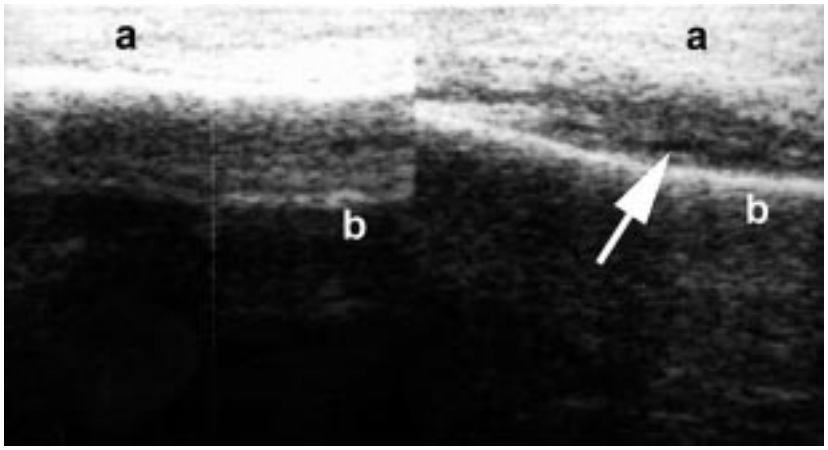

Figure 1 Ultrasonography of the distal pretibial region: the normal right leg (left) and echo-poor areas (arrow) in the left leg (right). a = position of the transducer at the skin surface; b = bone of the tibia.

occur in association with a wide variety of systemic diseases—for example, chronic inflammatory bowel disease. In a study by Holt *et al* it was suggested that PG is associated with inflammatory polyarthritis.[1] Its prominent features—namely, pain, oedema, and discolouration at the joint level, may resemble those of rheumatoid synovitis or even septic arthritis. Consequently, an early diagnosis of PG is difficult to make.

A 77 year old woman presented with painful swollen ankles associated with fever and weight loss. She had no history of trauma. One year before she had been diagnosed with rheumatoid factor negative polyarthritis based on the findings of a symmetrical inflammatory polyarthritis affecting the metacarpophalangeal and proximal interphalangeal joints of both hands and the metatarsophalangeal joints of the feet. The arthritis subsided on treatment with sulphasalazopyridine (2000 mg/day). On examination at admission both ankles were very painful and showed some non-pitting oedema and erythematous discolouration. Moreover, there was clinical evidence of active synovitis of the left ankle. Synovial fluid of the left ankle had low viscosity and was sterile on culture. An intra-articular injection with corticosteroids reduced the symptoms of fever and pain for some days.

Laboratory investigations showed an erythrocyte sedimentation rate of 70 mm/1st h, a C reactive protein of 129 mg/l (during admission rising to 210 mg/l), haemoglobin 6.5 mmol/l, and a white blood cell count of 14.5×10^9/l. Rheumatoid factor and antinuclear antibodies were negative. Antineutrophil cytoplasmic antibodies, p type, were positive 1/320.

Repeat blood cultures were negative. Joint and bone *x* ray examinations of the lower legs were normal.

Sonographic examination of the distal pretibial region was performed before specific clinical symptoms of PG were present. The left ankle showed fluid between the tendon apparatus and the periosteal bone, and the arthritis seemed to have disappeared. The right ankle seemed normal (fig 1).

In addition, technetium bone scintigraphy disclosed a remarkably increased uptake of the isotope in the soft tissues of the lower legs, especially at the left medial site. The bones and joints of the lower legs showed a normal uptake. In the meantime the areas of striking blue colour correlating with the aforementioned findings had evolved into ulcers around both ankles.

Histopathology of a lesion displayed oedema, a moderate perivascular lymphocytic and histiocytic infiltrate without endothelial necrosis, and abscess formation. Cultures for aerobic and anaerobic bacteria, and cultures and specific stains for mycobacteria and fungi from the pustular lesions were negative. Sigmoidoscopy, barium *x* ray studies, a rectal biopsy, and a computed tomography study of the thorax and abdomen were normal.

Ultimately, the clinical picture together with the histopathological findings led to a diagnosis of PG.

Treatment was started with prednisolone 60 mg/day. The PG lesions healed and the dose of corticosteroids was tapered. The joint disease remained quiescent.

In conclusion, ultrasonography in addition to careful history taking and physical examination can be a powerful diagnostic tool in the outpatient rheumatology department. This has already been established in patients with, for example, popliteal cysts,[2] synovitis of the hip joint,[3] and chronic shoulder complaints.[4]

In this case report we have shown that ultrasonography is also useful in accelerating the diagnostic process in a soft tissue disease like PG, before the clinical signs are fully developed. The scope of musculoskeletal ultrasonography in daily rheumatology practice is expanding.

