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 the erosive lesions, as visualised by these different imaging modalities. A recently published study by an independent group, comparing radiographic and sonographic imaging of MCP joints in patients with rheumatoid arthritis for ease of transducer access, as well as early, characteristic, and/or representative information about the potential role of ultrasonography in the diagnosis of rheumatoid arthritis (RA). Ultrasonography is undoubtedly more sensitive than x-ray in detecting bone erosions. Last generation broad band linear transducers (10–22 MHz) have an axial resolution power lower than 0.03 mm, and even minimal cortical defects of small joints can be clearly depicted.

We agree with Dr Klocke and colleagues that the 5th metatarsophalangeal (MTP) joint is the most common site of sonographic erosive 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, last generation power Doppler equipment may offer some additional information about the perifascial 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</td>
<td>0</td>
<td>8 (27)</td>
</tr>
<tr>
<td>3rd PIP* joint: radial</td>
<td>0</td>
<td>6 (20)</td>
</tr>
<tr>
<td>3rd PIP* joint: ulnar</td>
<td>0</td>
<td>7 (23)</td>
</tr>
<tr>
<td>1st MTP joint</td>
<td>1 (5)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>5th 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>

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

**MATTERS ARISING**

Authors’ reply

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

We agree with Dr Klocke and colleagues that the 5th metatarsophalangeal (MTP) joint is the most common site of sonographic erosive 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, last generation power Doppler equipment may offer some additional information about the perifascial 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 long 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 imply 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.
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 also used possible that some autoimmune diseases, including scleroderma, SS, and primary biliary cirrhosis, are fetal anti-maternal chronic graft versus host disease (GVHD), but 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 10 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 is more than one in 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 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 with CD4+ cytotoxic T cells, indicating that T cell invasion leads to the destruction of the ductal epithelium (Ogawa Y, Kuwana M, manuscript in preparation).

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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 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.

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, polyarthrits, and lupus nephritis (histological membranous glomerulonephritis WHO V a), as well as alopecia, 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 malar and discoid 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 a 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 venules were used) blood flow was about 80 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 a complete remission 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 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 fibronectin, 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 anaphylactic reactions according to an increased bradykinine 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 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 malignant immune complex disease.

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

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Figure 1 Discoid rash of both femurs (ventral side) before C1q immunoadsorption (A). After 12 C1q immunoadsorptions the rash resolved completely (B).

Table 1 Serological parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before C1q immunoadsorption</th>
<th>After 12 C1q immunoadsorptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>1/2560</td>
<td>1/2560</td>
</tr>
<tr>
<td>Anti-dsDNA (&lt;20 IU/ml)</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>C1q autoantibodies (&lt;20 U/ml)</td>
<td>64</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.

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 predonisone, 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 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
more than 10 g is given. 1 When rheumatologists prescribe CYC for the treatment of patients with rheumatic diseases, stringent monitoring of the haematological parameters should be required, even after the discontinuance of CYC. All possible efforts should be made to discontinue CYC to minimise the risk of developing treatment related malignancies after remission. Lastly, when myelosuppression develops, we should discontinue CYC as soon as possible to avoid the suppression of CYC. All possible efforts should be made to discontinue CYC to minimise the risk of developing treatment related malignancies after remission.

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. 2 The incidence of JIA in the UK varies from 10 to 20/100 000/year, with a prevalence of 1/1000. 3

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 purplish, 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. 4

Figure 1  Bone marrow findings in November 1988.

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 association 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 follow up is essential when a diagnosis is made in children as there is a possibility of them developing other rheumatological conditions. It is interesting to note that despite the fact that our patient was receiving methotrexate, the lesions did not regress and she developed a new lesion after starting methotrexate, and we need to be evaluated and there may be an increased risk for developing JIA. It is also interesting to note that our patient developed a patch in her upper arm, which might be a self-involuting atrophoderma of the lateral upper arm, a distinct entity which has been described recently.4 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.

