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Colonic ulceration as an unusual manifestation of vasculopathy in systemic sclerosis

SIR, SSc is a CTD characterized by fibrosis and vascular complications. We describe an lcSSc patient with an unusual manifestation of gastrointestinal vasculopathy. A 56-year-old Caucasian woman with lcSSc presented with left lower quadrant abdominal pain. She was diagnosed with lcSSc in 1988, with RP, telangiectasias, sclerodactyly, gastroesophageal reflux and positive ACA. In 2001, she was diagnosed with pulmonary arterial hypertension (PAH), New York Heart Association functional class III, with a mean pulmonary artery pressure (mPAP) of 60 mmHg and cardiac output (CO) of 4.2 l/min on right heart catheterization. She was treated with bosentan, sildenafil and warfarin. Bosentan was discontinued due to liver function test abnormalities, and inhaled iloprost was initiated. Her PAH worsened (mPAP 83 mmHg, CO 2.7 l/min), and she developed gangrene in the right third digit requiring amputation. She also had an acute decrease in haematocrit with gastric antral vascular ectasia (GAVE) identified on endoscopy. Warfarin was stopped and inhaled iloprost switched to i.v. epoprostenol. Three months before her current admission, mPAP had improved to 57 mmHg and CO to 4.3 l/min on epoprostenol 40 ng/kg/min. One month later, the patient developed intermittent, crampy abdominal pain with occasional nausea, vomiting, diarrhoea and a 12-pound weight loss. CT and flexible sigmoidoscopy showed acute diverticulitis. An empiric antibiotic course did not improve the symptoms.

On examination, the patient was afebrile with blood pressure 93/65 mmHg, pulse 93 beats/min and oxygen saturation 97% on room air. She had telangiectasias on her face and chest, sclerodactyly, nail-fold capillary drop-out and right third distal phalanx status post-amputation. She had a 3/6 systolic murmur and a loud pulmonic second sound with parasternal heave. Her lungs were clear, and she had no peripheral oedema. She had normo-active bowel sounds without abdominal tenderness, ascites or hepatosplenomegaly.

Laboratory data showed normal complete blood count and comprehensive metabolic panels except creatinine 1.5 mg/dl (pre-renal; baseline 1.0 mg/dl). Negative tests included serum lactate, complements and CRP; blood and stool cultures; ova and parasite; and PCR for CMV and EBV. ECG showed normal sinus rhythm, right axis deviation and right ventricular hypertrophy without ischaemic changes. CT of the abdomen/pelvis showed bowel wall thickening, submucosal oedema and mucosal hyperaemia with diverticulosis in the sigmoid colon. Colonoscopy revealed a deep cratered ulcer at 50 cm from the anal verge with diffusely decreased vascular pattern in the recto-sigmoid colon (Fig. 1A). Biopsy of the ulcer showed focal mucosal erosion and fibrinous change without significant vascular inflammation, consistent with ischaemia (Fig. 1C). A cine abdominal magnetic resonance angiogram evaluating the mesenteric vascular anatomy and postprandial change in vascular flow, showed normal mesenteric arteries but abnormal post-prandial flow in the superior mesenteric vessels following a 200 kcal meal [1]. These findings were compatible with small-vessel ischaemia (Fig. 1D). Hypercoagulability work-up, including aPLs, was negative.

Epoprostenol was uptitrated to 63 ng/kg/min and warfarin re-initiated. Within 1 week, the patient reported improvement in abdominal pain. A flexible sigmoidoscopy 1 month later showed resolution of the ulceration (Fig. 1B).

Vascular complications of SSC include digital ulcers/ischaemic loss, renal crisis and PAH [2]. The most common gastrointestinal manifestation of SSC is not vasculopathy but rather dysmotility, affecting up to 90% of the patients [3], and thought to be related to smooth muscle atrophy and fibrosis [2]. The resulting functional impairment can manifest as oesophageal dysmotility, delayed gastric emptying, pseudo-obstruction, faecal incontinence and rarely stercoral ulceration secondary to faecal impaction [4, 5]. Gastrointestinal vasculopathy in the form of GAVE can affect up to 5.7% of SSC patients, with frequent capillary rupture causing recurrent bleeding [6]. Our patient developed a colonic ulceration that improved with vasodilator and anti-coagulation therapy, suggesting this may be an unusual manifestation of gastrointestinal vasculopathy. Several factors may have contributed to the formation of the colonic ulcer. The lesion was in a watershed area at high risk for ischaemia. Also, the patient’s low CO (2.7 l/min at admission) resulted in poor perfusion of visceral organs. We hypothesize that her underlying vasculopathy had progressed to involve her colonic vasculature,
leading to ulceration. She did not have faecal impaction, making stercoral ulceration unlikely.

