CASE REPORT

Varicella complicated by cellulitis and deep vein thrombosis

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SUMMARY

We report a 16-month-old girl with varicella complicated by cellulitis, invasive Group A *Streptococcus* (GAS) infection and deep vein thrombosis. She presented with varicella lesions, fever and a painful firm tumefaction on the right lower leg (RLL). Ultrasound showed a local subcutaneous tissue thickening suggestive of cellulitis and antibiotics were initiated. Further swelling of the RLL motivated a second ultrasound that showed an obstructive thrombus for which she was started on enoxaparin. The blood culture confirmed GAS infection leading to directed antibiotherapy. Additional studies showed positive lupus anticoagulant, decreased protein S and antithrombin. She completed a 2-week course of intravenous antibiotics and anticoagulation therapy with clinical and laboratory markers improvement. However, 3 days later, a recrudescence of symptoms occurred and the ultrasound revealed a local abscess. Further amoxicillin treatment resulted on a complete resolution of symptoms. Doppler ultrasound after 1 month showed markedly increased vein patency.

BACKGROUND

Varicella is a common infectious disease in childhood, usually benign and self-limited, and complications are believed to be rare. However, serious complications may occur, such as cellulitis, invasive Group A *Streptococcus* (GAS) infection and deep vein thrombosis (DVT). A transient acquired thrombophilia, typically protein S deficiency, has been previously described in children with varicella zoster virus (VZV) infection, and GAS infection may act as a trigger in thrombus initiation. In such cases, an early treatment and extensive diagnostic workup are of critical importance. The purpose of this case report is to raise awareness to potential severe complications of varicella in immunologically healthy children.

CASE PRESENTATION

A previously healthy 16-month-old girl presented to the emergency department on the seventh day of varicella lesions, fifth day of fever and second day of a painful swelling of the RLL, noticed after an unwitnessed fall on the previous day. On admission she was distressed, febrile (38.8°C) but haemodynamically stable. On physical examination she had a firm swelling of the upper third of the RLL with local petechial and ecchymotic lesions and inflammatory signs towards the upper thigh, while varicella lesions were resolving.

The family history revealed a cerebral venous thrombosis in a 35-year-old maternal aunt with several risk factors (obesity, smoking habits, oral contraception) and negative thrombophilia testing.

INVESTIGATIONS

Investigations (see [table 1](#)) revealed a white cell count of $17.3 \times 10^9/L$ (normal $5-15 \times 10^9/L$) with raised neutrophil count of $11.3 \times 10^9/L$ and a slightly low platelet count of $142 \times 10^9/L$ and haemoglobin of 10.8 g/dL. C-reactive protein and erythrocyte sedimentation rate were both raised (26.3 mg/dL and 81 mm/h, respectively). Creatine phosphokinase was not elevated (27 U/L). The prolonged prothrombin time could be explained by lupus anticoagulant presence. Renal and liver function tests were normal. A blood culture was requested. The right leg X-ray had no abnormal findings and the initial ultrasound revealed subcutaneous tissue thickening in the medial area of the right thigh, suggestive of cellulitis, without collections or effusions.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses considered in this case were:

- ▶ Cellulitis,
- ▶ Pyomyositis,
- ▶ Accidental trauma.

TREATMENT

Considering the empirical treatment of cellulitis, intravenous flucloxacillin and clindamycin were started. The next day, despite the absence of fever and being haemodynamically stable, further swelling of the limb, with areas of redness and bruising ([figure 1](#)), was noticed, prompting the request of a second ultrasound that showed an obstructive thrombus from the external iliac vein to the saphenofemoral junction, without permeability ([figure 2](#)). The abdominal Doppler ultrasound was normal. After a multidisciplinary discussion with paediatric surgery and thrombosis/haemostasis specialist, anticoagulant treatment with subcutaneous enoxaparin 1 mg/kg/dose every 12 hours was initiated. The blood culture subsequently confirmed GAS infection and flucloxacillin was switched to ampicillin. Subsequent investigations showed a weakly

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Table 1 Laboratory values on admission, on the fourth day and at discharge

	Admission	Day 4	Discharge	Reference values
Total leucocyte count	17.3	27.6	12.3	5–15×10 ⁹ /L
Neutrophil count	11.3	13.7	2.8	1–8×10 ⁹ /L
Lymphocyte count	2.2	9.1	8.2	6–9×10 ⁹ /L
Platelet count	142	273	693	200–450×10 ⁹ /L
Haemoglobin	10.8	9.1	8.9	11.1–14.1 g/dL
PT	14.2		12.3	9–13 s
aPTT	23.6		40.7	25.1–36.5 s
INR	1.28		1.11	<1.2
CK	27			60–305 UI/L
ESR	81			<13 mm/h
CRP	26.3	6.52	0.8	<0.03 mg/dL
Free protein S antigen	40		79	55%–124%
Protein C	49		91	40%–92%
IgM anticardiolipin antibody	Positive		Negative	Negative
IgG anticardiolipin antibody	Positive		Negative	Negative
Antithrombin	67		96	82%–139%
Lupus anticoagulant	Positive		Negative	Negative

aPTT, activated partial thromboplastin time; CK, creatine phosphokinase; CRP, C-reactive protein; ESR, estimated sedimentation rate; INR, international normalised ratio; PT, prothrombin time.

positive acute lupus anticoagulant and anticardiolipin antibodies, decreased protein S (40%) and antithrombin (67%). A bone scintigraphy excluded osteomyelitis. The thrombophilia molecular screening (gene—mutation: factor V—G1691A; prothrombin—G20210A or MTHFR—C677T) was negative.

