

Purpura Fulminans in a Patient with Rheumatoid Arthritis

Ting Xiao, Zhe Guo, Jian Wu, Chun-Lin Zhou and Hong-Duo Chen*

Department of Dermatology, No.1 Hospital of China Medical University, 155 North Nanjing Street, Shenyang 110001, China. *E-mail: chenhd@cae.cn
Accepted June 30, 2009.

Sir,

Purpura fulminans (PF) is a rare disorder characterized by thrombosis of dermal vessels and skin necrosis with or without consumptive coagulopathy (1). PF is usually classified into three types: haemostasis-initiated PF or neonatal PF; acute infectious PF; and idiopathic PF (2). However, accumulated evidence has shown that there may be another type of PF: drug-induced PF (3–5).

Disseminated intravascular coagulation (DIC) exists in most, but not all, cases of PF. Some cases have only cutaneous manifestations but mild coagulation changes. The management of PF is difficult and varies with the clinical types of PF. Intravenous heparin inhibits

intravascular clotting and reduces consumption of anticoagulant factors. The role of systemic corticosteroid therapy is controversial.

We report here a case of drug-induced PF in a patient with rheumatoid arthritis (RA) who administered a pain-relieving traditional Chinese medication (TCM) called Anluotong Pian.

CASE REPORT

A 50-year-old Chinese woman presented in 2008 with a 10-day history of rapidly progressive painful ecchymoses, haemorrhagic bullae and skin necrosis (Fig. 1A–C). She was afebrile. She had a 3-year history of recurrent symmetric arthritis of



Fig. 1. Ecchymoses, haemorrhagic bullae or skin necrosis on (A) thighs, (B) lower legs and (C) upper arm. Intravascular thrombosis involving small and larger vessels of (D) dermis and (E) subcutaneous tissue (haematoxylin and eosin (H&E) stain, original magnifications $\times 200$). Lesions on the upper arm (F) resolved completely after administration of heparin and antibiotics. Lesions on (G) thighs and (H) lower legs resolved with atrophic scars.

multiple small joints with morning stiffness. RA was diagnosed by typical X-ray findings and elevated serum rheumatoid factor (RF) in 2005. She received 10-day oral Anluotong Pian therapy to treat arthralgia one week before the onset of the skin lesions. Laboratory tests revealed haemoglobin 9.4 g/dl, platelets $410 \times 10^9/l$, erythrocyte sedimentation rate (ESR) 95 mm/h, C-reactive protein (CRP) 13.4 mg/dl (range 0–0.8 mg/dl); RF 1580 IU/ml (range 0–30 IU/ml). Urinalysis was normal. Anti-streptolysin-0 (ASO) was normal. Anti-smooth muscle antibodies were positive (1:40 titre); anti-nuclear antibody (ANA), anti-platelet antibodies, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies and anti-mitochondrial antibodies were negative. Serum C3 level was 0.63 g/l (0.88–2.01 g/l). C4 was normal. IgA was 5.57 g/l (0.68–3.78 g/l). Coagulation studies showed prothrombin time 14.2 sec (range 11–14 sec), fibrinogen 6.89 g/l (range 2.0–4.0 g/l), D-Dimer 4.44 $\mu\text{g/ml}$ (range 0–0.5 $\mu\text{g/ml}$). Activated partial thromboplastin time (APTT), protein C and protein S were normal. Serum anti-herpes simplex virus and anti-cytomegalovirus IgM antibodies were positive. Repeated blood cultures for bacteria were negative. Histopathology showed intravascular thrombosis involving small and larger vessels of dermis and subcutaneous tissue with infiltration of lymphocytes and neutrophils (Fig. 1D, E).

PF was diagnosed. Intramuscular low-molecular-weight heparin calcium 4100 IU, twice daily, and intravenous antibiotics were administered for 2 weeks. The lesions on the upper arm resolved completely (Fig. 1F) and the ulcers on the legs improved slowly. There were new patches of ecchymoses on her limbs. Intravenous methylprednisolone 40 mg/day was administered and the ulcers improved rapidly. Methylprednisolone was tapered to 10 mg/day within 3 weeks. Laboratory tests except RF returned to normal. The lesions on the lower limbs resolved with atrophic scars after 2 months (Fig. 1G, H). No relapse occurred during a 6-month follow-up.