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Are DISH and OPLL genetically related?

Fifty years ago, Forestier and Rotés-Querol published their fundamental paper on, what they called, senile ankylosing hyperostosis of the spine[1]—according to today's nomenclature, diffuse idiopathic skeletal hyperostosis (DISH).[2] DISH is a systemic non-inflammatory disorder which might be classified as ossifying diathesis of entheses and ligaments. Ossification starts and extends from insertions of skeletal muscles, ligaments, and joint capsules. The most prominent features of DISH appear on the spine as flowing appositions of newly formed ectopic bone along the anterolateral aspect of the spine.

Ossification of the posterior longitudinal ligament of the spine (OPLL), on the other hand, involves the posterior aspect of vertebral bodies and discs, predominantly of the cervical spine.[3] Systematic studies of OPLL began in Japan 25 years ago. A varying proportion of patients with DISH have OPLL, and vice versa.[3 4] However, recent observations indicate that cervical OPLL may be fairly frequent in ankylosing spondylitis.[5]

Despite a series of clinical, *x* ray, and laboratory investigations the cause and pathogenesis are still unsolved, both in DISH and in OPLL. Some relations have been established between DISH and diabetes mellitus, or diminished glucose tolerance, obesity, gout, hypertriglyceridaemia, and hyperretinolaemia. This suggests, together with an occasional familial incidence of DISH, a suspicion of genetic predisposition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm it.[2] This discrepancy might partly be accounted for either by coincidence of DISH and ankylosing spondylitis, or by difficulties in differentiating between these two disorders.[6 7] OPLL, similarly to DISH, seems to have some associations with low glucose tolerance and obesity.[4] Attention has also focused on the role of bone formation promoting factors in OPLL.[8]

Recently, Japanese authors discovered a predisposing locus for OPLL on chromosome 6p, close to the HLA locus. They provided evidence of genetic linkage and allelic association of the COL 11 A2 gene which would constitute an inherited predisposition for OPLL. Among 20 genetic variants in this gene, a strong allelic association (p=0.0003) with OPLL was observed with intron 6 variant, which is at position −4 from the 3' splice junction.[9] However, as far as we know, no investigation of this type has been so far performed in patients with DISH.

As the common clinical and metabolic features of OPLL and DISH can suggest their common aetiopathogenesis, a genotyping study on the COL 11 A2 gene was done in a group of 60 Czech patients with DISH. Diagnosis of DISH was based on the *x* ray changes on the spine. Sixty healthy Czech blood donors were controls. Genotyping was performed in DNA samples, 200 ng each, extracted from peripheral blood leucocyte cells. Polymorphism at intron 6 (−4) in the COL 11 A2 gene was determined by mutagenically separated polymerase chain reaction (PCR).[10] For detection of the intron 6 (−4) allele, 16T and 16A primers, together with the common complementary strand primer G72, were used. In each PCR reaction, control DNAs of three known

Table 1 Intron 6 (−4) allele frequency

	T	*A*	*Total*
DISH (No (%))	75 (66)	39 (34)	114
Non-DISH (No (%))	74 (63)	44 (37)	118
Total	149	83	232
χ^2	0.239		
Odds ratio	1.143		

distinct genotypes and water as negative control were included. Comparison of the genotypic frequencies of single variants was made by contingency χ^2 test.

Table 1 shows that no significant differences were found between results in patients with DISH and in healthy controls, with allele A frequency 34% *v* 37%, respectively, χ^2=0.296 (df=1), p=0.587.

In conclusion, results of analysis of intron 6 (−4) polymorphisms in the COL 11 A2 gene in Czech patients with DISH do not agree with data from Japanese patients with OPLL. However, the principal question of possible genetic relations between DISH and OPLL warrants further study, using a broader spectrum of genotyping and larger cohorts of patients.

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Systemic small sized vessel vasculitis after massive antigen inhalation

We and others have proposed that desensitisation, vaccination, or inhalation of antigens by asthmatic patients may trigger Churg-Strauss syndrome (CSS).[1–4] Few observations of vasculitis occurring immediately after massive inhalation of a presumed antigen have been published.[2] We describe here four patients who experienced acute onset of systemic vasculitis after massive antigen inhalation.

