Sonographic erosions of the rheumatoid little toe

We read with interest the pictorial essay on ultrasonography of bone erosions by Grassi and colleagues. The presented site-specific comparison of radiographic and sonographic imaging of metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joint sites in rheumatoid subjects suggests strongly a homology of typical erosive lesions, as visualized by these different imaging modalities. A recently published study by an independent group, comparing radiographic and sonographic imaging of MCP joint sites in patients with rheumatoid arthritis for ease of transducer access, as well as early, characteristic, and/or representative involvement by RA erosions: 12 female; median disease duration (range) 13 (1.5–72) months; 12 rheumatoid factor positive; 12 receiving disease modifying (range) 13 (1.5–72) months; 12 rheumatoid arthritis criteria, was used. The following seven sites were chosen: 1st MTP joint (ulnar and radial aspect); 1st MCP joint (medial aspect); and the 5th MTP joint (lateral aspect). All four limbs were examined and to ensure comparability of sites, only bone lesions in the coronal plane were considered. All sites were examined in longitudinal and transverse planes in joint extension, and were classified as erosive, if they had at least one “break” in the cortical contour, visible in both planes and associated with an irregular floor. The latest available posteroanterior x-ray of hands and feet (median time interval preceding ultrasound) 6 (0.018 months) was assessed for the presence of erosions at corresponding sites by a radiologist with a special interest in musculoskeletal imaging (DG), who was unaware of the sonographic findings. The 1st MTP joint was excluded from the analysis wherever the radiograph showed osteoarthritic change, because sonographic assessment for erosions was felt to be unreliable. A total of 13 sites (in seven subjects) had radiographic erosions; all except for one ulnar site were identified by ultrasound. Sonography detected a total of 56 erosive sites (in 11 subjects)—that is, four times as many as radiography.

Two patients without radiographic erosions at the study sites had erosions elsewhere in the radiographs of their hands and feet, but both had erosive sites on ultrasound. Table 1 shows the frequency of radiographic and sonographic sites with erosions. Figure 1 shows an example of a sonographic erosion detected in the 5th MTP joint that was not seen on radiography. Recently a Dutch study of patients with early RA, followed up radiographically for six years, found the 5th MTP joint to be the most common hand or foot joint affected by erosions at baseline, as well as by new and progression of erosions in the first and fifth year of follow up. Although our study is limited by lack of data on sonographic reliability or corroborative MRI imaging, its findings add support to the notion that the rheumatoid 5th MTP joint is probably the most common site of sonographic as well as radiographic erosions. This offers yet further potential for earlier diagnosis and treatment of erosive arthritis, justifying more studies into the diagnostic specificity of sonographic erosions of this and other MTP joints.

Correspondence to: Dr Klocke

Authors’ reply

Dr Klocke and colleagues highlight interesting aspects about the potential role of ultrasonography in the diagnosis of rheumatoid arthritis (RA). Ultrasonography is undoubtedly more sensitive than x-ray in detecting bone erosions. Last generation broad band linear transducers (10–22 MHz) have an axial resolution power lower than 0.03 mm, and even minimal cortical defects of small joints can be clearly depicted.

We agree with Dr Klocke and colleagues that the 5th metatarsophalangeal (MTP) joint is the most common site of sonographic erosion in patients with RA. In our daily practice sonographic assessment of the 5th MTP joint and second metacarpophalangeal joint is included in the baseline approach to patients with RA.

We think that a few points need additional emphasis. Firstly, close sonographic monitoring of early erosion could have an interesting role for a better understanding of disease progression and efficacy of treatment. Secondly, latest generation power Doppler equipment may offer some additional information about the perfusional status of synovial membrane and pannus.