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 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.5 The classical improvement of 75% of patients with RA during pregnancy suggests that pregnancy is a natural situation where this balance is modified.8 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 familiar 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 frequent 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 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 arthralgia with massiveness, 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/µl, and serum albumin 21 g/l. Despite being treated with steroids intravenously and cyclosporin, with some effect on arthrititis, the colitis continued to deteriorate and a total colectomy 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 arthrititis, she had a very active, distal, and symmetrical arthrititis 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 arthritides 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 colonic 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.9,10
Here, both RA and UC were poorly active or inactive during pregnancy, and flares were seen postpartum relapse for the two sets of symptoms. Even if we cannot exclude a coincidental association of the two diseases, the simultaneous occurrence of the two 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.10 A CHA2 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 polyarthitis

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 polyarthitis.

Pyoderma gangrenosum (PG) is an uncommon ulcerative skin condition which may
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 10.5 g/l, and a haemoglobin 6.5 mmol/l, and a white blood cell count of 14.5 x 10^9/l. Rheumatoid factor and antinuclear antibodies were negative. Anti-neutrophil cytoplasmic antibodies, p type, and cultures and specific stains for mycobacteria, and fungi from the pustular lesions were negative. Sigmoidoscopy, barium x ray studies, a rectal biopsy, and a computed tomography study of the thorax and abdomen were normal.

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

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

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

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 spine—a according to today’s nomenclature, diffuse idiopathic skeletal hyperostosis (DISH). 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 vertebro bodies and discs, predominantly of the cervical spine. Systematic studies of OPLL began in Japan 25 years ago. A varying proportion of patients with DISH have OPLL, and vice versa. However, recent observations indicate that cervical OPLL may be fairly frequent in ankylosing spondylitis.

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

Recently, Japanese authors discovered a predisposing locus for OPLL on chromosome 6p, close to the HLA locus. They provided evidence of genetic linkage and allelic association of the COL 11 A2 gene which would constitute an inherited predisposition for OPLL. Among 20 genetic variants in this gene, a strong allelic association (p=0.0003) with OPLL was observed with intron 6 variant, which is at position +4 from the 3' splice juncture. 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. DNA was performed in DNA samples, 200 ng each, extracted from peripheral blood leucocyte cells. Polymorphism at intron 6, a single nucleotide polymorphism with low glucose tolerance and obesity, was assessed by the radiologist for the assessment of full thickness rotator cuff tears? J Rheumatol 1998;25:1800–6.
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% vs 37%, respectively, χ²=0.296 (df=1), p=0.587.

In conclusion, results of analysis of intron 6 (−4) polymorphisms in the COL11A2 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.

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 foot drop, which was found to be due to mononeuropathy 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/l, with 1870 eosinophils, serum creatinine 170 µmol/l, proteinuria 0.7 g/day, and microscopic haematuria. Specific antineutrophil cytoplasmic antibodies (ANCAs) 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 partial glomerulonephritis. We and others have proposed that desensitisation, vaccination, exposure to variadic substances, or too rapid steroid tapering. In one month later he developed vascular purpura on his legs. A bilateral basal opacity was seen on chest x ray examination. ANCA were not tested. Skin biopsy showed leucocytoclastic vasculitis in small 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 rengroentgenogram showed extensive bilateral basal nodules, and pulmonary biopsy disclosed vasculitic lesions, with fibrinoid necrosis of arteriole and venous walls. Despite treatment with prednisone the patient developed multiple cranial nerve disease. He received oral cyclophosphamide, but no improvement occurred and the patient underwent 13 plasma exchanges. The cranial nerve disease and chest nodules were regressive. Cyclophosphamide was discontinued after 12 months and the patient remains disease-free 18 years later.

Causative and precipitating agents of CSS have not been identified and have not been described before. Some drugs or environmental substances, or too rapid steroid tapering. In one case (previously published), the abundance of actinomyces in pneumocytes might suggest that they caused the vasculitis.

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

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Table 1 Introns 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 (69)</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>
</tr>
</tbody>
</table>
patients, to systemic dissemination and the acute onset of systemic vasculitis progressive immune complex formation and deposition.

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 drugs.

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, arthritis, and abdominal pain with diarrhea. Severe leukocytosis (up to \( 39 \times 10^9/\text{l} \)) and acute phase reactant (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 hyperemic 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, isoleucine at position 268 into threonine. On both alleles of the mevalonate kinase gene—Frenkel) showed the presence of mutations in different subpopulations, and in vitro lymphocyte proliferation assay 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.

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.


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.
Corticosteroid injection for the treatment of carpal tunnel syndrome

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