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 these erosive lesions, as visualised 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, reports ease of transducer access, as well as early, characteristic, and/or representative imaging (MRI) changes corresponding to spe-

The same study observed magnetic resonance imaging (MRI) changes corresponding to spe-

Table 1

<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>1 (37)</td>
<td>0</td>
</tr>
<tr>
<td>3rd MCP** joint</td>
<td>0</td>
<td>7 (23)</td>
</tr>
<tr>
<td>3rd PIP* joint: radial aspect</td>
<td>0</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1st MTP joint</td>
<td>1 (57)</td>
<td>7 (35)</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.

Authors' reply

Dr Klocke and colleagues highlight interesting aspects about the potential role of ultrasonography in the diagnosis of rheuma-


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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 of long acting corticosteroids in the treatment of carpal tunnel syndrome. We are skeptical of the conclusions 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 prove equivalence. A large scale, probably multicentre, study may provide a definitive answer to this question.

We are also skeptical of the suggestion that low dose steroid is potentially less toxic. The true incidence of complications related to steroid injection is not known, and discussion is mainly limited to case reports, with no specificity given for many preparations. With so few reported cases, one must assume they are truly rare or they have been under-reported. If the assumption is the former then one will not be expecting any adverse side effects from this group of 100 or so patients.

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Fetal microchimerism in Sjögren’s syndrome

Toda and colleagues report that microchimerism of fetal cells is uncommon in women with Sjögren’s syndrome (SS). 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 5x10^6 female cells. The amount of genomic DNA used in the PCR reaction was 3 µg, and more than five samples were tested for each woman. Eighteen healthy Spanish women (mean age 48.7 years (range 32–65)) who had male children were used as 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.

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.

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Table 1

<table>
<thead>
<tr>
<th></th>
<th>A versus C</th>
<th>B versus C</th>
<th>A versus D</th>
<th>B versus D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>0.61</td>
<td>0.58</td>
<td>0.03</td>
<td>0.67</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.42 to 0.80</td>
<td>0.38 to 0.77</td>
<td>0.02 to 0.26</td>
<td>0.44 to 0.89</td>
</tr>
</tbody>
</table>

Authors’ reply

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

Concerning the toxicity of various steroid preparations, the animal study to which we referred has not been repeated, and clearly the implication that toxicity is rare and therefore should not be considered is unacceptable.

The call for a larger study is inevitable when a counter-intuitive result has emerged. It cannot be assumed, as implied by Wong and Hui, that a higher dose of hydrocortisone, or the longer acting triamcinolone, is mainly limited to case reports, with no specificity given for any preparations. With so few reported cases, one must assume they are truly rare or they have been under-reported. If the assumption is the former then one will not be expecting any adverse side effects from this group of 100 or so patients.

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Behrens and those of our study host to host cells in circulation is less than one
et al. Behrens et al.

principally concordant with our study. This finding is
even pregnant. In contrast, blood cells in

sons raised the fascinating possibility that
donor cell microchimerism is often seen in

non-host to host cells in women with SS, in

that the pathogenic process in SS is not simi-

contrast with chronic GVHD, it is believed
tion, but these patients rarely develop

disease (GVHD),

who had male children. This finding is

fetal anti-maternal chronic graft versus host
doctrine of male children. This finding is

with chronic GVHD. In patients with SS, the
cells had infiltrated into the ductal epithelia
detected in the periductal area, and some T
clearly indicated a substantial di

After haemopoietic stem cell transplantation

898

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Toda I, Kuwana M, Tsubota K, Kawakami Y.


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cellular chimeric patients by

polymerase chain reaction analysis of HLA-Cw


Our recent electron microscopic analysis of

lymph node tissues of patients with SS who were
previously pregnant. In contrast, blood cells in

women with SS who have sons.

3 Welsh KL. Scleroderma: chimerism, the blind

V

C1q is thought to play a crucial part in the pathogenesis of systemic lupus erythema-
sus (SLE). 

C1q immunoadsorption

is a promising candidate for adsorption of
genotypic relevant molecules from the

plasma of patients with SLE. A C1q immuno-

adsorbent 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,
in January 1999. Accompanying oral and
genital ulcers, polyarthritides, and lupus nperi-

tis (histological membranous glomerulo-

nephritis, WHO IVa), as well as hypergammaglobulinemia

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) and low dose

prednisone (5 mg/day) the disease continued.