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MATTERS ARISING

Table 1 The frequency of sites that showed erosions by radiography and ultrasound in the 15 patients with rheumatoid arthritis (see text)

<table>
<thead>
<tr>
<th>Site</th>
<th>Radiography (%)</th>
<th>Ultrasound (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar head/styloid</td>
<td>4 (13)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Radial head/styloid</td>
<td>2 (7)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>2nd MCP joint</td>
<td>12 (3)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>3rd MCP* joint</td>
<td>0 (0)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>3rd PIP* joint</td>
<td>7 (23)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1st MTP joint</td>
<td>5 (15)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>5th MTP joint</td>
<td>6 (20)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (7)</td>
<td>15 (50)</td>
</tr>
</tbody>
</table>

* MCP = metacarpophalangeal; PIP = proximal interphalangeal; MTP = metatarsophalangeal.

References


Authors’ reply

Dr Klocke and colleagues highlight interesting aspects about the potential role of ultrasonography in the diagnosis of rheumatoid arthritis (RA). Ultrasonography is undoubtedly more sensitive than x-ray in detecting bone erosions.1,2 Last generation broad band linear transducers (10–22 MHz) have an axial resolution power lower than 0.03 mm, and even minimal cortical defects of small joints can be clearly depicted.

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We think that a few points need additional emphasis. Firstly, close sonographic monitoring of early erosion could have an interesting role for a better understanding of disease progression and efficacy of treatment. Secondly, latest generation power Doppler equipment may offer some additional information about the perfusional status of synovial membrane and pannus.3


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Corticosteroid injection for the treatment of carpal tunnel syndrome

We read with interest the article by O’Gradaigh and Merry on a comparison between low and high dose, and short and long acting corticosteroids in the treatment of carpal tunnel syndrome. We are skeptical of the conclusion drawn by the authors that low dose steroid is as effective as high dose or long acting preparations. We calculated the 95% confidence interval for each group: group A 66% (47 to 81%), group B 63% (44 to 79%), group C 5% (0.1 to 25%), group D 72% (47 to 90%), and group E 67% (43 to 85%). Owing to the small sample size, the reported response rate cannot reliably reflect the true response rate, as illustrated by the wide confidence interval.

The authors argued that a large sample size was required to detect small differences between groups that might not be clinically important. However, it remains a real possibility that there is a clinical difference between treatments, which was not detected because of a type II error. Furthermore, to declare equivalence between treatments, one needs an adequate sample size with special attention to the upper boundaries of the difference in confidence interval. Failure to detect statistical difference does not prove equivalence. A large scale, probably multicentre, study may provide a definitive answer to this question.

We are also skeptical of the suggestion that low dose steroid is potentially less toxic. The steroid should be better (bearing in mind the absence of any data to support this); (b) justify the possible increased risk of (nervous) toxicity, however small—primum non nocere.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>A versus C</th>
<th>B versus C</th>
<th>A versus D</th>
<th>B versus D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>0.61</td>
<td>0.58</td>
<td>0.03</td>
<td>0.67</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.42 to 0.80</td>
<td>0.38 to 0.77</td>
<td>−0.20 to 0.26</td>
<td>0.44 to 0.89</td>
</tr>
<tr>
<td></td>
<td>−0.024 to 0.34</td>
<td>−0.024 to 0.34</td>
<td>−0.024 to 0.34</td>
<td>−0.024 to 0.34</td>
</tr>
</tbody>
</table>

Authors’ reply

We are pleased to have the opportunity to respond to Drs Wong and Hui. While their calculations of confidence intervals within each group are noted, it is more relevant to calculate the confidence intervals for the difference between the proportions of subjects who improve in the control and treatment groups (table 1). The response rates in our study for each group were very similar to those reported elsewhere, indicating that although the confidence intervals reflect the sample size, the reported response rates do reflect true response rates.

Concerning the toxicity of various steroid preparations, the animal study to which we referred has been repeated, and clearly cannot be replicated in humans. This study was not primarily established to compare adverse effects, and we would agree that the sample size was small to detect an uncommon side effect. The implication that toxicity is rare and therefore should not be considered is unacceptable.

