MATTERS ARISING

Sonographic erosions of the rheumatoid little toe

We read with interest the pictorial essay on ultrasonography of bone erosions by Grassi and colleagues. The present site-specific comparison of radiographic and sonographic imaging of metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joint sites in rheumatoid subjects suggests strongly a homology of 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, supports this impression.

In our experience, based on pilot data on rheumatoid patients with a disease duration of up to six years, sonographic erosions could be shown in half of all 5th MTP joints examined. Fifteen patients with RA, according to standard criteria, (median age (range) 48 (23–78) years; eight females; 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. Ann Rheum Dis 2000;43:160–71.)

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. Second, latest generation power Doppler equipment may offer some additional information about the perfusional status of synovial membrane and pannus.

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.3 Last generation broadband 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 joint is the most common site of sonographic erosions 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.

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>0</td>
<td>11 (37)</td>
</tr>
<tr>
<td>3rd MCP* joint/ radial aspect</td>
<td>0</td>
<td>7 (23)</td>
</tr>
<tr>
<td>3rd PIP* joint/ ulnar aspect</td>
<td>0</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1st MTP joint</td>
<td>1 (5)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>2nd MTP joint</td>
<td>6 (20)</td>
<td>15 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (7)</td>
<td>56 (28)</td>
</tr>
</tbody>
</table>

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


Figure 1 Example of a sonographic erosion (arrown) at the left 5th metatarsophalangeal joint of one of the patients with rheumatoid arthritis, visualised in transverse (left side) and longitudinal (right side) plane.

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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.1 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 rates cannot reliably reflect the true response rate, as illustrated by the wide confidence interval.

The authors argued that a huge 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 95% confidence interval.2 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 true incidence of complications related to steroid injection is not known, and discussion is mainly limited to case reports, with no specificity given for any preparations. With so few reported cases, one must assume they are truly rare or they have been under-reported. If the assumption is the former then one will not be expecting any adverse side effects from this group of 100 or so patients.

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Fetal microchimerism in Sjögren’s syndrome

Toda and colleagues report that microchimerism of fetal cells is uncommon in women with Sjögren’s syndrome (SS).3 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)).4 These women had male children and were selected from our series of 92 female patients2 who fulfilled four or more of the diagnostic criteria for SS proposed in 1993 by the European Workshop Community Study Group. 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 5x10^6 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 no 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, the results being controversial.2,5 It has also been investigated in primary biliary cirrhosis and inflammatory myopathies by non-quantitative methods, yielding negative or non-conclusive results.6 One of the reasons for the failure in these studies is that the sample size was too 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 Toda and Hui, that a higher dose of hydrocortisone, or the longer acting triamcinolone, is 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 (nerve) toxicity, however small—primum non nocere.

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Our patient, a 25 year old woman, had a relapsing malar and discoid rash, which extended to almost the whole integument, since January 1999. Accompanying oral and genital ulcers, polyarthritism, and lupus nephritis (histological membranous glomerulonephritis, WHO IV A), as well as iritis and uveitis, abnormalities led to the diagnosis, SLE. Despite treatment with chloroquine (400 mg/day) initially and methotrexate (7.5–15 mg/week) since August 1999 in combination with prednisone (10 mg/day) for the lupus nephritis, the SLE lesions occurred. The dose of prednisone was repeatedly increased up to >60 mg/day. The lupus nephritis with a proteinuria of about 1.5 g/day and a non-active urine sediment remained unchanged, too. Continuing disease activity was also documented by abnormal serological parameters (table 1). Therefore, C1q immunoadsorption with MIRo adsorbers (Fresenius 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 venules were used) blood flow was about 50 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 evidence of cutaneous exacerbation or increase in clinical disease activity. Treatment with methotrexate (15 mg/week) and low dose prednisone (5 mg/day) was continued.