The dose of prednisone was repeatedly increased up
to >60 mg/day. The lupus nephritis with a prote-

inuria of about 1.5 g/day and a non-active

urine sediment remained unchanged, too.

Continuing disease activity was also docu-

tented by abnormal serological parameters

(table 1). Therefore, C1q immunoadsorption with

MIRO adsorbers (Fresenius HemoCare)

was started.

Twelve C1q immunoadsorptions with an

average treated plasma volume of 2 litres

equal to 34 ml/kg body weight) for each

diasorption were carried out over a period of

four weeks. The plasma volume was

slightly reduced after the fourth session

because of a fibrinogen decrease to <0.8 g/l.

For plasma separation a centrifugal method

in a closed continuous flow system was used.

The veno-venous (both cubital veins were

used) blood flow was about 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 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

did not change (table 1).

A follow up of 12 months after stopping the

C1q immunoadsorption showed a complete

clearance of cutaneous exacerbation or increase in

disease activity. Treatment with methotrexate (15 mg/week) and low dose

prednisone (5 mg/day) was continued.

The C1q immunoadsorbers (MIRO ad-
sorbers) consist of polyacrylamide beads

coated with covalyantly bound swine C1q.

Effective clearance of circulating immune

complexes as well as of C1q autoantibodies

can be achieved. Moreover, additional mole-

cules, 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 thrombocytopathy or ana-

phylactic reactions according to an increased

bradykinine synthesis, were not seen. In

contrast with the plasma exchange treatment,

only selective plasma components are re-

moved, and plasma replacement, for exam-

ple by fresh frozen plasma, is not required.

Therefore, the risk of transmitting infections

by products derived from blood is mini-

mised. 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 SLE

complex disease. However, the

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 erythema-
sus (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

genotypic relevant molecules from the plasma of patients with SLE. A C1q immuno-

adsorbent was developed in 1990 and has been used in several patients.

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

*CIC = circulating immune complexes; C3c, C4 = complement components.

Figure 1 Discoid rash of both femurs (central 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 (negative)</td>
<td>1/2560</td>
<td>1/2560</td>
</tr>
<tr>
<td>Anti-dsDNA (≤20 IU/ml)</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>C1q autoantibodies (≤20 U/ml)</td>
<td>84</td>
<td>29</td>
</tr>
<tr>
<td>C1q* (IgM) (&lt;55 µg/ml)</td>
<td>108</td>
<td>83</td>
</tr>
<tr>
<td>C3c* (0.9–1.8 g/L)</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>C4* (0.1–0.4 g/L)</td>
<td>0.05</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*lupus nephritis was not improved, as indicated by an unchanged proteinuria. This may be because the lupus nephritis was not active. Therefore, proteinuria may be the result of chronic renal damage. Used with other treatment, C1q immunoadsorption proved to be effective and safe. One might speculate that SLE-specific active cutaneous lesions, such as malar and discoid rash, may well respond to this immunoadsorption treatment. Because conventional plasma exchange treatment as an adjunct to C1q adsorption proved to be effective and safe.

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

Clinical use of cyclophosphamide (CYC) improves the prognosis of Wegener’s granulomatosis (WG), though treatment related malignancies have been recorded. Among treatment related malignancies, the development of erythroleukaemia has been rarely reported. In addition, there have been no reports of erythroleukaemia arising in patients with WG. A 59 year old woman presented with nasal bleeding, nasal obstruction, and fever in December 1994. A biopsy specimen from nasal mucosa was compatible with WG, and cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) were 13 EU (normally undetectable). A chest x ray examination on admission showed the presence of a cavity in the right lung field. She received 30 mg/day of prednisolone, with limited improvements. CYC (100 mg/day) was therefore given orally from 19 December. As a result, her complaints ameliorated and her nasal cavity cleared up in February 1995.

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

Recently, the use of CYC has been reported to improve the prognosis of WG, though we should be aware of its possible carcinogenicity. Among neoplastic disorders, treatment related malignancy can develop after the use of such cytotoxic agents as CYC, azathioprine, etc. CYC is a high carcinogenic agent and induces renal cancer, bladder cancer, MDS, and myelogenous leukaemia. Among 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 discontinuance of CYC, the patient developed erythroleukaemia 12 months later.