The call for a larger study is inevitable when a counter-intuitive result has emerged. It cannot be assumed, as implied by Wong and Hui, that a higher dose of hydrocortisone, or the longer acting triamcinolone, would have been found to be more effective but for a type II error. On the contrary, we have explained in our article how the lower dose may be sufficient to treat all steroid-responsive carpal tunnel syndrome. Those who suggest rejecting our findings, and continue to use other treatments, must (a) indicate why a higher dose or longer acting steroid should be better (bearing in mind the absence of any data to support this); (b) justify the clinical relevance of any small difference that might have been missed in this study; (c) justify the possible increased risk of (nervous) toxicity, however small—primum non nocere.

Fetal microchimerism in Sjögren’s syndrome

Toda and colleagues report that microchimerism of fetal cells is uncommon in women with Sjögren’s syndrome (SS).1 They performed a nested polymerase chain reaction (PCR) that amplified a Y chromosome-specific sequence to detect male cells in peripheral blood of women who had male offspring to prove the hypothesis that microchimerism can induce Sjögren’s syndrome as a manifestation of a chronic graft-versus-host like reaction.

We have also analysed for the presence of the Y chromosome in DNA extracted from peripheral blood nucleated cells of 20 Spanish women with SS (mean age 54.6 years (range 31–77)). These women had male children and were selected from our series of 92 female patients1 who fulfilled four or more of the diagnostic criteria for SS proposed in 1993 by the European League Against Rheumatism. All 20 female patients analysed for the presence of fetal microchimerism were also classified as having definite SS according to the San Diego criteria. A PCR was performed that could detect one male cell in a background of 5×10⁶ female cells. The amount of genomic DNA used in the PCR reaction was 3 µg, and more than five samples were tested for each woman. Eighteen healthy Spanish women (mean age 48.7 years (range 32–65)) who had male children comprised the control group. Using this method, we found no Y chromosome-specific DNA in either patients or controls.

Clinical manifestations of Sjögren’s syndrome, as those of other autoimmune diseases such as systemic sclerosis, polymyositis, or primary biliary cirrhosis, are similar to those of chronic graft versus host disease. Microchimerism of fetal cells has been investigated in patients with systemic sclerosis by both quantitative and non-quantitative methods, with variable results.5 We have also been involved in primary biliary cirrhosis and inflammatory myopathies by non-quantitative methods, yielding negative or non-conclusive results.6 On the contrary, we never exclude the possibility that microchimerism may play a part in the pathogenesis of Sjögren’s syndrome. To support this hypothesis, quantitative methods should be used and other sources of microchimerism should be searched for, as has been done already in systemic sclerosis and juvenile dermatomyositis.5,10

We read with interest this letter by Mijares-Boeckh et al. who had male children. This finding is controversial.

However, the results of Mijares-Boeckh et al., based on the study by Mijares-Boeckh et al. and our study, the ratio of non-host to host cells in circulation is less than one (table 1). Therefore, C1q immunoadsorption with MIR0 adsorbers (Presenius HemoCare) was started.

Twelve C1q immunoadsorptions with an average treated plasma volume of 2 litres (equal to 34 ml/kg body weight) for each adsorption were carried out over a period of four weeks. The plasma volume was slightly reduced after the fourth session because of a fibrinogen decrease to <0.8 g/l. For plasma separation a centrifugal method in a closed continuous flow system was used. The veno-venous (both cubital veins were used) blood flow was about 40 ml/min and the plasma flow about 30-40 ml/min. The C1q immunoadsorption was well tolerated by the patient, and no side effects were noticed.

The treatment with methotrexate (15 mg/week) and prednisone (10 mg/day) was continued. During C1q immunoadsorption a rapid and complete resolution of the malar and discoid rash was seen (fig 1), whereas the lupus nephritis with a proteinuria of about 1.5-2.0 g/day persisted. In addition, the pathological values of anti-dsDNA and C1q autoantibodies completely normalised and the circulating immune complexes (IgM) also declined (table 1).

A follow up of 12 months after stopping the C1q immunoadsorption showed no signs of cutaneous exacerbation or increase in clinical disease activity. Treatment with methotrexate (15 mg/week) and low dose prednisone (5 mg/day) was continued.
CIC = circulating immune complexes; C3c, C4 = complement components.

