Non-thrombotic inflammatory venous involvement in a patient with Sweet's syndrome, suggesting a complex autoinflammatory disease

Sirs,

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is a rare autoinflammatory condition characterised by fever, leucocytosis, tender erythematous skin lesions and diffuse upper dermal infiltrate of mature neutrophils. It can be associated with various systemic diseases, such as cancer, immunological disorders and others (1). Systemic corticosteroids are the mainstay treatment of Sweet's syndrome; other possible pharmacological strategies may include: colchicine, iodide, indomethacin, tacrolimus, dapsone, and pentoxifylline. Anakinra, an anti-interleukin-1 receptor antagonist, may be a potential effective therapy. However, recurrences occur in one-third of patients despite the use of colchicine or new biological drugs (2, 3).

Sweet's syndrome may involve extracutaneous organs, all of which presenting a sterile neutrophilic inflammation. The involvement of both large arteries (aorta) and small vessels has been described (4-6). To date, there is no data on the venous manifestations of Sweet's syndrome; however venous involvement has been reported in VEXAS syndrome, a complex adult autoinflammatory disease also including Sweet syndrome.

Hereby, we describe the case of an adult man affected by Sweet's syndrome presenting a concomitant venous involvement, which progressively improved after the reintroduction of corticosteroid therapy.

In January 2020, a 71-year-old man was admitted to our hospital for worsening general conditions, fever, anuria, and a tender skin eruption on both arms and legs of new onset. He reported a diagnosis of ulcerative colitis associated with Sweet's Syndrome seven years earlier. At the time of admission, the patient was being treated with anakinra 100 mg/thrice a week and colchicine 0.5 mg/day, the latter discontinued at the recommendation of the general practitioner due to the onset of diarrhoea.

Physical examination revealed tender erythematous nodules with a serpiginous pattern on both arms and legs, following the superficial veins vascular course and suggesting an acute recrudescence of Sweet's syndrome. Chest CT scan and haemogasanalysis showed an interstitial lung disease.

Laboratory findings showed an elevation of acute phase proteins (C-reactive protein [CRP] 16.2 mg/L), erythrocyte sedimentation rate [ESR] 51 mm (0-30), leucocytosis (8.88 x 10^9/L) and signs of acute kidney injury (creatinine 2.28 mg/dL). A Doppler ultrasound (DUS) examination of the upper and lower extremity showed a diffuse wall thickening of the superficial venous system with no sign of thrombosis, suitable for vascular inflammatory disease, involving the right cephalic vein, left basilic vein, right great saphenous vein and left small saphenous vein (Fig. 1).

Therefore, the diagnosis of Sweet's syndrome recurrence with inflammatory vascular injury was made. Systemic steroid

