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 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 (median interphalangeal joint (ulnar and radial aspect); 1st MTP joint (medial aspect); and the 5th MTP joint (lateral aspect). All four limbs were examined 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 radiographically.

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 site of sonographic 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.

A recent Dutch study of patients with early RA, followed up radiographically for six years, found the 5th MTP joint to be the most common site of sonographic 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 site of sonographic 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.

**Table 1** The frequency of sites that showed erosions by radiography and ultrasound in the 15 patients with rheumatoid arthritis. The percentages refer to a total of 30 examined joints for each site, except at the 1st metatarsophalangeal joint, where 10 sites were excluded because of the radiographic presence of osteoarthritic (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>11 (37)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>3rd PIP* joint</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3rd PIP joint</td>
<td>0</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1st MTP joint</td>
<td>5 (17)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>5th MTP joint</td>
<td>15 (50)</td>
<td>15 (50)</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. 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 joint is the most commonly 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.
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 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.1 Failure to detect statistical difference does not mean 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,1 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.

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 American College of Rheumatology 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 5 x 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 the results being controversial.3,4 It has also been investigated in primary biliary cirrhosis and inflammatory myopathies by non-quantitative methods, yielding negative or non-conclusive results.2 One must assume they are similar to those reported by Toda and colleagues1; nevertheless, this does not 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.5,6

Table 1

<table>
<thead>
<tr>
<th>Group</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>
</tbody>
</table>

We read with interest this letter by Mijares-Boeckh-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 et al have shown 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 controversial.

Based on the study by Mijares-Boeckh-Behrens et al and our study, the ratio of non-host to host cells in circulation is less than one to 104 cells in women with SS who were previously pregnant. In contrast, blood cells in patients with chronic GVHD who received haemopoietic stem cell transplantation are 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 cell chimerism is often seen 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 has been shown to be more than one to 106 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 epithelium 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 mostly CD8+ cytotoxic 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-Boeckh-Behrens et al 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 pentameric 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.
**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>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.

---

**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 improvement. 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 thrombocytopoenia 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. 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. 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 discontinuation 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. 7 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 to minimise the risk of developing treatment related malignancies. 

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 to minimise the risk of developing treatment related malignancies.

**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 has responded well to the methotrexate and her joint symptoms are under good control.

**Atrophoderma and juvenile idiopathic arthritis**

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of arthropathies occurring in children under the age of 16. It is a complex multifactorial disease with genetic, immunological, and environmental factors strongly associated with causation. 8 The incidence of JIA in the UK varies from 10 to 20/100 000/year, with a prevalence of 1/1000. 9

Atrophoderma, as described by Pasini and Pierini, is a distinctive form of dermal atrophy seen particularly in children and younger people. 1 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.

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 recognised indications of anti-tumour necrosis factor (TNF) treatment, indicating that these diseases may have important mechanisms in common, at least in part, through the contribution of the Th1/Th2 cytokine balance.

The classical improvement of 75% of patients with RA during pregnancy suggests that pregnancy is a natural situation where this balance is modified. 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 increased which was found to be from a large haemorrhoid.

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 coloscopy 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 ulcerative colitis 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 12 600/l, and serum 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 increased which was found to be from a large haemorrhoid. The patient developed joint symptoms in a child with a new benign variant of morphea, which might be a self-involving atrophoderma of the lateral upper arm. A new benign variant of morphea?

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.

A distinctive entity which has been described recently. Although the cause of both is not clearly understood, immunological mechanisms to as yet unidentified antigens appear to underlie the pathogenesis. We speculate that the underlying trigger may be a common infective pathogen which activates the immune system.
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 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 of the left ankle had low viscosity and was very painful and showed some non-pitting oedema and erythematous discolouration. 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 purulent 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, poikilodermatous,1 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.

P M HOUTMAN
E N GRIEP
Department of Rheumatology,
Medical Centre Leeuwarden,
PO Berlinh, 8901 BR Leeuwarden,
The Netherlands
p.m.houtman@wxs.nl

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;25:1806–00.

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 spondylitis.5

Despite a series of clinical, x ray, and laboratory investigations the cause and pathogenesis is 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 hyperretinol-aeemia. This suggests, together with an occasional familial incidence, a possibility of genetic predisposition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm it.6 This discrepancy might partly be accounted for either by coincidence of DISH and ankylosing spondylitis, or by difficulties in differentiating between these two disorders.7 OPLL, similarly to DISH, seems to show associations with low glucose tolerance and obesity.8 Attention has also focused on the role of bone formation promoting factors in OPLL.9

Recently, Japanese authors discovered a predisposing locus for OPLL through 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 site.10 However, as far as we know, no investigation of this type has been so far performed in patients with DISH. As the common clinical and metabolic features of OPLL and DISH can suggest their common aetiopathogenesis, a genotyping study on the COL 11 A2 gene was done in a group of 60 Czech patients with DISH. Diagnosis of DISH was based on the x ray changes on the spine. Sixty healthy Czech blood donors were controls. Genotyping was performed in DNA samples, 200 ng each, extracted from peripheral blood leucocyte cells. Polymorphism at intron 6 (+4) in the COL 11 A2 gene was determined by mutagenically separated polymerase chain reaction (PCR).11 For detection of the intron 6 (+4) allele, 16T and 16A primers, together with the common complementary strand primer G72, were used. In each PCR reaction, control DNAs of three known
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% v 37%, respectively, χ²=0.296 (df=1), p=0.587.