Although the findings of chromosomal changes failed to support CYC induced leukaemia, we should stress treatment related malignancy in patients receiving this.
drug, especially when a cumulative dose of more than 10 g is given. When rheumatologists prescribe CYC for the treatment of patients with rheumatic diseases, stringent monitoring of the haematological parameters should be required, even after the discontinuance of CYC. All possible efforts should be made to discontinue CYC to minimise the risk of developing treatment related malignancies after remission. Lastly, when myelosuppression develops, we should discontinue CYC. All possible efforts should be required, even after the discontinuation of CYC. 

Figure 1 Bone marrow findings in November 1988.

Atrophoderma and juvenile idiopathic arthritis

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

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

CASE REPORT

A 13 year old girl was referred by her general practitioner with a four month history of joint swelling and stiffness. The symptoms were mainly of the small joints of the hands and wrists. She also had early morning stiffness of the same joints and of the neck. On initial examination she was noted to have a diffuse purple, slightly atrophic patch on her lower back, which was symmetrical and pear shaped. The patch measured 22×15 cm and showed subtle features of dermal atrophy with more visible vascular marking than in the surrounding skin (fig 1). Her musculoskeletal examination showed swelling with synovial thickening of all the proximal interphalangeal and distal interphalangeal joints with some metacarpophalangeal joint effusions 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.

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

Rheumatoid arthritis (RA) or Crohn's disease (CD) are both recognized indications of anti-tumour necrosis factor (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. 10 It is thus of interest to describe the clinical course of a patient with the association of two inflammatory diseases, RA and ulcerative colitis (UC) and its modulation by pregnancy.

Rectal bleeding and mild foot arthralgias started in a 36 year-old woman with no particular personal or familial history one year before her first pregnancy. These symptoms remained the same until and during pregnancy. Two weeks after a normal delivery, rectal bleeding became more abundant and painful. Acute infectious gastroenteritis was diagnosed and symptomatic treatment was prescribed. After one month and a half there was no improvement, with up to 10–20 watery and bloody stools a day. A 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 arthropathy with massy bloody diarrhhea, 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 cyclosorpin, with some effect on arthritis, the colitis continued to deteriorate and a total colectomy with ileostomy was performed. 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/DRD1 DRQ5. Foot x rays showed bilateral erosions of the fifth metatarso-phalangeal 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 UC have been described, and the influence of pregnancy on the association of RA and UC has never been seen before.11

Here, both RA and UC were poorly active or inactive during pregnancy, and a severe postpartum relapse for the two sets of symptoms. Even if we cannot exclude a coincidental association of the two diseases, the simultaneous occurrence of the two diseases 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. 12 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

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

Pyoderma gangrenosum (PG) is an uncommon ulcerative skin condition which may
occur in association with a wide variety of systemic diseases—for example, chronic inflammatory bowel disease. In a study by Holt et al it was suggested that PG is associated with inflammatory polyarthritides. Its prominent features—namely, pain, oedema, and discolouration at the joint level, may resemble those of rheumatoid synovitis or even septic arthritis. Consequently, an early diagnosis of PG is difficult to make.

A 77 year old woman presented with painful swollen ankles associated with fever and weight loss. She had no history of trauma. One year before she had been diagnosed with rheumatoid factor negative polyarthritides based on the findings of a symmetrical inflammatory polyarthritides affecting the metacarpophalangeal and proximal interphalangeal joints of both hands and the metatarsophalangeal joints of the feet. The arthritis subsided on treatment with sulphasalazopyridine (2000 mg/day). On examination at admission both ankles were very painful and showed some non-pitting oedema and erythematous discolouration. Moreover, there was clinical evidence of active synovitis of the left ankle. Synovial fluid of the left ankle had low viscosity and was sterile on culture. An intra-articular injection 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 anti-nuclear antibodies were negative. Antibiotic therapy was started and the patient was treated with sulphasalazopyridine (2000 mg/day). On 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 anti-nuclear antibodies were negative. Antibiotic therapy was started and the patient was treated with sulphasalazopyridine (2000 mg/day).

