biochemical factors and exclusion of any other underlying factors such as sepsis, but therapy should not be delayed until all biochemical information is available (3,4). Patients with lower platelet counts and lower concentrations of PS or PC can be expected to have a more severe (9,10,13,14).

Early recognition and treatment of IPF and its underlying cause are essential to reduce mortality and to prevent major long-term health sequelae. This was already written down by Fishbein in 1969 (15). However, there is still no consensus on the treatment of IPF, although an aggressive, multi-modality approach is usually advocated to reduce the significant morbidity and mortality (2). Plasmapheresis and Ig-therapy have been suggested as the most effective treatment against the PS inhibitor, with FFP being beneficial in temporarily replacing PS and PC in circulating plasma (2,3,9). Immunosuppressive therapy, including intravenous Ig and prednisolone, should be considered to suppress further production of autoantibodies to PS (2,3,5,8,9). As IPF is predominantly a thrombotic process resulting from a deficiency of antithrombotic factors, most if not all patients are anticoagulated with LMWH at the time of diagnosis (2,3,8). Ongoing anticoagulation may be required if there is large vessel thrombosis (3). Others advocate the use of anticoagulants until the protein S levels return to normal (2,8). However, normal and safe levels of many thrombotic markers in childhood have yet to be determined, specifically in infants and young children. Several other treatment modalities require further investigation before they can be withheld, such as protein C concentrate or activated protein C therapy (4,16). The balance between of clotting and anticoagulant substances is usually restored after about three months. Autoantibodies appear to be transient and disappear completely within a few weeks to months, regardless of the therapy used (1,3, 9–11). The skin lesions that have occurred will often take weeks or even months to heal, depending on the degree of necrosis. Surgical debridement, fasciotomy or amputation may be necessary. Contractures, prolonged hospital stay and cosmetic injuries, among others, can cause developmental, physical and psychosocial limitations in these patients. A multidisciplinary approach with close collaboration between PICU team, paediatric haematologist, surgeons and physiotherapists should be initiated, often followed by prolonged stay in rehabilitation centres (3).

Conclusion

IPF is a serious complication of varicella and is associated with high mortality and morbidity. Early recognition and treatment are essential to improve outcome, but there is still no consensus on how to establish the diagnosis and how to treat efficiently and safely. IPF should be suspected when purpura fulminans occurs several days after varicella infection. However, the initial phase is often clinically confused with purpura fulminans due to sepsis, delaying the appropriate treatment. Awareness of this syndrome, and its clinical progression from macula to purpura, is therefore important.

The pathophysiology of IPF is also not yet fully elucidated. Although molecular mimicry is thought to be at the basis, other immunological pathways also need to be investigated. Many diagnostic and therapeutic options have been described, but a clear guideline is lacking. Although more research is needed, we hope that we have given the paediatrician some helpful guidance on how to recognise and treat IPF.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

REFERENCES

1. Woods CR, Johnson CA. Varicella purpura fulminans associated with heterozygosity for factor V Leiden and transient protein S deficiency. Pediatrics. 1998, 102(5): 1208–1210.
2. Busuttil DP, Hay CRM, Lewis MA, Wynn RF. Aggressive multiple modality therapy for varicella-associated purpura fulminans. Br Jl Haematol. 2000, 110(4): 1012–1013.
3. Chalmers E, Cooper P, Forman K, Grimley C, Khair K, Minford A, et al. Purpura fulminans: recognition, diagnosis and management. Arch Dis Child. 2011, 96(11): 1066–1071.

4. Colling ME, Bendapudi PK. Purpura Fulminans: Mechanism and Management of Dysregulated Hemostasis. Transfus Med Rev. 2018, 32(2): 69–76.
5. Levin M, Eley BS, Louis J, Cohen H, Young L, Heyderman RS. Postinfectious purpura fulminans caused by an autoantibody directed against protein S. J Pediatr. 1995, 127(3): 355–363.
6. Francis RB. Acquired purpura fulminans. Semin Thromb Hemost. 1990, 16(4): 310–325.
7. Talwar A, Kumar S, Gopal M, Nandini A. Spectrum of purpura fulminans: report of three classical prototypes and review of management strategies. Indian J Dermatol Venereol Leprol. 2012, 78(2): 228.
8. Abdulmalik A, Al-Ateeqi W, Al-Khawari M, Al-Osaimi S. Varicella-associated purpura fulminans: chicken pox is not always benign. Med Princ Pract. 2006, 15(3): 232–234.
9. Theron A, Dautremay O, Boissier E, Zerroukhi A, Baleine J, Moulis L, et al. Idiopathic purpura fulminans associated with anti-protein S antibodies in children: a multicenter case series and systematic review. Blood Adv. 2022, 6(2): 495–502.
10. Josephson C, Nuss R, Jacobson L, Hacker MR, Murphy J, Weinberg A, et al. The varicella-autoantibody syndrome. Ped Res. 2001, 50(3): 345–352.
11. Regnault V, Boehlen F, Ozsahin H, Wahl D, De Groot PG, Lecompte T, et al. Anti-protein S antibodies following a varicella infection: detection, characterization and influence on thrombin generation. J Thromb Haemost. 2005, 3(6): 1243–1249.
12. Januário G, Ramroop S, Shingadia D V., Novelli V. Postinfectious purpura fulminans secondary to varicella-induced protein S deficiency. Pediatr Infect Dis J. 2010, 29(10): 981–983.
13. Manco-Johnson MJ, Nuss R, Key N, Moertel C, Jacobson L, Meech S, et al. Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. J Pediatr. 1996, 128(3): 319–323.
14. Z Kurugöl, F Vardar, F Özkinay, K Kavakli, C Özkinay. Lupus anticoagulant and protein S deficiency in otherwise healthy children with acute varicella infection. Acta Paediatr. 2000, 89(10): 1186–1189.
15. Fishbein RH. Purpura fulminans: an analysis of the lesion and its treatment. J Pediatr Surg. 1969, 4(3): 320–329.
16. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014, 2(1): 1–8.