C1q immunoadsorbers (MIRo adsorbers) consist of polyacrylamide beads coated with covalently bound swine C1q. Effective clearance of circulating immune complexes as well as of C1q autoantibodies can be achieved. Moreover, additional molecules, such as fibrinogen, are bound by the collagen-like region of C1q. As fibrinogen decreased to <0.8 g/l in our patient during treatment, the plasma volume had to be slightly reduced. Other possible side effects such as marked thrombocytopaenia or ana- phylactic reactions according to an increased bradykinin synthesis, were not seen. In contrast with the plasma exchange treatment, only selective plasma components are removed, and plasma replacement, for example by fresh frozen plasma, is not required. Therefore, the risk of transmitting infections by products derived from blood is minimised. With decreasing levels of lupus immune complexes and C1q autoantibodies the malar and discoid rash rapidly resolved in our patient. This observation emphasises the pathogenetic role of these molecules in SLE-specific cutaneous manifestations of systemic lupus erythematosus. Currently, C1q autoantibodies and C1q immunoadsorption are used in several patients.

Letters to the Editor

Rapid improvement of SLE-specific cutaneous lesions by C1q immunoadsorption

C1q is thought to play a crucial part in the pathogenesis of systemic lupus erythematosus (SLE). & C1q deficiency and the presence of C1q autoantibodies are associated with increased disease activity in SLE. Therefore, C1q is a promising candidate for adsorption of pathogenic relevant molecules from the plasma of patients with SLE. A C1q immunoadsorbent was developed in 1990 and has been used in several patients.

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6 In further glandular destruction.

7 Rapid improvement of SLE-specific cutaneous lesions by C1q immunoadsorption

C1q is thought to play a crucial part in the pathogenesis of systemic lupus erythematous (SLE). & C1q deficiency and the presence of C1q autoantibodies are associated with increased disease activity in SLE. Therefore, C1q is a promising candidate for adsorption of pathogenic relevant molecules from the plasma of patients with SLE. A C1q immunoadsorbent was developed in 1990 and has been used in several patients.
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 (negative)</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 (&lt;20 U/ml)</td>
<td>84</td>
<td>29</td>
</tr>
<tr>
<td>CIC* (IgM) (&lt;55 µg/ml)</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>CIC* (IgG)</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>C3c* (0.9–1.8 g/l)</td>
<td>108</td>
<td>83</td>
</tr>
<tr>
<td>C4* (0.1–0.4 g/l)</td>
<td>0.50</td>
<td>0.58</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 (ventral side) before C1q immunoadsorption (A). After 12 C1q immunoadsorptions the rash resolved completely (B).

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), though treatment related malignancies have been recorded. Among treatment related malignancies, the development of erythroleukaemia has been rarely reported. 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, 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. CYC is a highly carcinogenic agent and induces renal cancer, bladder cancer, MDS, and myelogenous leukaemia. Though we should be aware of treatment related malignancies in WG have also been reported, though no erythroleukaemia was recorded.

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 −5/5q−, −7/7q−, whereas our case did 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 discontinu-
ance of CYC. All possible efforts should be made to discontinue CYC to minimise the risk of developing treatment related malignancies after remission. Lastly, when myelo-suppression develops, we should discontinue CYC as soon as possible to avoid the development of treatment related leukaemia.

Figure 1 Bone marrow findings in November 1988.

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.

8 Krause JR. Chronic idiopathic thrombocyto-

Idiopathic atrophoderma, as described by Pasini and Pierrini, 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.

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 musculo-skeletal 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 exam-
ination 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 ass-
ays, 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 subcutane-
ously as she did not favour the oral route. She has responded well to the methotrexate and her joint symptoms are under good control. Six months after the onset of the arthritis she developed a new patch of atrophoderma on the left deltoid area measuring about 9×10 cm.

