

What may underlie recurrent purpura fulminans?

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A woman presenting with recurrent purpura fulminans was eventually found to have inflammatory bowel disease. We suggest the inflammatory state resulted in a deficiency of functional protein C. (MJA 2007; 186: 373-375)

Clinical record

First admission

A 28-year-old woman presented to hospital with a 1-week history of diarrhoea (three soft, non-bloody stools daily), 2 days of vomiting, and a 12-hour history of a purpuric truncal rash.

Five years previously, she had experienced a 1-month diarrhoeal illness, managed as an outpatient. At that time, the full blood count and erythrocyte sedimentation rate were within the normal range. Faecal microscopy had shown scanty leukocytes. Colonoscopy was scheduled; however, the symptoms disappeared and investigation did not proceed. The patient subsequently suffered from mild, intermittent diarrhoea. Her uncle had a history of inflammatory bowel disease, although the patient was not aware of this when she first presented to us.

On presentation, her vital signs were normal. There was mild right upper quadrant abdominal tenderness, and multiple large, purpuric lesions over the trunk. Blood tests suggested a systemic inflammatory response and mild disseminated intravascular coagulation (Box 1). Faecal microscopy was positive for leukocytes and erythrocytes.

The differential diagnosis was broad, and included systemic infection (such as meningococcaemia), Henoch Schönlein purpura, the antiphospholipid syndrome, thrombotic thrombocytopenic purpura, and purpura fulminans associated with protein C deficiency.

Ceftriaxone and enoxaparin were commenced as empirical treatment for infection and/or purpura fulminans. Over the next day, the skin lesions became larger and confluent, with new lesions on the legs and perineum. A morphine infusion was required for analgesia. Four units of fresh frozen plasma were infused for suspected protein C deficiency, while awaiting laboratory test results. These confirmed a slightly reduced functional protein C level (63%). This was considered most likely an acquired deficiency, as seen in inflammatory states. Further fresh frozen plasma or protein C replacement was regarded as unnecessary.

Additional tests for prothrombotic (Box 1) and autoimmune diseases (antinuclear, extractable nuclear antigen, and double-stranded DNA antibodies) revealed no abnormality. Thrombocytopenic purpura was excluded by the finding of a normal

haptoglobin level. There was no significant bacterial growth from blood, urine or faeces. Ceftriaxone was ceased on Day 3.

Purpura fulminans was confirmed on skin biopsy by the finding of dermal venous and capillary thrombosis, without evidence of vasculitis (Box 2).

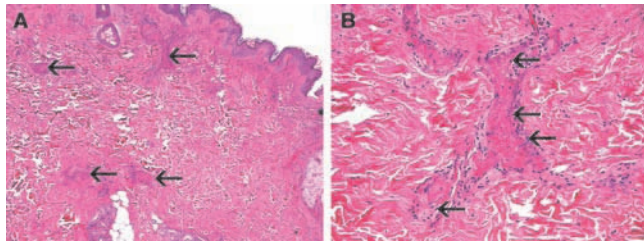
There was no further progression in the number or size of the skin lesions. However, on Day 5, the lesions formed bullae and ulcerated (Box 3). Metronidazole and dicloxacillin were added to treat secondary infection of the ulcers. The morphine infusion was ceased on Day 14, and oral oxycodone was substituted. The results of blood tests taken on Day 22 (Box 1) reflected an ongoing intense systemic inflammatory response. At the time of discharge on Day 23, the patient continued to pass three soft stools daily and had multiple ulcers over the trunk and perineum, which required daily

1 Results of laboratory tests

Test, unit (reference range)	First admission			Recovery period		Recurrent symptoms	Second admission
	Day 1	Day 2	Day 22	Day 36	Week 15	Week 25	Week 46
Haemoglobin, g/L (115–160)	129	123	84	93	126	122	126
White cell count, 10 ⁹ /L (4–11)	5.4	4.8	7.9	8.5	8.0	9.1	11.6
Platelet count, 10 ⁹ /L (150–400)	150	56	888	948	395	510	414
ESR, mm/h (1–20)	—	16	106	112	14	44	36
Total bilirubin, μmol/L (2–20)	15	10	4	7	2	6	12
ALT, U/L (< 55)	52	29	7	67	16	31	51
ALP, U/L (20–110)	204	209	157	1039	99	108	129
GGT, U/L (12–43)	34	48	48	293	56	33	50
Albumin, g/L (33–50)	34	31	24	30	42	39	42
C-reactive protein, mg/L (0–10)	—	197	97	31	<5	25	239
Haptoglobin, g/L (0.6–2.7)	—	2.1	—	—	—	—	2.9
Prothrombin time, s (9–15)	17	18	15	—	—	—	17
APTT, s (23–34)	31	33	40	—	—	—	32
Fibrinogen, g/L (1.5–4.0)	4.6	2.9	4.4	—	—	—	5.9
XDP, mg/L (0–0.19)	3.24	4.30	0.22	—	—	—	0.75
Functional protein C (70%–130%)	—	63%	—	—	—	—	65%
Free protein S Ag (50%–130%)	—	106%	—	—	—	—	116%
Antithrombin III (70%–145%)	—	95%	—	—	—	—	63%
Lupus anticoagulant, factor V Leiden, and prothrombin mutations	—	Not detected	—	—	—	—	—
ACA IgG (< 8)	—	2	—	—	—	—	—