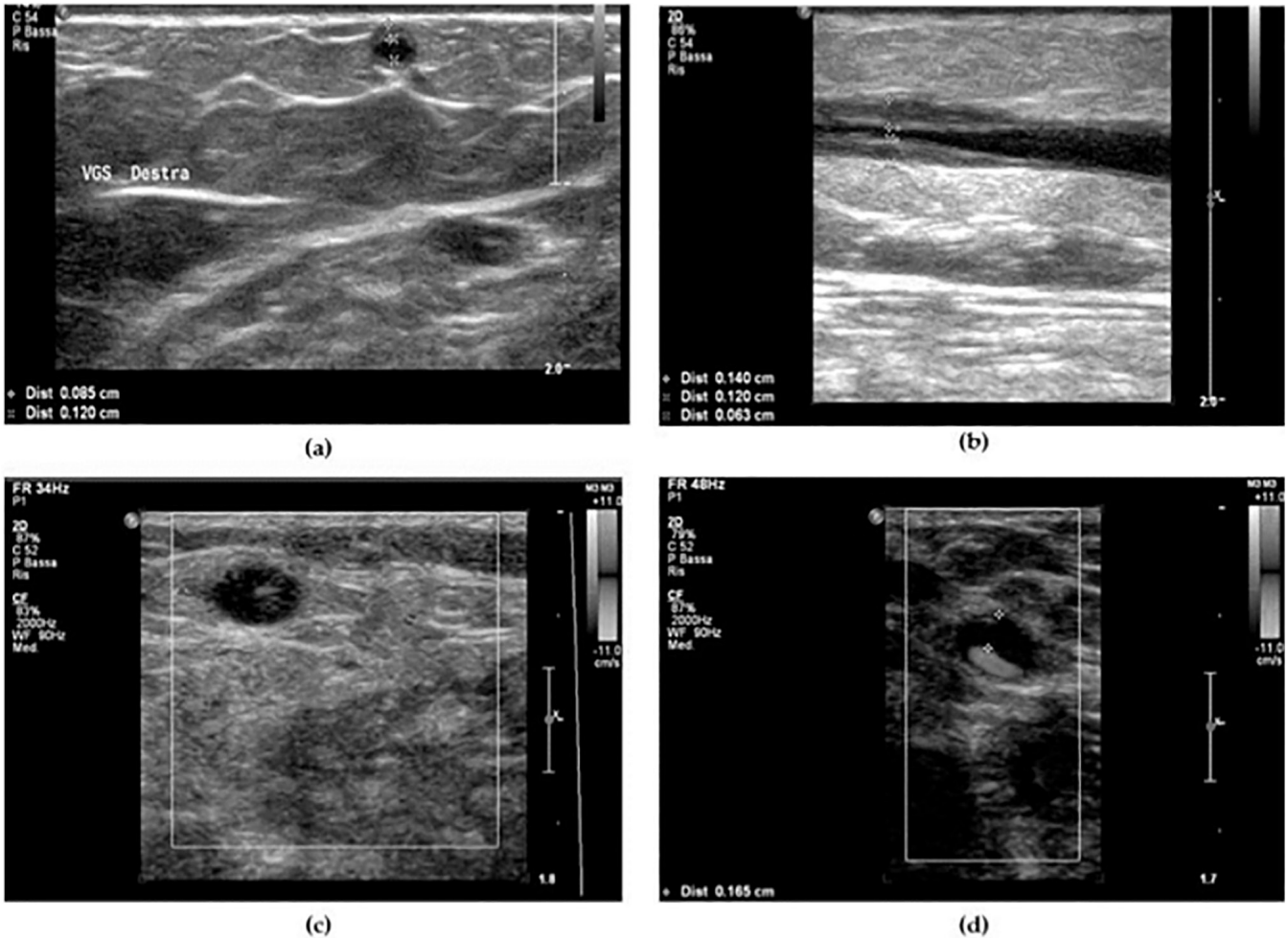

Fig. 1. The figures show a hypoechoic cuff around the veins of the superficial venous system, suitable for vascular inflammatory lesions. The complete vein wall coaptation with compression by the transducer excludes the presence of thrombi. (**a**,**b**) B-mode image of the right great saphenous vein; (**c**,**d**) Colour-flow Doppler image of the right cephalic vein demonstrating a blood flow in the lumen.

therapy with metilprednisolone 40 mg/day was started, and colchicine 0.5 mg/day was reintroduced. Patient's clinical conditions gradually improved; DUS was repeated four weeks later, showing the resolution of the venous wall thickening. There were no further episodes of phlebitis.

Sweet's syndrome, first described by Roubert Douglas Sweet in 1964, is a rare autoinflammatory condition characterised by fever, painful skin lesions and neutrophilia. Although a constellation of extracutaneous manifestations of Sweet's syndrome is described, vascular involvement is infrequently reported, and mostly includes arteries and aorta (5, 6). Diagnostic criteria initially proposed by Su and Liu and modified by von den Driesch in 1994, allow the diagnosis of Sweet's syndrome on the basis of clinical, laboratory and histopathological findings.

The distribution of lesions is provided by a large cohort study of 77 patients with Sweet's syndrome, in which the majority had more than one body area affected by rash, with a predominant involvement of the upper extremities (86%), trunk (56%), lower extremities (55%) and less frequently head (29%), neck (25%) and oral mucosa (4%) (8).

Our case shows an acute exacerbation of a previously known Sweet's syndrome, with an unusual and diffuse involvement of superficial veins, revealed by DUS. Ultrasonographic characteristics of lesions provide information about the perivascular distribution of the inflammatory process, which appears as a hypoechoic cuff around the vein. The superficial venous involvement was responsible for the cutaneous lesions, which differed from the typical pattern of Sweet's syndrome and reflected the vascular inflammatory process. Rapid and complete resolution of lesions after steroid treatment, which is one of the minor diagnostic criteria for Sweet's syndrome, further confirmed the clinical suspicion.

The two major criteria are always required for the diagnosis of Sweet's syndrome, even in the absence of two minor criteria (9). Indeed, the main limitation of our case report is the lack of histological analysis of the vascular lesions as proof of the atypical flare-up of the disease.

The etiopathogenesis of venous involvement in Sweet's syndrome is not yet elucidated; however it has been reported in VEXAS syndrome, a complex adult autoinflammatory disease including Sweet's syndrome and interstitial lung disease, and due to somatic mutation of UBA1, the major E1 enzyme that initiates ubiquitylation (10). As our patient presented all clinical markers of VEXAS syndrome, an enzymatic and vacuole search in myeloid precursors in bone marrow is currently ongoing.

The relapse of inflammation based on clinical and laboratory data and in the context of a diagnosed Sweet's venous biopsy is not required and the main role of DUS is to allow an accurate assessment of both vessels anatomy and precise distribution of lesions on arms and legs, ensuring the correspondence with rash. However, even if histological confirmation is advisable because imaging findings are not specific, DUS is an affordable, non-invasive, widely available method for monitoring the progression of the disease and the effects of treatment over time.

In conclusion, this report provides the DUS evidence of non-thrombotic inflammatory venous disease in Sweet's Syndrome, and the response to high-dose intravenous glucocorticoids.

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