DISCUSSION

Drug-induced PF may be distinguished from the other three types of PF in following respects: (i) it occurs in patients with a history of administering certain medications; (ii) and with no prodromal infections; (iii) serum protein C and protein S levels may be normal; (iv) it responds to corticosteroids; (v) generally with a good prognosis (3–5). Propylthiouracil was reported to induce PF in two patients with Grave's disease (3, 4). The first case responded well to high-dose methylprednisolone (3); the second case resolved rapidly after withdrawal of propylthiouracil without using systemic corticosteroids (4). Hengge et al. (5) reported a 39-year-old man who developed PF following the intramuscular injection of diclofenac. There are also two reports in the Chinese literatures on PF induced by whitening cosmetics and pesticides in a 20-year-old and a 28-year-old healthy Chinese woman, respectively (6, 7). The latter administered systemic corticosteroids. Both patients eventually underwent acral amputation. Interestingly, neither patient had any documented prodromal infections or underlying diseases. Their serum levels of protein C and protein S were not reported.

Anluotong Pian is a pain-relieving TCM tablet containing *Marasmius androsaceus* extracts. There are

also many unidentified ingredients in the drug. There were no previous reports on adverse drug reactions of Anluotong Pian. We suggest the drug as the causative agent of the present PF case because: (i) there was a definite history of administering the drug; (ii) the incubation period was one week; (iii) there were no prodromal infections; (iv) the patient administered no other drugs simultaneously; (v) there was an excellent response to corticosteroids; (vi) there was no relapse after withdrawal of the suspected drug and corticosteroids.

Our patient's typical clinical and histological manifestations are highly suggestive of a drug-induced PF, although she had normal serum protein C and protein S levels and no DIC. The manifestations of our PF case were similar to those of the first propylthiouracil-induced PF case (3). However, in this case, there is still a lack of evidence for a stronger link between the PF and any substance present in the *M. androsaceus* extract than the contemporary intake of the extract. The fact that the patient had RA may increase the likelihood that the PF was drug-induced, since patients with auto-immune diseases may more often have adverse drug reactions due to aberrant management of immune complexes.

In summary, we report here a case of PF in association with RA; this case further extends previous observations that drug-induced PF manifests mainly in skin without DIC.

ACKNOWLEDGEMENT

This work was supported by the Program for Innovative Research Team in University (IRT0760) from the Ministry of Education of China.

REFERENCES

- Adcock D, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. *Semin Thromb Hemost* 1990; 16: 283–292.
- Adcock D, Brozna J, Marlar R. Proposed classification and pathologic mechanisms of purpura fulminans and skin necrosis. *Semin Thromb Hemost* 1990; 16: 333–340.
- Park KEJ, Chipps DR, Benson EM. Necrotizing vasculitis secondary to propylthiouracil presenting as purpura fulminans. *Rheumatology* 1999; 38: 790–792.
- Ligier S, Pham CD, Watters AK, Kassis J, Fortin PR. Purpura fulminans and anticardiolipin antibodies in a patient with Grave's disease. *Scand J Rheumatol* 2002; 31: 371–373.
- Hengge UR, Jochum C, Tschakarjan E, Maschke J, Erbel R, Schmid KW, et al. Purpura fulminans Fatale Folge einer alltäglichen Therapie? *Hautarzt* 2002; 53: 483–487.
- Liu LP, Chen YT, Zhang JW, Chen WJ. A case of purpura fulminans caused by cosmetics. *J Henan Med University* 2001; 36: 227–228 (in Chinese).
- Zhao YY, Zhao TZ. A case of purpura fulminans associated with primary pulmonary hypertension. *Ningxia Med J* 2000; 22: 180 (in Chinese).