**Table 1 Serological parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before C1q immunoadsorption</th>
<th>After 12 C1q immunoadsorptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>1/2560</td>
<td>1/2560</td>
</tr>
<tr>
<td>Anti-dsDNA (&lt;20 IU/ml)</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>C1q autoantibodies</td>
<td>84</td>
<td>29</td>
</tr>
<tr>
<td>C1q* (IgM) (&lt;55 µg/ml)</td>
<td>108</td>
<td>83</td>
</tr>
<tr>
<td>C3c* (0.9–1.8 g/l)</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>C4* (0.1–0.4 g/l)</td>
<td>0.05</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* CIC = circulating immune complexes; C3c, C4 = complement components. CIC (IgG) were not raised and therefore not tested during the course of C1q immunoadsorptions.

![Figure 1 Discoid rash of both femurs (central side) before C1q immunoadsorption (A). After 12 C1q immunoadsorptions the rash resolved completely (B).](image)

Development of erythroleukaemia after myelodysplastic syndrome in a patient with Wegener’s granulomatosis

Clinical use of cyclophosphamide (CYC) improves the prognosis of Wegener’s granulomatosis (WG).15 though treatment related malignancies have been recorded.17 Among treatment related malignancies, the development of erythroleukaemia has been rarely reported.18 In addition, there have been no reports of erythroleukaemia arising in patients with WG.

A 59 year old woman presented with nasal bleeding, nasal obstruction, and fever in December 1994. A biopsy specimen from nasal mucosa was compatible with WG, and cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) were 13 EU (normally undetectable). A chest x-ray examination on admission showed the presence of a cavity in the right lung field. She received 30 mg/day of prednisolone, with limited improvements. CYC (100 mg/day) was therefore given orally from 19 December. As a result, her complaints ameliorated and her nasal cavity cleared up in February 1995.

Her clinical condition was well controlled until July 1996 when her platelet count fell to 13.8×10^10/L. Because CYC was effective against WG, and no further thrombocytopenia was verified, CYC was continued (50 mg/day), with stringent monitoring of the complete blood cell count. In November 1997 anaemia developed, and bone marrow specimens showed dysplasia of the trilineages accompanied by pseudo-Pelger-Huet anomaly indicating myelodysplastic syndrome (MDS), though we could not verify abnormal chromosomal changes in the specimen at that time. Despite stopping CYC (a cumulative dose of 9.7 g), she finally became febrile and exhausted in November 1998. The bone marrow specimens showed a marked proliferation of erythroblasts (92.5% of nucleated cells), indicating erythroleukaemia (fig 1). An analysis of chromosomes in the bone marrow specimens showed the complex heterogeneous karyotypic abnormalities: 46, XX, +1, +8, del (10) (q22), −21, −22. Because of the rapid progress of anaemia and thrombocytopenia, we initiated intensive chemotherapy. Despite such chemotherapy, she eventually died of disseminated intravascular coagulation in December 1998. A necropsy was not permitted.

Recently, the use of CYC has been reported to improve the prognosis of WG,1 though we should be aware of its possible carcinogenicity. Among neoplastic disorders, treatment related malignancy can develop after the use of such cytotoxic agents as CYC, azathioprine, etc.18 CYC is a highly carcino- genic agent and induces various malignancies. Thrombocytopenia developed 20 months after the initiation of CYC, and then changed into MDS 36 months later. Despite stopping CYC, the patient developed erythroleukaemia with chromosomal abnormalities: 46, XX, +1, +8, del (10) (q22), −21, −22. Because of the rapid progress of anaemia and thrombocytopenia, we initiated intensive chemotherapy. Despite such chemotherapy, she eventually died of disseminated intravascular coagulation in December 1998. A necropsy was not permitted.