In conclusion, results of analysis of intron 6 (–4) polymorphisms in the COL 11A2 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 31198/1585).

Table 1  Intron 6 (–4) allele frequency

<table>
<thead>
<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>
<td></td>
</tr>
</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). 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, sinusitis, and high fever, which regressed with short term steroid treatment. After three months he complained of bilateral hot 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 the blood count was 16.12×10³/μl, with 1870 eosinophils, serum creatinine 170 μmol/l; proteinuria 0.7 g/day, and microscopic haematuria. Specific antineutrophil 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, but non-invasive granulomato-nephritis. We retained the diagnosis of Wegener's granulomatosis. Despite corticosteroids and intravenous cyclophosphamide, the patient underwent 13 plasma exchanges. The patient continues to have recurrent daily headache 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 inhale 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 these sites on both hands. Supra-aortic angiography showed bilateral occlusion in the radial and ulnar arteries; microaneurysms were seen in digital arteries. A skin biopsy detected vasculitis at the dermal-hypodermal junction with mononuclear cell and eosinophil infiltrates in the artery walls without leucocytoclastic or necrotising vasculitis. Ulnar artery biopsy showed complete occlusion of the artery lumen without evidence of vasculitis. CSS was diagnosed and prednisone was prescribed, which was progressively tapered over 18 months. Eight years later, the patient remains well.

Case 3: A 53 year old woman who worked in a bakery for 30 years had had asthma for 20 years, with sensitivity for flour, antigens. In March 1988, 10 days after massively inhaling flour dust (a flour sack broke), she experienced acute fever and mild tenderness in her arms and right foot, with motor and sensory mononeuropathies. Clin Exp Rheumatol 1993;11:603–8.

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 and systemic anticoagulation. One month later he developed vascular purpura on his legs. A bilateral basal opacity was seen on chest x ray examination. ANCA were not tested. Skin biopsy showed leukocytoclastic vasculitis in small sized vessels, without fibrinoid necrosis. Prednisone (1 mg/kg/day) was prescribed, then tapered and discontinued when all symptoms resolved. After one month, the same symptoms reappeared after another exposure to pigeons. A chest roentgenogram showed extensive bilateral basal nodules, and pulmonary biopsy disclosed vasculitic lesions, with fibrinoid necrosis of arteriole and venule walls. Despite prednisone and intravenous cyclophosphamide, the patient developed multiple cranial nerve disease. He received oral cyclophosphamide, but no improvement occurred and the patient underwent 13 plasma exchanges. The cranial nerve disease and chest nodules were regressive. Cyclophosphamide was discontinued after 12 months and the patient remains disease-free 18 years later.

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

Stephens et al described bronchoalveolar aspergillosis evolving to CSS,2 and Orrids 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 microscopic polyangiitis within a few hours or days after massive antigen inhalation has not been described previously. Small vessel vasculitis mechanisms implicate ANCA, neutrophils and proinflammatory cytokines, and their interactions with external antigens.2 In case 2, 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/and 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.

I. MOUTHON
M. KHALED
P. COHEN
L. GUILLEVIN
Service de Médecine Interne,
Hôpital Avicenne,
Université Paris-Nord,
Bobigny, France

J.F. SUBRA
Service de Néphrologie,
Centre Hospitalier Universitaire d’Angers,
Angers, France

Correspondence to: Dr L Mouton, Service de Médecine Interne, Hôpital Avicenne, 125 Route de Stalingrad, 93009 Bobigny Cedex, France

luc.mouthon@avc.ap-hop-paris.fr


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.1

<table>
<thead>
<tr>
<th>Table 1 Therapeutic regimens followed sequentially and the clinical responses detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of fever (days)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>No treatment</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Naproxene</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 treatments.

The child was born to 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 diarrhea. Severe leucocytosis (up to 39 x 10⁹/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 hypertrophic 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 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 kinase and its metabolites in urinary samples was shown by gas chromatography and mass spectrometry; moreover, blunted mevalonate kinase synthesis in cultured skin fibroblasts (5.3 pmol/min/mg proteinase 3 and myeloperoxidase in patients with Churg-Strauss angiitis: arguments favoring the responsibility of inhaled antigens. Chest 1991;100:1472–3.


Are DISH and OPLL genetically related?

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

Ann Rheum Dis 2001 60: 902-903

Updated information and services can be found at:
http://ard.bmj.com/content/60/9/902

These include:

References
This article cites 8 articles, 2 of which you can access for free at:
http://ard.bmj.com/content/60/9/902#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/