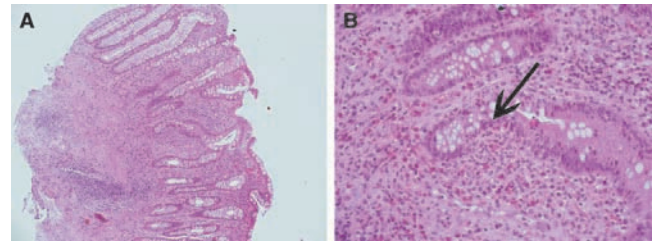
Bold indicates abnormal results. — = not measured. ACA = anti-cardiolipin antibody. ALP = serum alkaline phosphatase level. ALT = serum alanine transaminase level. APTT = activated partial thromboplastin time. ESR = erythrocyte sedimentation rate. GGT = serum γ-glutamyl transferase level. XDP = cross-linked fibrin degradation products.

2 Skin lesions: histopathology



A: Thrombosis of venules and capillaries is visible in both superficial and deep dermis (arrows) with intact overlying epidermis (haematoxylin and eosin [H&E]; $\times 50$). **B:** Higher power view of thrombosed venule showing some apoptotic debris (arrows) but no inflammation (H&E; $\times 200$). ◆

5 Colonic mucosa: histopathology



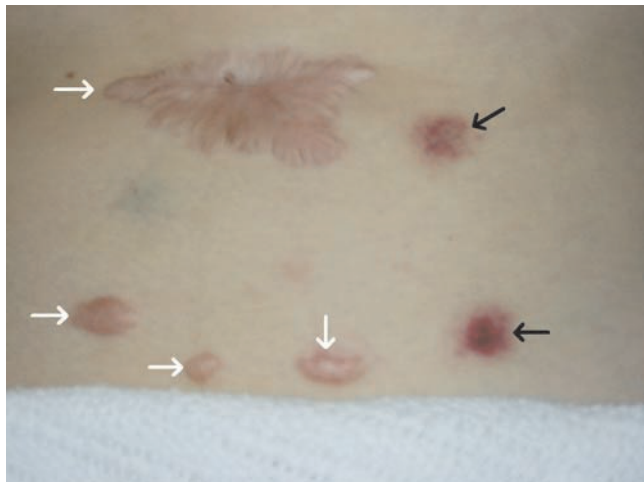
A: There was some crypt shortening and architectural distortion, and the lamina propria contained a brisk mixed inflammatory infiltrate, which extended into the submucosa (haematoxylin and eosin [H&E]; $\times 100$). **B:** Eosinophils and neutrophils were prominent in the lamina propria, and there was patchy cryptitis (arrow) (H&E; $\times 400$). ◆

3 Skin lesions: first hospital admission



Three bullous lesions (arrows) involving the abdomen, with mild surrounding erythema and diffuse purpura. The largest lesion involves the umbilicus. ◆

4 Skin lesions: second hospital admission



Within 24 hours of presentation, multiple purpuric lesions developed over the patient's abdomen and perineum. Two of these early lesions (black arrows) can be seen adjacent to the large scar involving the umbilicus and three smaller scars (white arrows) from the previous episode. ◆

nursing care for wound management. The discharge diagnosis was purpura fulminans, possibly precipitated by an enteric infection.

After discharge

By Day 36 of the illness, the diarrhoea had resolved. However, the patient remained fatigued, and the blood tests (Box 1) indicated persistent systemic inflammation and rising serum liver enzyme concentrations. Abdominal ultrasound was normal. The liver abnormalities were considered secondary to the oxycodone. Over the ensuing weeks, the analgesia was reduced and stopped, the blood parameters normalised, and the patient returned to her normal level of function. The skin lesions had healed by Week 15, but left significant scarring.

Twenty-five weeks following the onset of the illness, the patient re-presented as an outpatient with a 1-week history of diarrhoea (six watery stools daily). There was one mouth ulcer, but no new skin lesions. A faecal specimen showed only erythrocytes. The erythrocyte sedimentation rate, C-reactive protein, and platelets were slightly elevated (Box 1). The symptoms and abnormal blood parameters resolved completely over the following week. Referral was made for colonoscopy to investigate for inflammatory bowel disease.

