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 metatarsophalangeal (MCP) and metatarsophalangeal (MTP) joint sites in rheumatoid subjects suggests strongly a homology of the 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: ulnar head/styloid; radial head/styloid; 2nd MCP joint (ulnar aspect); 3rd MCP joint (ulnar aspect); 1st MTP 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 (range) 3 (0–18) 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 site 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 at 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.1 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.

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>
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<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)</td>
<td>0</td>
<td>7 (23)</td>
</tr>
<tr>
<td>3rd PIP* joint (ulnar)</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>5th MTP joint</td>
<td>1 (5)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (7)</td>
<td>56 (28)</td>
</tr>
</tbody>
</table>

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


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. 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.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 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. Failure to detect statistical difference does not declare 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 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 could have been 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 reject 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.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>A versus C</th>
<th>B versus C</th>
<th>A versus B</th>
<th>D versus C</th>
<th>D versus E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>0.61</td>
<td>0.58</td>
<td>0.03</td>
<td>0.67</td>
<td>0.05</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>
<td>−0.024 to 0.34</td>
</tr>
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</table>

Fetal microchimerism in Sjögren’s syndrome

Toda and colleagues report that microchimerism of fetal cells is uncommon in women with Sjögren’s syndrome (SS). 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 patients who fulfilled four or more of the diagnostic criteria for SS proposed in 1993 by the European Sjögren’s Syndrome 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 5x10^4 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 were matched to 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 the results being controversial. It has also been investigated in primary biliary cirrhosis and inflammatory myopathies by non-quantitative methods, yielding negative or non-conclusive results.

We are also skeptical of the suggestion 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.

Authors’ reply

We read with interest this letter by Mijares-Bocckl-Behrens et al commenting on our previous paper. They failed to detect fetal DNA in peripheral blood nucleated cells from women with Sjögren’s syndrome (SS) who had male children. This finding is principally concordant with our study. Nelson presented an interesting possibility that some autoimmune diseases, including scleroderma, SS, and primary biliary cirrhosis, are fetal anti-maternal chronic graft versus host disease (GVHD), though this theory is still considered.

Based on the study by Mijares-Bocckl-Behrens et al and our study, the ratio of non-host to host cells in circulation is less than one to 10 cells in women with SS who were previously pregnant. In contrast, blood DNA in patients with chronic GVHD, who received haemopoietic stem cell transplantation were totally replaced by donor derived cells. Because of the exceedingly low ratio of non-host to host cells in women with SS, in contrast with chronic GVHD, it is believed that the pathogenic process in SS is not similar to that in chronic GVHD. In this regard, donor DNA is often observed in patients who received solid organ transplantation, but these patients rarely develop chronic GVHD. The ratio of non-host to host cells in patients receiving liver transplantation is more than one to 10 peripheral blood nucleated cells—that is, at least 10 times more frequent than the ratio in women with SS who have sons. Our recent electron microscopic analysis of laryngeal biopsy specimens from patients with SS and those with chronic GVHD after haemopoietic stem cell transplantation clearly indicated a substantial difference in pathogenic processes between these two disease conditions. T cells were mainly detected in the periductal area, and some T cells had infiltrated into the ductal epithelia through disrupted basal laminae in patients with chronic GVHD. In patients with SS, the T cells were diffusely found in both acinar and periductal areas, but scarcely detected in the ductal epithelia. T cells which had infiltrated into the ductal epithelia in chronic GVHD were CD8+ T cells. CD8+ T cells, indicating that T cell invasion leads to the destruction of the ductal epithelium (Ogawa Y, Kuwana M, manuscript in preparation). Based on this finding, chronic GVHD in the lachrymal gland can be simply explained by an allo-immune response to the ductal epithelium by donor-derived T cells. On the other hand, a recently proposed pathogenic process in SS described an inappropriate apoptosis in lachrymal epithelial cells as the initial phase, followed by lymphocyte infiltration and autoimmune aggregation, resulting in further glandular destruction.