Figure 1 Symmetrical, pear shaped, slightly atrophic patch on the lower back.
Rheumatoid arthritis associated with ulcerative colitis: a case with severe flare of both diseases after delivery

Rheumatoid arthritis (RA) or Crohn's disease (CD) are both recognized indications of anti-tumour necrosis factor α treatment, indicating that these diseases may have important mechanisms in common, at least in part, through the contribution of the Th1/Th2 cytokine balance. A retrospective analysis of treatment of 75% of patients with RA during pregnancy suggests that pregnancy is a natural situation where this balance is modified.1 It is thus of interest to describe the clinical course of a patient with the association of two inflammatory diseases, RA and ulcerative colitis (UC) and its modulation by pregnancy. Rectal bleeding and mild foot arthralgias started in a 36 year-old woman with no particular personal or familial history one year before her first pregnancy. These symptoms remained the same until and during pregnancy. Two weeks after a normal delivery, rectal bleeding became more abundant and painful. Acute infectious gastroenteritis was diagnosed and symptomatic treatment was prescribed. After one month and a half there was no improvement, with up to 10–20 watery and bloody stools a day. A colonoscopy showed an inflammation of the whole colon consistent with UC. She was treated with mesalazine, 3 g/day, and steroids, 1 mg/kg/day. No improvement was seen and the patient went to hospital for parenteral nutrition. After three weeks there was a major improvement, she had a normal coloscopy and went home. Two weeks later, she was sent back to the hospital after a chronic atrophic gastritis with massive bloody diarrhea, abdominal pain, and rapid weight loss. Laboratory investigations showed erythrocyte sedimentation rate 52 mm/1st h, C reactive protein 89 mg/l, haemoglobin 90 g/l, leucocytes 12 900/µl, and serum albumin 21 g/l. Despite being treated with steroids intravenously and cyclosporin, with some effect on arthritis, the colitis continued to deteriorate and a total colecystectomy with ileostomy was performed. A histological analysis of the colon showed a diffuse inflammation of the colon with an infiltration of the mucosa and lamina propria with lymphocytes, plasma cells, and granulocytes. When first seen for arthritis, she had a very active, distal, and symmetrical arthritis affecting mostly hands and feet, with severe synovitis. She had pain at night and morning stiffness of at least one hour. A Rose-Waaler test was positive 1/128, antinuclear antibody negative, and HLA A3/A24 B7/B38 DRB1*0101/DR14 DQ5. Foot x rays showed bilateral erosions of the fifth metatarsal and ankle joint. No sacroilitis was found and the lumbar spine was normal. Treatment with methotrexate 7.5 mg, then 15 mg/week intramuscularly and salazopyrine 3 g/day associated with calcium, vitamin D, and pamidronate was begun. The treatment was not completely effective. UC is commonly associated with arthritic manifestations, and differential diagnosis between RA and UC associated arthritis can be difficult. In this patient the diagnosis of RA was made according to the 1987 American Rheumatism Association criteria with a DR1 genotype. The diagnosis of UC was made on the basis of the clinical course, endoscopic findings, and colon pathology. A bibliographic search showed that only a few cases of associations between RA and CD or UC have been described, and the influence of pregnancy on the association of RA and UC has never been seen before.2

Here, both RA and UC were poorly active or inactive during pregnancy, and a severe postpartum relapse for the two sets of symptoms. Even if we cannot exclude a coincidental association of the two diseases, the simultaneous occurrence of these 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.3 A Th2-like cytokine profile 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.

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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
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 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 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 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 of the left ankle had low viscosity and was sterile on culture.

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, synovitis of the hip joint,1 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.

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 spine1—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 OPLL may be fairly frequent in ankylosing spondyli-

Despite a series of clinical, x ray, and laboratory investigations the cause and pathogenesis are still unresolved, both in DISH and in OPLL. Some relations have been established between DISH and diabetes mellitus, or diminished glucose tolerance, obesity, gout, hypertriglyceridaemia, and hyperretinol-aemia. This suggests, together with an occasional familial incidence, a possible association of genetic predisposition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm it.5 This discrepancy might partly be accounted for either by coincidence of DISH and ankylosing spondylitis, or by difficulties in differentiating between these two disorders.4 OPLL, similarly to DISH, seems to be associated with complications with low glucose tolerance and obesity.6 Attention has also focused on the role of bone formation promoting factors in OPLL.7

Recently, Japanese authors discovered a predisposing locus for OPLL through a small region within 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 site. 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. Sixty healthy Czech blood donors were controls. DNA 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).8 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 frequency 34% v 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 spectrum of genotyping and larger cohorts of patients.

This study was supported by a grant from the Grant Agency of the Czech Republic (No 311/98/1585).

