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Intestinal perforation and jejunal haemorrhage due to Wegener's granulomatosis

Sirs,

Wegener's granulomatosis (WG) is a necrotising vasculitis of the small and medium-sized arteries that characteristically affects the upper and lower respiratory tract. Involvement of the gastrointestinal tract appears rare, apart from mouth ulcers. However, bloody diarrhoea, intestinal necrosis, ulceration and perforation have all been reported (1).

A 54-year-old woman presented with a 6-week history of earache, nasal stuffiness, malaise, myalgia, oral ulcers and a rash over her upper and lower limbs. Biopsy of the rash revealed a leukocytoclastic vasculitis. Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) were positive, with anti proteinase 3 antibodies (PR3) of 27 Iu/ml. Three pulses of intravenous methyl prednisolone (1 gm) were given on consecutive days and one pulse of intravenous cyclophosphamide (1 gm), followed by oral prednisolone (60 mg daily). She developed transient renal impairment (creatinine 146 umol/l) which resolved with therapy. Renal biopsy was not performed due to an acute deterioration in the patients condition.

The patient developed bloody diarrhoea which increased in frequency, causing her haemoglobin to drop from 10.5 g/l to 7.0 g/l, and required a 3-unit blood transfusion. Upper gastrointestinal endoscopy was normal but colonoscopy was abandoned due to patient discomfort. The diarrhoea continued, and non-tender distention of the abdomen developed. An abdominal CT scan showed thickened segments of small bowel with a small walled off perforation. Urgent laparotomy showed multiple perforations of the terminal ileum and proximal colon. A small bowel resection and right hemicolectomy were performed with ileostomy formation. Two days post operatively a massive haematemesis (900 ml) of fresh blood occurred. The haemoglobin fell to 6.6 g/l. Upper gastrointestinal endoscopy was normal but a mesenteric angiogram showed bleeding of a jejunal branch of the superior mesenteric artery. This was embolised with coils and the bleeding stopped. Histological examination of the resected bowel revealed widespread ischaemia with a granulomatous vasculitis associated with areas of bowel perforation (Fig, 1). The patient was discharged at 2 months post laparotomy on prednisolone 30 mg once daily and monthly IV infusions of 1 g cyclophosphamide.

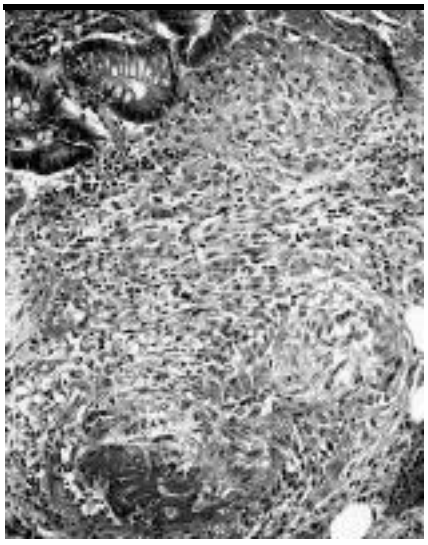

Fig. 1. Histological specimen of the small bowel resection showing destruction of a blood vessel by local granulomatous inflammatory infiltrate, in keeping with Wegener's granulomatosis.

Our case demonstrates that patients with WG may develop diarrhoea, abdominal pain, intestinal ischaemia, intestinal necrosis and intestinal ulceration with subsequent haemorrhage and perforation. There is a high incidence of laparotomy and death associated with reported cases of intestinal WG (2-8). Intestinal WG can also mimic other inflammatory gastrointestinal diseases like ulcerative colitis or Crohn's disease (9). Intestinal involvement in WG is considered uncommon. However, post mortem studies suggest a high incidence with histological evidence of intestinal vasculitis in 24% of cases (10). This suggests that the occurrence of intestinal WG is underestimated, possibly due to asymptomatic involvement or due to immunosuppressive treatments masking symptoms.

This case demonstrates the serious consequences of intestinal vasculitis in WG. The incidence of intestinal involvement in WG is probably underestimated with immunosuppressive therapy contribuing to this by masking gastrointestinal involvement.