Vascular injury early in SSc disease leads to endothelial apoptosis and increased circulating endothelial cells [7]. Subsequent endothelial dysfunction manifests as a decrease in vasodilators (endothelial nitric oxide synthase, prostacyclin synthase) and an increase in vasoconstrictors (ET-1) [8]. The imbalance contributes to adventitial fibroblast activation with resultant intimal proliferation, luminal narrowing and tissue hypoxia [9]. Epoprostenol, a prostacyclin analogue, which enhances vasodilation and inhibits platelet aggregation, has been shown to improve haemodynamics in severe SSc-associated PAH, and to prevent and heal digital ulcers [10].

Since patients with SSc are known to have low-circulating prostacyclin levels, we hypothesized that systemic replacement with epoprostenol would improve blood flow to the ischaemic area in the colon, and that warfarin would counteract the fibrinolytic dysregulation underlying SSc vasculopathy. The patient’s abdominal pain improved on these therapies, and the colonic ulcer healed on sigmoidoscopy 1 month later. Unfortunately, the patient died of right ventricular failure from PAH 3 months later.

Rheumatology key message

- Colonic ulceration in SSc may be a manifestation of underlying vasculopathy.

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data, showing the increase of anti-Grp94 antibodies in pa-

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suffers with several methodological errors that heavily

affect validity of the results. One critical aspect relates to

ELISA for measuring auto-antibodies in serum. The

authors made determinations without previously validating
the assay; i.e., they omitted to construct the calibration
curve with both negative and true-positive samples
(to establish the lower and higher limits of sensitivity),

and determine intra- and inter-assay variability [6, 7].

Reproducibility of measures should also be tested using

at least two dilutions of each serum sample in duplicate
and the values, read on the linear portion of the curve,

should be expressed as antibody titre (dilution factor of

serum) or antibody concentration (µg/ml). Normalization

by plasma proteins is preferable, since in patients with

immune diseases (and also in normal subjects) protein

concentration [especially that of immunoglobulin G (IgG)]
cannot be assumed that is equal, and averaging antibody

values without this correction might generate big errors.

It is not clear why the authors used western blotting (WB)
to assess specificity of the immune reaction after having

already made the same measure in ELISA. As a rule, WB

is used first to identify both true-positive and negative sam-

ples that then serve for constructing the calibration curve

in ELISA. The only difference between the two methods is

the higher sensitivity and reliability of ELISA, which in add-

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same antigenic proteins are used in both methods (with

the exception of a lower quantity of antigen in ELISA),

the reason why the authors omitted Grp94 in experiments

of WB to detect true-positive reactions (Fig. 2 in their

paper) appearing to contradict the principle of the

method and negating validity of results obtained with

Grp94 in ELISA (Table 1 in their paper).

A matter of concern is also the lack of adequate controls

for excluding non-specific reactions of both serum sam-

ples and secondary anti-human IgG antibodies with the

antigen. The authors used only BSA as control in half of

the plate wells, BSA can be taken as the blank for positivity
due to un-blocked sites in the plate, but the real blank is

made with antigen incubated in the absence of primary

antibodies (thus, rigorously speaking, with plasma

proteins other than anti-chaperone antibodies; i.e., with

control human serum albumin (HSA) and/or IgG at approxi-

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ples). In particular, the authors do not seem to know that

Grp94 can also irreversibly bind IgG at sites other than the

antigen-binding site [8], thus giving rise to significant

false-positive reactions with IgG antibodies (of different

species). We investigated this crucial property of Grp94

in depth and found that non-specific binding of Grp94 to

IgG could only be prevented by thermal denaturation of

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Comment on: Antibodies to the endoplasmic reticulum-resident chaperones calnexin, Bip and Grp94 in patients with rheumatoid arthritis and systemic lupus erythematosus

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