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).

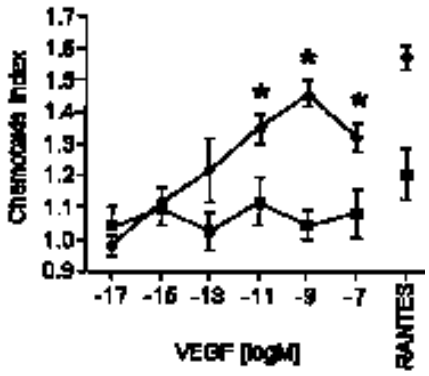

Fig. 1. Chemotactic effects of different concentrations of VEGF on human eosinophils. RANTES (10 ng/ml) served as positive control. Chemotaxis experiments were performed in modified Boyden chambers. Results are given as the mean ± SEM of the chemotaxis index, which is the ratio of the distance of migration (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.

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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

ng/dl (0.8–1.9). Anti-TG antibodies (Ab) and anti-TPO Ab were in the normal range, while the levels of anti-TSH receptor Ab were high: 85.3 U/L (< 1.5). Blood cell count, kidney and liver function tests, urate, acute phase reactants, auto-Ab (ANA, ACA, ENA, anti-dsDNA, anti-cardiolipin, RF), C3, C4 were in the normal range.

Plain radiographs of the hands revealed soft tissue swelling and a bilateral periosteal reaction that was more evident on the diaphyseal portion of several phalanges (Fig.1). On radiographs of the feet (not shown) a bilateral diaphyseal periosteal involvement of the first metatarsals was evident. No joint abnormalities were observed. The clinical history and radiological features were consistent with a diagnosis of TA associated with Graves'ophthalmopathy and pre-tibial mixedema.

TA is a rare extra-thyroidal manifestation of autoimmune thyroid disease, usually Graves' disease, although it has also been described in Hashimoto thyroiditis (2), together with ophthalmopathy and dermopathy. These peripheral manifestations of Graves' disease typically appear in chronological order, with exophthalmos first (30% of patients), followed by dermopathy (4% of patients) and then acropachy (0.1-1% of patients) (3,4). In these patients acropachy usually takes the form of clubbing of the fingernails and/or toenails with or without swelling and tightness of the skin; only 10% of patients with acropachy present the complete clinical picture with clubbing, soft tissue swelling, pain in the distal small joints and a periosteal reaction seen on plain radiographs (1). Typically, the periosteal reaction is solid, and localized on tubular bones (particularly in the hands and feet) with a symmetrical distribution. These radiological features and the past history of Graves' disease allow the differential diagnosis from other conditions associated with a periosteal reaction (5).

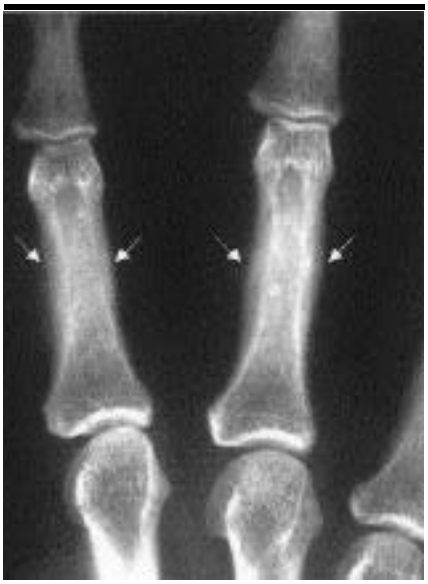

Fig. 1. Magnified view of right hand radiograph showing a periosteal reaction on both radial and ulnar side of the second and third proximal phalanges (**arrows**).

In most patients TA appears 1-2 years after the diagnosis of thyroid dysfunction (1), but its appearance up to 25 years after the onset of thyroid disease has been reported (6). In our patient the chronology of extra-thyroidal manifestations (ophtalmopathy, dermopathy and acropachy) was that usually described and they appeared in succession 17 years after the diagnosis of Graves'disease, despite her euthyroid status. Furthermore, she presented a complete clinical picture of TA that led her to consult our rheumatology unit whereas TA is usually observed by endocrinologists (1,7), dermatologists (4) and radiologists (8, 9).

Of particular relevance is the recent observation that TA and dermopathy are markers of severe Graves' ophtahlmopathy and identify patients in need of more frequent follow-up and more aggressive therapy for ophthalmopathy (7), such as our patient. No specific treatment for TA is available at present nor does its appearance seem to be inhibited by a good pharmacological euthyroid state (1). In our patient, physical therapy and a short course of therapy with a COX-2-specific inhibitor mitigated the articular pain without changing the soft tissue swelling of the fingers and toes; this clinical picture was stable at follow-up till May 2004.

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Calcinosis universalis in systemic sclerosis with limited scleroderma

Sir,

Calcinosis universalis is a rare complication of dermatomyositis, psoriasis, uremia and systemic sclerosis of the limited cutaneous subset (lSSc) (1-5); it is characterized by intracutaneous, subcutaneous, fascial and intramuscular deposits of crystals of calcium phosphate (hydroxyapatite). We describe here a new case of calcinosis universalis complicating lSSc.

A 70-year-old Caucasian woman was recently admitted to the Department of Clinical and Experimental Medicine, because of severe difficulty in walking and rising from a chair and from the bed, and because of a worsening of dyspnea and dysphagia. She had a history of Raynaud's phenomenon and cutaneous ulcerations beginning at the age of 35. In 1973 (when she was 40 years old), the patient underwent surgical resection of numerous subcutaneous calcifications in her thighs and shoulders without any improvement in the ability to walk or move her arms. The diagnosis of lSSc was established 10 years later, in 1983. She was placed on low-dose warfarin for 1 year and subsequently on long-term treatment with colchicine 1 mg daily for more than 10 years without any beneficial effect on her calcinosis. She was permanently on kinesi- and masso-therapy and used to spend the winter on an African island. Her therapy for lSSc consisted of pentoxifylline, domperidone and methylprednisolone 4 mg/day.

On admission physical examination of the abdomen and chest was normal. She presented sclerodactylia, skin fibrosis of face, neck and forearms, and other typical sclerodermic features such as telangiectasias. The thighs and shoulders presented multiple calcifications which made her unable to walk and stand up.

The laboratory investigations showed an increased erythrocyte sedimentation rate (57 mm/Ih; normal value < 35 mmIh), C reactive protein (15.3 mg/Ln.v < 5), fibrinogen (632 mg/dl, n.v.: < 350), hyposidere-