R.L. STRIVENS[1], *MBBS*
A. BATEMAN[2], *BSc, MD, FRCPath*
N.K. ARDEN[3], *MSc, MD, MRCP*
C.J. EDWARDS[1,3], *BSc, MD, MRCP*

[1]Department of Rheumatology & [2]Department of Histopathology, Southampton General Hospital, Southampton, UK and [3]University of Southampton, Southampton, UK.
Address correspondence to: Dr. C.J. Edwards, Consultant Rheumatologist and Honorary Senior Lecturer, Department of Rheumatology, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK.
E-mail: cedwards@soton.ac.uk

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Circulating eosinophils lack *ex vivo* chemotaxis toward vascular endothelial growth factor in a patient with Churg-Strauss syndrome

Sirs,

Vascular endothelial growth factor (VEGF) is a key promoter of angiogenesis in rheumatoid arthritis and asthma. Increased circulating concentrations of free VEGF in these conditions may be produced by exudation from inflamed organs and release from platelets and other blood cells including eosinophils (1). Platelets contribute to secondary tethering processes of eosinophils to activated endothelium (2). Eosinophil-platelet interactions may therefore play a role in allergic inflammation and in thrombotic disorders of hypereosinophilic patients (3, 4). The recent demonstration of VEGF-induced chemotaxis of eosinophils via VEGF receptor flt-1 was made using peripheral blood eosinophils from healthy donors (5). Whether VEGF affects the chemotactic response of eosinophils in allergic inflammation with hypereosinophilia is unknown. Here we report on the lack of chemotactic effects of VEGF on circulating eosinophils from a patient with Churg-Strauss syndrome (CSS).

A 64-year-old woman was first seen with dyspnoea on exertion 2 months ago that had been treated with oral steroids and bronchodilators for asthma. Prior to admission, steroids had been stopped and occasional dyspnoea was treated with inhalative bronchodilators as needed. Then symptoms worsened with fever, Raynaud's phenomenon

of fingers 3 to 5 of the right hand and paresthesias of the right upper extremity, atypical chest pain on exertion and a vasculitic rash. ECG and chest X-ray were normal. Laboratory values were as follows: white blood cell count 31,000/mm^3 with 66% eosinophils; C-reactive protein 6.9 mg/dL(normal < 0.5 mg/dL); and IgE 3420 U/mL (normal < 100 IU/mL). The troponin T level was elevated to 0.69 ng/mL (normal range up to 0.44 ng/mL). Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and blood culture were negative. C3 and C4 levels were normal. ESR was 71 mm/1st h. Biopsy of affected skin showed vascular accumulation and tissue infiltration of eosinophils. Her symptoms remitted promptly after treatment with 60 mg prednisolone daily for 5 days followed by 40 mg for 6 weeks. Before initiation of treatment, informed consent was obtained and 20 ml of forearm venous blood drawn for further analyses.

Eosinophils were isolated from the peripheral blood of the patient and a healthy donor with no history of atopic or hypereosinophilic conditions by colloidal superparamagnetic microbeads conjugated with monoclonal anti-human CD16 mAb (5). Migration assays were performed using a modified 48-well Boyden microchemotaxis chamber with a 5 µm pore size cellulose nitrate filter, and VEGF-receptor expression was assessed by FACS (5).

Concentrations ranging from 100 nmol/Lto 10 pmol/Lof rhVEGF significantly increased the migration of eosinophils taken from the healthy donor in a dose-dependent manner. Eosinophils from the CSS patient did not migrate toward rhVEGF and migration toward RANTES was also markedly reduced (Fig. 1). In the FACS analysis, a slight but significant shift of fluorescence in eosinophils from the healthy donor was observed by anti-VEGF flt-1 antibody, as previously reported (5). Less anti-VEGF receptor flt-1-specific fluorescence was seen on eosinophils from the CSS patient (data not shown).