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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). Few observations of vasculitis occurring immediately after massive inhalation of a presumed antigen have been published. 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, sinustis, 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 16.12×10⁹/l, with 1870 cosinophils, serum creatine 170 µmol/l; proteinuria 0.7 g/day, and microscopic haematuria. Specific antimeyeloperoxidase 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 interstitial glomerulonephritis. We retained the diagnosis of Wegener’s granulomatosis. Despite corticosteroids and intravenous cyclophosphamide, the patient remained disease-free 18 years later.

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 vasculitic lesions 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 arteries. Despite treatment with prednisone 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 severe reactions for flour and 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 mononeuropathy limiting the left peroneal nerve upon clinical examination. ANCA were not tested. Neuromuscular biopsy showed microvascularitis with perivascular 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 with prednisone which was tapered within 18 months and maintained at 5 mg/day to control asthma. The patient remains asymptomatic 12 months after. The causes 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. In case 4 (previously published), the abundance of actinomyces in pneumatocytes might suggest that they caused the vasculitis.

Stephens et al described bronchial allergic aspergillosis evolving to CSS, and Orriëns et al reported a case of CSS induced by free base cocaine. Some drugs have been associated with the occurrence of CSS, particularly recently zafirlukast. Rapid onset of microscopical 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. In our cases, 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
patients, to systemic dissemination and the acute onset of systemic vasculitis progressive immune complex formation and deposition.

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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 (%)</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>5</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 drug regimens. The child was born healthy, unrelated Italian parents. He came to our attention because of periodic fever spikes, which occurred every 20–30 days. During fever flare ups, he usually developed arthralgias without arthritis, malaise, and abdominal pain with diarrhoea. Severe leucocytosis (up to 39 × 10^6/l) and acute phase reactant positivity (C reactive protein 2.9 mg/l; normal values <4 mg/l) were also detected. An abdominal echo scan disclosed enlarged mesenteric lymph nodes, as well as thickened and hyperaemic colonic walls.

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 mevalonate kinase, an enzyme that has a pivotal role in the synthesis of isoprenoids and cholesterol.


5 Orrids R, Munoz X, Ferrer J, Huget P, Morell F. Common causes of fever were ruled out; antinuclear antibodies, complement fractions, adenosine-deaminase, lymphocyte subpopulations, and in vitro lymphocyte proliferation to antigens and mitogens were in the normal ranges. The commonest mutations (met 680 ile, met 694 val, met 694 ile, val 762 ala) known to occur in the Italian population at exon 10 of the pyrin gene were absent. When our patient was 3 years old, frankly increased IgA plasma concentrations (9.39 g/l) and IgD plasma concentrations at the upper level of normal (98 IU/l), normal values below 100 IU/l) were found. At the same time, the presence of mevalonate acid and its metabolites in red blood cell samples was shown by gas chromatography and mass spectrometry; moreover, blunted mevalonate kinase synthesis in cultured skin fibroblasts (5.3 pmol/min/mg controls 144 (67), kindly performed by Dr Wanders) was detected. A genetic analysis (kindly performed by Dr Joos Frenkel) showed the presence of mutations in both alleles of the mevalonate kinase gene that is, alanine at position 148 into threonine; isoleucine at position 268 into threonine. On the basis of this a diagnosis of HIDS was proposed. Because a randomised trial of treatment was refused by our patient’s parents, a cycle of treatment with colchicine (1 mg/day) was given for 15 months. During this period the intercritical periods were longer; however, some side effects occurred such as recurrent abdominal pain and skin rash. When the diagnosis of HIDS was suggested, the patient was treated with a single dose (12.5 mg) of prednisone at the beginning of the flare up episodes. Fever promptly receded and the other symptoms (abdominal pain, diarrhoea, etc) were milder or absent. Notably, the fever remained periodic. To avoid the possible side effects of long term administration of steroids, we decided to treat the patient with the non-steroidal inflammatory drug, naproxene, given in single dose (250 mg) at the beginning of the flare ups.

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 fulfill 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.

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Are DISH and OPLL genetically related?

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