However, the results of Mijares-Bocckl-Behrens and those of our study do not exclude the possibility that microchimerism has a role in the pathogenesis of SS. The presence of a small population of non-host cells would not evoke a putative GVHD mechanism itself, but would result in induction and/or promotion of autoimmunity. For example, non-host cells could differentiate into immune regulatory cells, thereby disregulating the immune system under certain exogenous conditions, such as concurrent infection. Because persistent fetal microchimerism is common in normal women, further work should aim at functional studies of immune cells originating from fetal cells in patients with SS and from healthy women who were previously pregnant.

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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 erythematosis (SLE). C1q deficiency and the presence of C1q autoantibodies have been associated with increased disease activity in SLE. Therefore, C1q is a promising candidate for adsorption of pathogenetic relevant molecules from the plasma of patients with SLE. A C1q immunoadsorbent was developed in 1990 and has been used in several patients.

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, polyarthritits and lupus nephritis (histological membranous glomerulonephritis and WHO IVa, i.e. minor 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) the severe and persistent symptoms had not been improved. 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 I). Therefore, C1q immunoadsorption with MIRO 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 during 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 60 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 methotreaxate (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 I).

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. The C1q immunoadsorptions (MIRO adsorbers) consist of polyacrylamide beads coated with covalently bound swine C1q. Effective clearance of circulating immune complexes as well as of C1q autoantibodies could 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 potential side effects such as marked thrombocytopenia or anaaphylactic reactions according to an increased bradykinin synthesis, were not seen. In contrast with the plasma exchange treatment, only selective plasma components were 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 minimized. With decreasing levels of circulating 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 the immune complex disease. However, the...
*CIC = circulating immune complexes; C3c, C4 = complement components.

CIC (IgG) were not raised and therefore not tested during the course of C1q immunoadsorptions.

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 high carcinogenic agent and induces renal cancer, bladder cancer, MDS, and myelogenous leukaemia. CYC related second 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. Alkylation 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.

**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>54</td>
<td>29</td>
</tr>
<tr>
<td>CIC* (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 (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.
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 discontinuation 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.

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Matters arising, Letters

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. 1 The incidence of JIA in the UK varies from 10 to 20/100 000/year, with a prevalence of 1/1000. 2


Atrophoderma, as described by Pasini and Pierini, is a distinctive form of dermal atrophy seen particularly in children and younger people. 3 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 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 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.

Atrophoderma and juvenile idiopathic arthritis

Figure 1 Symmetrical, pear shaped, slightly atrophic patch on the lower back.
DISCUSSION
Atrophoderma of Pasini and Pierini (APP) can occur at any age, but usually develops in the teens or the 20s. Childhood presentation is not uncommon, and various reviews have shown that this subtype comprises between 10 and 15% of all childhood morphea.1,2 The cause remains uncertain although infective agents, particularly Borrelia burgdorferi have been implicated in few reports.1 APP has a female to male ratio of 2:1. The distinction of this condition from morphea was thought to be important to avoid the use of aggressive immunosuppressive treatment. There are no reports of associations between APP and JIA or the presence of antinuclear antibody and rheumatoid factor.

We feel our case illustrates a few important features about APP, especially that prolonged pregnancy suggests that pregnancy is a natural selection for the Th1/Th2 cytokine balance. It is interesting to note that our patient was receiving methotrexate, the lesions did not regress and she developed a new lesion after starting methotrexate. The classical improvement of 75% of patients with RA during pregnancy suggests that pregnancy is a natural state arising from the balance is modified.3 It is thus of interest to discuss the clinical course of a patient with the association of two inflammatory diseases, RA and ularative colitis (UC) and its modulation by pregnancy. Rectal bleeding and mild foot arthralgias started in a 30 year old, pregnant 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 intermittent and constant. Acute inflammatory 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 colonoscopy and went home. Two weeks later, she was sent back to the hospital after a chronic arthropathy associated with massive bloody diarrhoea, abdominal pain, and rapid weight loss. Laboratory investigations showed erythrocyte sedimentation rate 32 mm/1st h, C reactive protein 89 mg/l, haemoglobin 90 g/l, leucocytes 12 900/ml, 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 colostomy with ileostomy was performed. The pathological 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 metatarsophalangeal joint. No sacroiliitis 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 DRI 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.4,5

Here, both RA and UC were poorly active or inactive during pregnancy. The presence of 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 different. Pregnancy is thought to induce a shift from Th1 to Th2 response, increasing the contribution of anti-inflammatory cytokines.1 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.