Second admission

The patient presented again, 46 weeks after her original hospitalisation, with a 1-week history of bloody diarrhoea and colicky abdominal pain. The colonoscopy was due the following week. Her vital signs were normal. She had left lower quadrant tenderness. Laboratory tests indicated inflammation and mild coagulation abnormalities (Box 1). She was admitted to hospital. Over the next 24 hours, a purpuric rash consistent with purpura fulminans developed on her abdomen, sacrum and vulva (Box 4). Colonoscopy revealed widespread inflammation involving the entire colon, with multiple deep ulcers, but relative rectal sparing. The histology showed active chronic pancolitis, most suggestive of ulcerative colitis (Box 5). The consensus diagnosis was inflammatory bowel disease (colitis, unspecified). Methylprednisolone 60 mg intravenously was administered daily for 1 week. The skin lesions regressed, without ulceration, and the diarrhoea ceased. She was discharged on a reducing dose of prednisolone. Five months after ceasing prednisolone, she has remained asymptomatic.

Discussion

Purpura fulminans is an uncommon condition characterised by rapidly progressive dermal vascular thrombosis leading to haemor-

rhagic necrosis of the skin, which may extend to the muscle and bone, resulting in severe scarring.^{1,2} It has been described in three settings: (1) hereditary or acquired abnormalities in the protein C anticoagulant pathway; (2) infections, especially meningococcaemia; and (3) idiopathic.³

Purpura fulminans is associated with high mortality and morbidity rates, reflecting the seriousness of the underlying disease, such as bacterial sepsis, and the complications of tissue necrosis, such as secondary infection and limb loss.^{4,5} Therapy should be primarily aimed at treating the underlying cause and providing supportive care. Surgical intervention such as fasciotomy, skin grafting and amputation may be required.^{2,4,6} However, because of its rarity, there are few data to support specific treatments for purpura fulminans. Fresh frozen plasma is recommended for idiopathic purpura fulminans or protein C or S deficiencies.^{1,2,7} Idiopathic purpura fulminans has also been reported to respond to heparin.² Protein C replacement has been most widely used for purpura fulminans as a result of severe sepsis or congenital protein C deficiency.^{2,5,7,8} The use of corticosteroids in treating purpura fulminans remains controversial.^{1,5}

There has been one other report of purpura fulminans associated with ulcerative colitis, involving a 60-year-old man who was deficient in protein S, protein C and antithrombin III.⁹ There was no improvement with heparin or methylprednisolone. Fresh frozen plasma was administered and he underwent total colectomy. No further skin lesions developed, but he died as a consequence of nosocomial infections.

In retrospect, our patient had symptoms of inflammatory bowel disease for several years. Purpura fulminans, a rare manifestation of inflammatory bowel disease, had dominated the initial clinical presentation, distracting clinicians from the underlying condition. We believe that a possible pathophysiological explanation for this case is that the inflammation associated with the colitis led to a deficiency in protein C, thus precipitating purpura fulminans. Methylprednisolone appeared most effective in halting the progression of purpura fulminans, although this may have been secondary to treatment of the colitis, rather than of the purpura fulminans per se. What remains to be seen is whether future exacerbations of her colitis will be associated with recurrent purpura fulminans.

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Competing interests

None identified.

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References

- Stein RH, Sapadin AN. Purpura fulminans. *Int J Dermatol* 2003; 42: 130-131.
- Nolan J, Sinclair R. Review of management of purpura fulminans and two case reports. *Br J Anaesth* 2001; 86: 581-586.
- Ward KM, Celebi JT, Gmyrek R, et al. Acute infectious purpura fulminans associated with asplenism or hyposplenism. *J Am Acad Dermatol* 2002; 47: 493-496.
- Gurgey A, Aytac S, Kanra G, et al. Outcome in children with purpura fulminans: report on 16 patients. *Am J Hematol* 2005; 80: 20-25.
- Warner PM, Kagan RJ, Yakuboff KP, et al. Current management of purpura fulminans: a multicenter study. *J Burn Care Rehabil* 2003; 24: 119-126.
- Childers BJ, Cobanov B. Acute infectious purpura fulminans: a 15-year retrospective review of 28 consecutive cases. *Am Surg* 2003; 69: 86-90.
- Smith OP, White B. Infectious purpura fulminans: diagnosis and treatment. *Br J Haematol* 1999; 104: 202-207.
- Kravitz GR, Dries DJ, Peterson ML, et al. Purpura fulminans due to *Staphylococcus aureus*. *Clin Infect Dis* 2005; 40: 941-947.
- Kempton CL, Bagby G, Collins JF. Ulcerative colitis presenting as purpura fulminans. *Inflamm Bowel Dis* 2001; 7: 319-322.

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