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, 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.

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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—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 vertebral 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 hyperretinolidaemia. This suggests, together with an occasional familial incidence, a genetic basis. A number of studies have reported possible associations with HLA, but none has yet provided unequivocal evidence of genetic predisposition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm it. This discrepancy might partly be accounted for either by coincidence of DISH and ankylosing spondylitis, or by difficulties in differentiating between these two disorders.

OPLL, similarly to DISH, seems to share some associations 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, located on chromosome 6p, close to the HLA locus. They found evidence of genetic linkage and allelic association of the COL 11 A2 gene which would constitute an inherited predisposition for OPLL. Among 20 genetic variants in this gene, a strong allelic association (p=0.0003) with OPLL was observed with intron 6 variant, which is at position +4 from the 3’ splice site. However, as far as we know, no investigation of this type has been so far performed in patients with DISH.

As the common clinical and metabolic features of OPLL and DISH can suggest their common 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 theradiology, and laboratory findings in 15 patients with special reference to polyarthritides. Medicine (Baltimore) 1980;59:114–33.


4 Swen WAA, Jacobs JWG, Neve WC, Bal D, Bijlsma JW. Is sonography performed by the radiologist as useful as arthrography examination (PCR)? 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 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.

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Systemic small sized vessel vasculitis after massive antigen inhalation

We and others have proposed that desensitisation, vaccination, or inhalation of antigens by asthmatic patients may trigger Churg-Strauss syndrome (CSS).1–2 Few observations of vasculitis occurring immediately after massive inhalation of a presumably antigen have been published.3 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 white blood cell count was 16.12×10⁹/l, with 1870 cosinophils, serum creatinine 170 µmol/l; proteinuria 0.7 g/day, and microscopic haematuria. Specific anti-myeloperoxidase perinuclear labelling anti-neutrophil cytoplasmic antibodies (ANCA) were detected (30 IU). A neuromuscular biopsy showed necrotising vasculitis of the vasa nervorum and small sized muscle vessels, together with granulomas. Renal biopsy showed partial thickening of glomerular basement membrane. We retained the diagnosis of Wegener’s granulomatosis. Despite corticosteroids and intravenous cyclophosphamide, the patient developed left orchitis and underwent plasma exchanges and received oral cyclophosphamide. Clinical and biological signs improved, except serum creatinine which persisted at 150 µmol/l. After three years, receiving daily prednisone and cyclophosphamide, the patient remains in clinical remission.

Case 2: A 38 year old woman presented in August 1990 with acute dyspnoea and purpura. While 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 arterioles. A skin biopsy detected vasculitis at the dermo-hypodermal border 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 mononeuropathy multiplex in the left peroneal nerve upon clinical examination. ANCA were not tested. Neuromuscular biopsy showed microvasculitis with perivascular lymphoplasmacytic infiltrates. CSS was diagnosed and prednisone was prescribed, which was tapered within 18 months and maintained at 5 mg/day to control asthma. The patient remains asymptomatic nine years later.

Case 4: A 27 year old man was admitted in September 1980 for acute dyspnoea and high fever that occurred a few hours after massively inhaling cereal dust in a store that raised and sold penguins. These signs reappeared after oral prednisone because of a massive inhalation of a presumed antigen on 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 penguins. A chest roentgenogram showed extensive bilateral basal nodules, and pulmonary biopsy disclosed vascular lesions, with fibrinoid necrosis of arteriole and venule 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. 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 1, 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 arterioles. A skin biopsy detected vasculitis at the dermo-hypodermal border 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.

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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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Table 1  
Therapeutic regimens followed sequentially and the clinical responses detected

<table>
<thead>
<tr>
<th>Therapeutic Regimens</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 in sequence. 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 chills, arthralgias without arthritis, malaise, and abdominal pain with diarrhoea. Severe leucocytosis (up to 39 × 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 hyperaemic colonic walls. Common causes of infections were ruled out; antinuclear antibodies, complement fractions, adenine-deaminase, lymphocyte subpopulations, and in vitro lymphocyte proliferation to antigens and mitogens were within 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 and hyper-IgD syndrome associated with zafirlukast. Chest 1999;114:332–4.

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

Are DISH and OPLL genetically related?

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