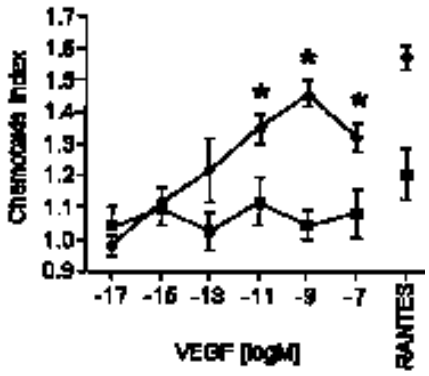

Fig. 1. Chemotactic effects of different concentrations of VEGF on human eosinophils. RANTES (10 ng/ml) served as positive control. Chemotaxis experiments were performed in modified Boyden chambers. Results are given as the mean ± SEM of the chemotaxis index, which is the ratio of the distance of migration (in micrometers) toward attractant and the distance toward medium. Mean (± SD) distance of random migration or replicates of 4 was 51 ± 2.9 µm and 45 ± 6.9 µm for healthy and CSS eosinophils, respectively. ◆ control; ■ CCS.
*p < 0.05, Mann-Whitney U test versus medium after multiple group comparison by Kruskal-Wallis test. CSS: Churg-Strauss syndrome.

In CSS, eosinophils in the peripheral blood are activated to various degrees possibly related to the clinical stage (6). The present investigation suggests that in CSS circulating eosinophils from forearm venous blood down-regulate VEGF receptor flt-1 and the functional response to VEGF as assessed in comparison to normal circulating cells. Increased levels of VEGF in the airway have been implicated in the pathogenesis of the eosinophilic inflammation and asthma (7) which are characteristic of CSS (5). Assuming that eosinophils from the peripheral blood of patients with CSS are activated, our observation may indicate that due to *in vivo* activation the responsiveness of circulating eosinophils to VEGF *ex vivo* is down-regulated. Systemic deactivation of chemotaxis receptors may protect the cells from premature activation and emigration.

VEGF binds with high affinity to two tyrosine kinase receptors, the fms-like tyrosine kinase (flt-1) and the kinase domain receptor, which are produced predominantly by endothelial cells; flt-1 is also present on hematopoietc cells (8) including eosinophils (5). Eosinophils are among the sources of VEGF which may act in an autocrine manner (8). Down-regulation of flt-1 occurs in leukocytes upon ligand binding (9). Whether the abrogated chemotaxis of eosinophils from CSS toward VEGF is related to receptor internalisation and/or other mechanisms of chemotaxis deactivation remains unknown.

A.KANEPPELE[1], *MD*
B. MOSHEIMER[2], *MD*
K. BIJUKLIC[2], *MD*
A. DJANANI[2], *MD*
C.CRIVELLARO[1], *MD*
A. ZELGER[1], *MD*
J.R. PATSCH[2], *MD*
C.J. WIEDERMANN[1], *MD*

[1]Department of Medicine, Central Hospital of Bolzano, Bolzano, Italy, and [2]Division of General Internal Medicine, Department of Internal Medicine, Medical University of Innsbruck, Innsbruck, Austria.
Address correspondence to: Prof. Christian Wiedermann, MD, Department of Medicine, Central Hospital of Bolzano, Lorenz Böhler Street 5, I-39100 Bolzano, Italy.
E-mail: christian.wiedermann@asbz.it

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Thyroid acropachy: An unusual rheumatic manifestation of Graves'disease

Sirs,

Thyroid acropachy (TA) is an uncommon rheumatic manifestation of hyperthyroidism which takes the form of soft tissue swelling of the hands and feet associated with clubbing and a characteristic periosteal reaction (1). A 43-year-old, non-smoking female presented to our out-patient rheumatology unit because of recent painful swelling of the fingers and toes. The patient's past medical history was unremarkable except for Graves'disease, diagnosed in 1984, for which she underwent total thyroidectomy on 1994. Since then she has been euthyroid and taking thyroxine therapy (100 µg/die).

In 2001 a progressive exophthalmos appeared that required high dose corticosteroids and, more recently, retroorbital radiotherapy, without a positive response. From the beginning of 2002 localized soft tissue swelling of the extremities occurred. Clinical examination revealed non-pitting soft tissue swelling on the fingers and toes without evidence of articular inflammation; pain was caused by palpation over the metacarpophalangeal, metatarsophalangeal and proximal interphalangeal joints bilaterally.

Laboratory examination (normal values in parentheses) revealed a normal thyroid function status: TSH = 1.71 µU/ml (0.4–4), fT3 = 1.91 pg/ml (1.5–4.1), fT4 = 1.18