OUTCOME AND FOLLOW-UP

As an inpatient, she remained afebrile and had a progressive clinical improvement on mobility and inflammatory signs (figure 3). After 2 weeks of intravenous antibiotic with clinical

Figure 1 Clinical photograph taken 24 hours after admission, showing a diffuse, erythematous, indurated, non-fluctuant and painful swelling of the right leg, with ecchymotic areas and crusted varicella lesions.

Figure 2 Right leg venous Doppler ultrasound, showing an obstructive thrombus (red arrow) from the right external iliac vein (A) and common femoral vein (B) to the right saphenofemoral junction (C).

resolution of all her symptoms and signs and normalisation of laboratory findings she was discharged on warfarin and amoxicillin. Three days after being discharged, she returns with a recrudescence of fever and a painful tumefaction on the right medial thigh region. The ultrasound identified a poorly defined fluid collection on the medial compartment of the right thigh (12×7 mm) with no extension to the deep tissues, suggestive of a local abscess, which had a spontaneous rupture and drainage during the exam. The culture of the exudate revealed GAS, with sensitivity to all the antibiotics tested. Further treatment with amoxicillin for 2 weeks resulted on a complete and final resolution of symptoms on follow-up clinics. The Doppler ultrasound evaluation at 1 month follow-up showed a marked increase in external iliac vein patency, without functional impact. Anticoagulation therapy with warfarin was continued for 3 months, with protein S level persistently higher than 70% on discharge and at treatment completion.

DISCUSSION

Although often a mild and benign disease in childhood, varicella can cause significant morbidity and sometimes mortality in otherwise healthy children. Rare and potentially serious

Figure 3 Clinical photographs taken on the fifth day as an inpatient, showing a marked improvement of the swelling and inflammatory signs on the right leg (A) and symmetrical lower limbs (B).

complications of varicella include aseptic meningitis, encephalitis, cellulitis, pyomyositis, necrotising fasciitis and thrombotic complications as the purpura fulminans and thromboembolic events.¹⁻³ Several cases of thrombosis postvaricella infection have been described⁴⁻⁷ and some of those patients presented with concurrent cellulitis or invasive GAS infection.⁷ The VZV infection is the most important predisposing factor for GAS invasive disease in children, particularly if complicated by cellulitis.¹ The most commonly reported thrombotic complication in association with varicella is purpura fulminans, followed by thromboembolism. Different pathophysiological mechanisms in varicella, such as microvascular congestion, hypercoagulability or endothelial dysfunction, can lead to an underlying propensity for vasculopathy, which may occasionally trigger a thrombotic event.^{4,7} The hypercoagulable state is explained by a transient immune response that comprises lupus anticoagulants, acquired antibodies against antithrombin, cardiolipin, protein C and most often protein S.^{2,4,6,7} Two cross-sectional studies,^{7,8} with incidence estimates of thrombosis in VZV infection ranging from 18% to 20%, revealed that children with varicella complicated by thrombotic events have significantly higher autoantibodies and decreased protein S levels when compared with children with uncomplicated varicella or asymptomatic controls. Doppler ultrasound is the initial imaging exam of choice for suspected DVT.^{9,10} In spite of the limited use of MR venography as a screening tool, it remains the most sensitive and specific imaging modality.¹¹ Molecular genetic testing is important to rule out underlying coagulopathies.⁶ The most important treatment measure is prompt anticoagulation with therapeutic doses of heparin. Anticoagulation therapy is recommended for 3 months and should be suspended only after normalisation of the original thrombophilic abnormalities.¹² VZV infection increases the risk of secondary bacterial disease and the most frequently identified agents are GAS and *Staphylococcus aureus*.¹³ Our case was further complicated by abscess formation, which is a frequent evolution of cellulitis (suppurative stage).¹⁴ Moreover, GAS coinfection, present in this case, may have acted as a trigger or thrombotic initiation cofactor.^{7,15} On GAS invasive disease, the duration of antibiotic therapy should be individualised and according to the clinical response, considering that a minimum of 14 days is recommended.¹⁶ The current limited knowledge of the autoantibody syndrome in VZV infection and the infrequency of DVT occurrence in children significantly hinders obtaining evidence that would allow informed paediatric guidelines for therapy. The authors raise the question of whether the initiation of empirical anticoagulation treatment as a primary prophylaxis for DVT should be recommended in children with complicated varicella, considering that ultrasound assessment may initially be normal.

In conclusion, cases of varicella complicated by cellulitis unresponsive to initial antibiotic treatment should prompt a high index of suspicion among clinicians for invasive GAS infection and DVT. Although rare, DVT should be ruled out in children presenting with cellulitis, as the overlapping clinical features may delay the diagnosis and treatment, leading to severe and life-threatening complications.

Learning points

- Cellulitis associated with deep vein thrombosis (DVT) is a rare occurrence in children with varicella zoster virus (VZV) infection.
- VZV infection predisposes children to a transient prothrombotic autoimmune response with an increased clearance of natural anticoagulants, mainly protein S.
- VZV infection is a known risk factor for cellulitis and subsequent invasive bacterial disease, which may contribute to thrombotic initiation.
- Suspected DVT in patients with cellulitis should always be evaluated by a Doppler ultrasound.

Contributors GNO took part in patient's guidance and wrote this case report. SB performed the doppler ultrasound investigations and participated in the interpretation of the images. NN and TS took part in patient's guidance, contributed to the revision of the manuscript for intellectual content and approved the final manuscript.

Competing interests None declared.

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