Case 1: Several hours after massively inhaling dark diesel fumes, a 55 year old man developed rapid onset dyspnoea, sinusitis, and high fever, which regressed with short term steroid treatment. After three months he complained of bilateral foot drop, which was found to be due to mononeuritis multiplex in the left peroneal nerve upon clinical examination. The erythrocyte sedimentation rate was 72 mm/1st h, white blood cell count was 16.12×10^9/l,[3] with 1870 eosinophils, serum creatinine 170 µmol/l; proteinuria 0.7 g/day, and microscopic haematuria. Specific anti-myeloperoxidase perinuclear labelling anti-neutrophil cytoplasmic antibodies (ANCA) were detected (30 IU). A neuromuscular biopsy showed necrotising vasculitis of the vasa nervorum and small sized muscle vessels, together with granulomas. Renal biopsy showed patchy necrotising glomerulonephritis. We retained the diagnosis of Wegener's granulomatosis. Despite corticosteroids and intravenous cyclophosphamide, the patient developed left orchitis and underwent plasma exchanges and received oral cyclophosphamide. Clinical and biological signs improved, except serum creatinine which persisted at 150 µmol/l. After three years, receiving daily prednisone and cyclophosphamide, the patient remains in clinical remission.

Case 2: A 38 year old woman presented in August 1990 with acute dyspnoea and purpura. While in the countryside during the harvest season, she had inhaled grain dust and developed dyspnoea within a few hours and red spots on her legs in the following days. In December 1990, digital vasculitis occurred in all the fingers of both hands. Supra-aortic angiography showed bilateral occlusion in the radial and ulnar arteries; microaneurysms were seen in digital arterioles. A skin biopsy detected vasculitis at the dermal-hypodermal junction with mononuclear cell and eosinophil infiltrates in the artery walls without leucocytoclastic or necrotising vasculitis. Ulnar artery biopsy showed complete occlusion of the artery lumen without evidence of vasculitis. CSS was diagnosed and prednisone was prescribed, which was progressively tapered over 18 months. Eight years later, the patient remains well.

Case 3: A 53 year old woman who worked in a bakery for 30 years had had asthma for 20 years, with skin tests positive for flour antigens. In March 1988, 10 days after massively inhaling flour dust (a flour sack broke), she experienced acute fever and mild tenderness in her arms and right foot, with motor and sensory mononeuritis multiplex in the left peroneal nerve upon clinical examination. ANCA were not tested. Neuromuscular biopsy showed microvasculitis with perivenular lymphoplasmacytic infiltrates. CSS was diagnosed and prednisone was prescribed, which was tapered within 18 months and maintained at 5 mg/day to control asthma. The patient remains asymptomatic nine years later.

Case 4: A 27 year old man was admitted in September 1980 for acute dyspnoea and high fever that occurred a few hours after massively inhaling cereal dust in a store that raised and sold pigeons. These signs regressed after oral prednisone treatment, but one month later he developed vascular purpura on his legs. A bilateral basal opacity was seen on chest *x* ray examination. ANCA were not tested. Skin biopsy showed leucocytoclastic vasculitis in small and medium sized vessels, without fibrinoid necrosis. Prednisone (1 mg/kg/day) was prescribed, then tapered and discontinued when all symptoms resolved. After one month, the same symptoms reappeared after another exposure to pigeons. A chest roentgenogram showed extensive bilateral basal nodules, and pulmonary biopsy disclosed vasculitic lesions, with fibrinoid necrosis of arteriole and venule walls. Despite treatment with prednisone the patient developed multiple cranial nerve disease. He received oral cyclophosphamide, but no improvement occurred and the patient underwent 13 plasma exchanges. The cranial nerve disease and chest nodules were regressive. Cyclophosphamide was discontinued after 12 months and the patient remains disease-free 18 years later.

Causative and precipitating agents of CSS have rarely been identified; we have noted that onset is sometimes associated with desensitisation, vaccination, exposure to various drugs or environmental substances, or too rapid steroid tapering.[4] In case 4 (previously published[2]), the abundance of actinomycetes in pneumocytes might suggest that they caused the vasculitis.

Stephens *et al* described bronchoallergic aspergillosis evolving to CSS,[4] and Orrids *et al* reported a case of CSS induced by free base cocaine.[5] Some drugs have been associated with the occurrence of CSS, particularly recently zafirlukast.[6] Rapid onset of microscopic polyangiitis within a few hours or days after massive antigen inhalation has not been described previously. Small vessel vasculitis mechanisms implicate ANCA, neutrophils and proinflammatory cytokines, and their interactions with external antigens.[7 8] In our patients, the occurrence of vasculitis may reflect hypersensitivity to the inhaled antigen, because they had daily professional exposure or contact with diesel fumes (case 1), harvest grain dust (case 2), flour (case 3), or pigeons and/or cereal dust (case 4) and because massive antigen inhalation was the only potential triggering event identified before the onset of systemic vasculitis. Such overwhelming antigen exposure probably contributes, in these