The patient did not exhibit karyotypic abnormalities at the diagnosis of MDS, but did show such abnormalities after the development of erythroleukaemia. Alkylating agent related leukaemia is likely to manifest unique karyotypic disorders including 5q−, 7q−, 7q−, though our case does not have such abnormalities. Although the chromosomal changes may not be consistent with CYC induced leukaemia, we cannot rule out the possibility of treatment induced malignancy. We chronologically observed the developing process of CYC related erythroleukaemia: it began with thrombocytopenia, followed by MDS, and finally ended with erythroleukaemia with chromosomal abnormalities. Thrombocytopenia developed 20 months after the initiation of CYC, and then changed into MDS 36 months later. Despite the discontinuance of CYC, the patient developed erythroleukaemia 12 months later. Although the findings of chromosomal changes failed to support CYC induced leukaemia, we should be aware of treatment related malignancy in patients receiving this.
drug, especially when a cumulative dose of more than 10 g is given. When rheumatologists prescribe CYC for the treatment of patients with rheumatic diseases, stringent monitoring of the haematological parameters should be required, even after the discontinuance of CYC. All possible efforts should be made to discontinue CYC to minimise the risk of developing treatment-related malignancies after remission. Lastly, when myelosuppression develops, we should discontinue CYC as soon as possible to avoid the development of treatment-related leukaemia.

CYC as soon as possible to avoid the development of treatment-related leukaemia. We report on a 13 year old girl with JIA and atrophoderma. Although considered a variant of morphea, atrophoderma is thought to be a distinct nosological entity. We believe that this is the first time an association between the two has been described.

CASE REPORT
A 13 year old girl was referred by her general practitioner with a four-month history of joint swelling and stiffness. The symptoms were mainly of the small joints of the hands and wrists. She also had early morning stiffness of the same joints and of the neck. On initial examination she was noted to have a diffuse purple, slightly atrophic patch on her lower back, which was symmetrical and pear shaped. The patch measured 22×15 cm and showed subtle features of dermal atrophy with more visible vascular marking than in the surrounding skin (fig 1). Her musculoskeletal examination showed swelling with synovial thickening of all the proximal interphalangeal and distal interphalangeal joints with some metacarpophalangeal joints affected also. The rest of the systemic examination was normal. Her baseline haematology, including an erythrocyte sedimentation rate of 8 mm/1st h (normal <10), and biochemistry, including C reactive protein <6 mg/l (normal <6), were within normal limits. Antinuclear antibody was positive at 1 in 100 dilution and extractable nuclear antigen was negative. She was also rheumatoid factor positive at a dilution of 1 in 256. The rest of her immunology, including complement assays, was normal.

A diagnosis of JIA was made and treatment was started with ibuprofen 30 mg/kg/day. Although she showed some response, the joint swelling and early morning stiffness persisted and hence treatment was started with methotrexate at 12.5 mg/week subcutaneously as she did not favour the oral route. She was started with ibuprofen 30 mg/kg/day. She also had some response, the patch measured 22×15 cm and showed subtle features of dermal atrophy with more visible vascular marking than in the surrounding skin (fig 1). Her musculoskeletal examination showed swelling with synovial thickening of all the proximal interphalangeal and distal interphalangeal joints with some metacarpophalangeal joints affected also. The rest of the systemic examination was normal. Her baseline haematology, including an erythrocyte sedimentation rate of 8 mm/1st h (normal <10), and biochemistry, including C reactive protein <6 mg/l (normal <6), were within normal limits. Antinuclear antibody was positive at 1 in 100 dilution and extractable nuclear antigen was negative. She was also rheumatoid factor positive at a dilution of 1 in 256. The rest of her immunology, including complement assays, was normal.

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Atrophoderma and juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of arthritis occurring in children under the age of 16. It is a complex multifactorial disease with genetic, immunological, and environmental factors strongly associated with causation. The incidence of JIA in the UK varies from 10 to 20/100 000/year, with a prevalence of 1/1000.

Idiopathic atrophoderma, as described by Pasini and Pietrini, is a distinctive form of dermal atrophy seen particularly in children and younger people. There are usually no clinical signs of inflammation or symptoms. We report on a 13 year old girl with JIA and atrophoderma. Although considered a variant of morphea, atrophoderma is thought to be a distinct nosological entity. We believe that this is the first time an association between the two has been described.