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 as 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.2 The classical improvement of 75% of patients with RA during pregnancy suggests that pregnancy is a natural situation where this balance is modified.3 It is thus of interest to discuss the clinical course of a patient with the association of two inflammatory diseases, RA and ularative colitis (UC) and its modulation by pregnancy. Rectal bleeding and mild foot arthralgias started in a 30 year old, pregnant 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 intermittent and constant. Acute inflammatory 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 colonoscopy and went home. Two weeks later, she was sent back to the hospital after a chronic arthropathy associated with massive bloody diarrhoea, abdominal pain, and rapid weight loss. Laboratory investigations showed erythrocyte sedimentation rate 32 mm/1st h, C reactive protein 89 mg/l, haemoglobin 90 g/l, leucocytes 12 900/ml, 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 colostomy with ileostomy was performed. The pathological 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 metatarsophalangeal joint. No sacroiliitis 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 DRI 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.4,5

Here, both RA and UC were poorly active or inactive during pregnancy. The presence of 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.1 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.

Ultrasonography is useful to distinguish between intra- and extra-articular disease in pyoderma gangrenosum complicating polyarthritis
Ultrasoundography, 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 involve the joints.
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. 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 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 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 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 cytoplasmatic 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 and bone. 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, poliphtal cysts, synovitis of the hip joint, and chronic shoulder complaints.1

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.

4 Swen WAA, Jacobs JWG, Neve WC, Bal D, Bijlsma JW. Is sonography performed by the rheumatologist as useful as arthrography executed by the radiologist for the assessment of full thickness rotator cuff tears? J Rheumatol 1998;25:1800–6.

Figure 1 Ultrasonography of the distal pretibial region: the normal right leg (left), a = position of the transducer at the skin surface; b = bone of the tibia.
distinct genotypes and water as negative control were included. Comparison of the genotype 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% 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 311981585).

Table 1 Intron 6 (−4) allele frequency

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Non-DISH (No (%))</td>
<td>74 (63)</td>
<td>44 (37)</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>83</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 desensitisation, vaccination, or inhalation of antigens by asthmatic patients may trigger Churg-Strauss syndrome (CSS). Other 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, sinuses, 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/lst h, while the white blood cell 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 cytoplasmatic antibodies (ANCA) were detected (30 IU). A neumococcal biopsy showed necrotising vasulitis 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 under- went 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 arteriograms. The cranial nerve disease and chest nodules regressed after oral prednisone treatment, but progressed after oral cyclophosphamide. The patient developed left peroneal nerve upon clinical examination. 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. In case 4 (previously published), the abundance of actinomycetes in pneunymctes might suggest that they caused the vasculitis.

Stephens et al described bronchoalveolar aspergillosis evolving to CSS, and Orids 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 microscopically polyangitis within a few hours or days after massive antigen inhalation has not been described previously. Small vessel vasculitis mechanisms implicate ANCA, neutrophils and proinflammatory cytokones, and their interactions with external stimuli. In some 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 or 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 8

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patients, to systemic dissemination and the acute onset of systemic vasculitis progressive immune complex formation and deposition.

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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, arthralgias without arthritis, malaise, and abdominal pain with diarrhea. Severe leukocytosis (up to 39 × 10^9/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.

Common causes of infections 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 subpopulations, and antigens (Churg-Strauss syndrome). Am Rev Respir Dis 1988; 137: 1226–8.  


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

<table>
<thead>
<tr>
<th>Therapy</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>14 (6)</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 (1)</td>
<td>18 (7)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Naproxene</td>
<td>1 (1)</td>
<td></td>
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</table>

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.


Are DISH and OPLL genetically related?

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

Ann Rheum Dis 2001 60: 902-903

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