Figure 1 Symmetrical, pear shaped, slightly atrophic patch on the lower back.
We feel our case illustrates a few important features about APP, especially that prolonged association of the two diseases, the simultaneous occurrence of the two symptoms suggests that the underlying mechanisms of inflammation in the two diseases are common. Pregnancy is thought to induce a shift from Th1 to Th2 response, increasing the contribution of anti-inflammatory cytokines. A previous report showed that pregnancy has a protective effect on RA, UC, and other Th1 mediated inflammatory diseases which is terminated after delivery. Understanding of the underlying mechanisms may have clinical therapeutic applications in these conditions. 

**References**


**Ultrasonography is useful to distinguish between intra- and extra-articular disease in pyoderma gangrenosum complicating polyarthritis**

Ultrasonography, although non-specific, is useful for discriminating between intra-articular and extra-articular disease. We report the case of early pyoderma gangrenosum in a 77 year old woman with seronegative polyarthritis.

**Pyoderma gangrenosum (PG) is an uncommon ulcerative skin condition which may be associated with inflammatory diseases, RA and ulcerative colitis**. The classical clinical features of PG include a self-limiting, fluctuant, painful, inflammatory lesion that is often associated with constitutional symptoms. The lesions are typically located on the extremities, particularly the lower limb, and may be secondary to minor trauma or surgery. Histologically, PG is characterized by a subcutaneous abscess with a surrounding area of acute inflammation.

If you require further assistance or have any questions, feel free to ask.
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 polyarthritides.\(^1\) Its prominent features—namely, pain, oedema, and discoloration 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 polyarthritides 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 discoloration. 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 of 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. Antibodies to neutrophil 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 pretilial region was performed before specific clinical symptoms of PG were present. The left ankle showed fluid between the tendon apparatus and the periostial 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, poptleal 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 Rozés-Querol published their fundamental paper on, what they called, senile ankylosing hyperostosis of the spine—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.\(^4\) However, recent observations indicate that cervical DISH 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 hyperretinolaeemia. This suggests, together with an occasional familial incidence of OPLL, a possible genetic predisposition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm it. This discrepancy might partly be accounted for either by coincidence of DISH and ankylosing spondylitis, or by difficulties in differentiating between these two disorders.\(^6\) OPLL, similarly to DISH, seems to share some associations with low glucose tolerance and obesity.\(^7\)

Attention has also focused on the role of bone formation promoting factors in OPLL.\(^8\)

Recently, Japanese authors discovered a predisposing locus for OPLL through a candidate gene analysis of some 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 aetio-pathogenesis, 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. Twenty 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 (−4) allele, 16T and 16A primers, together with the common complementary strand primer G72, were used. In each PCR reaction, control DNA of three known
distinct genotypes and water as negative control were included. Comparison of the genotypic frequencies of single variants was made by contingency χ² 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% vs 37%, respectively, χ²=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 specrum of genotyping and larger cohorts of patients.

This study was supported by a grant from the Grant Agency of the Czech Republic (No 31198/1580).

Table 1 Introns (−4) allele frequency

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<tr>
<th></th>
<th>T</th>
<th>A</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISH (No (%))</td>
<td>75 (66)</td>
<td>39 (34)</td>
<td>114</td>
</tr>
<tr>
<td>Non-DISH (No (%))</td>
<td>74 (63)</td>
<td>44 (37)</td>
<td>118</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>83</td>
<td>232</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.143</td>
<td></td>
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</tbody>
</table>

Systemic small sized vessel vasculitis after massive antigen inhalation

We and others have proposed that desensitization, vaccination, or inhalation of antigens by asthmatic patients may trigger Churg-Strauss syndrome (CSS).4 5 Few observations of vasculitis occurring immediately after massive inhalation of a presumed antigen have been published.6 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, while blood count was 16.12×10³/l, 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 patches of presumed glomerulonephritis. We retained the diagnosis of Wegener’s granulomatosis. Despite corticosteroids and intravenous cyclophosphamide, the patient developed left orbital 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 she was on holiday during the harvest season, she had inhaled grain dust and developed dyspnoea within a few hours. She was admitted to hospital with fever that occurred a few hours after massive inhaling cereal dust in a store that raised and sold pignes. These signs regressed after oral prednisone and cyclophosphamide, which was tapered within 18 months and maintained at 5 mg/day to control asthma. The patient remains asymptomatic nine years later.

Case 3: A 53 year old woman who worked in a bakery for 30 years had had asthma for 20 years, with the same triggers for flours, 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 perivascular lymphoplasmacytic infiltrates. CSS was diagnosed and prednisone was used, 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 pignes. These signs regressed after oral prednisone and cyclophosphamide, which was tapered within 18 months and maintained at 5 mg/day to control asthma. The patient remains asymptomatic nine years later.

Causative and precipitating agents of CSS have recently 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 5 In case 4 (previously published), the abundance of actinomyces in pneumocytes might suggest that they caused the vasculitis.

Stephens et al described bronchoalveolar aspergillosis evolving to CSS,7 and Orrids et al reported a case of CSS induced by free base cocaine.8 Some drugs have been associated with the occurrence of CSS, particularly recently zafirlukast.9 Rapid onset of microscopic polyangiitis within a few hours or days after massive antigen inhalation has not been described previously. Small vessel vasculitits mechanisms implicate ANCA, neutrophils and proinflammatory cytokines, and their interactions with external antigens. 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 pigeon 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...
The synthesis of isoprenoids and cholesterol. Kinase, an enzyme that has a pivotal role in mutations of the gene coding for mevalonate hyper-IgD syndrome in the treatment of non-steroidal inflammatory drug, naproxene, given in single dose (250 mg) at the beginning of the flare ups.

Intriguingly, its therapeutic effect was dramatic; fever suddenly disappeared and related symptoms were well tolerated. Table 1 summarises the therapeutic regimens given sequentially and the clinical responses detected in our patient. In conclusion, colchicine was effective at prolonging intercritical remission periods, but the severity of symptoms remained unchanged; moreover, it was poorly tolerated.

Treatment with a single dose of prednisone or naproxene was effective, both at suppressing fever spikes and in reducing the discomfort during the attacks, even if the duration of intercritical periods was shorter than those seen during colchicine treatment. Thus, in our experience, naproxene appears to provide an effective treatment of HIDS. Combined treatment with colchicine and a non-steroidal anti-inflammatory drug is suggested in order to fulfil the double goal of prolonging the intercritical period and reducing the severity of fever spikes. This schedule was proposed for our patient but it was not possible to carry it out owing to the poor compliance with colchicine. Further studies are needed to confirm this observation.

### Table 1  Therapeutic regimens followed sequentially and the clinical responses detected

<table>
<thead>
<tr>
<th>Therapeutic regimen</th>
<th>Duration of fever (days)</th>
<th>Intercritical period (days)</th>
<th>Months of treatment</th>
<th>Flare ups (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>4 (2)</td>
<td>17 (8.2)</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Colchicine</td>
<td>4 (1)</td>
<td>33 (25)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 (1)</td>
<td>14 (6)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Naproxene</td>
<td>1 (1)</td>
<td>18 (7)</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

So far, there is no consensus about how HIDS should be treated. Here we report our experience with a child with HIDS treated with different drugs and our results were summarised in Table 1.

### Non-steroidal anti-inflammatory drugs in the treatment of hyper-IgD syndrome

Hyper-IgD syndrome (HIDS) is due to mutations of the gene coding for mevalon kinase, an enzyme that has a pivotal role in the synthesis of isoprenoids and cholesterol.

Hyper-IgD syndrome (HIDS) is due to mutations of the gene coding for mevalon kinase, an enzyme that has a pivotal role in the synthesis of isoprenoids and cholesterol.

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Are DISH and OPLL genetically related?

S HAVELKA, M VESELÁ, A PAVELKOVÁ, S RUZICKOVÁ, H KOGA, S MAEDA, I INOUE and L HALMAN

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