MATTERS ARISING

Sonographic erosions of the rheumatoid little toe

We read with interest the pictorial essay on ultrasonography of bone erosions by Grassi and colleagues. The presented site-specific comparison of radiographic and sonographic imaging of metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joint sites in rheumatoid subjects suggests strongly a holism of early 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 each site, except at the 1st 15 patients with rheumatoid arthritis. The erosions by radiography and ultrasound in the criteria, Fifteen patients with RA, according to stand-up to six years, sonographic erosions could be (depending on disease duration) 3.4- to that had sonographic erosions, and found (ulnar on disease duration) 3.4- to 6.5-fold more erosions with ultrasound than with radiography.

In our experience, based on pilot data on rheumatoid patients with a disease duration of up to six years, sonographic erosions could be shown in half of all 5th MTP joints examined. Fifteen patients with RA, according to standard criteria, (median age (range) 48 (23–78) years; eight females; median disease duration (range) 13 (1.5–72) months; 12 rheumatoid factor positive; 12 receiving disease modifying treatment), were examined for erosions by a rheumatologist, trained in musculoskeletal ultrasonography (RK). An L12–5, 38 mm linear array, high frequency transducer with an ATL HDI 5000 ultrasound system (Advanced Technologies Laboratories, Bothell, WA, US) was used. The following seven sites were chosen as early, characteristic, and/or representative imaging modalities of the erosive lesions, as visualised by lack of data on sonographic reliability. We agree with Dr Klocke and colleagues that the 5th metatarsophalangeal (MTP) joint is the most common site of sonographic erosions in patients with RA. In our daily practice sonographic assessment of the 5th MTP joint and second metacarpophalangeal joint is included in the baseline approach to patients with RA.

We think that a few points need additional emphasis. Firstly, close sonographic monitoring of early erosion could have an interesting role for a better understanding of disease progression and efficacy of treatment. Secondly, latest generation power Doppler equipment may offer some additional information about the perfusional status of synovial membrane and pannus.

Table 1 The frequency of sites that showed erosions by radiography and ultrasound in the 15 patients with rheumatoid arthritis. 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 osteoarthritis (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></td>
<td>11 (37)</td>
</tr>
<tr>
<td>3rd PIP* joint</td>
<td>0</td>
<td>7 (23)</td>
</tr>
<tr>
<td>3rd PIP* joint</td>
<td>0</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1st MTP joint</td>
<td>1 (5)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>5th MTP joint</td>
<td>1 (5)</td>
<td>20 (60)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (43)</td>
<td>56 (183)</td>
</tr>
</tbody>
</table>

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

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

Authors’ reply

Dr. Klocke and colleagues highlight interesting aspects about the potential role of ultrasonography in the diagnosis of rheumatoid arthritis (RA). Ultrasonography is undoubtedly more sensitive than x-ray in detecting bone erosions.¹ 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 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.

REFERENCES

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 emphasis that might not be clinically impossible.

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).2 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 patients2 who fulfilled four or more of the diagnostic criteria for SS proposed in 1993 by the AECG (International Autoimmune Disease Research 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 5x10⁷ 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 the control group. Using this method, we found no Y chromosome-specific DNA in either patients or controls.

Clinical manifestations of Sjögren’s syndrome, as those of other autoimmune diseases such as systemic sclerosis, polymyositis, or primary biliary cirrhosis, are similar to those of chronic graft versus host disease. Microchimerism of fetal cells has been investigated in patients with systemic sclerosis by both quantitative and non-quantitative methods, the results being controversial.3,4 It has also been investigated in primary biliary cirrhosis and inflammatory myopathies by non-quantitative methods, yielding negative or non-conclusive results.5 One reason why the results are similar to those reported by Toda and colleagues; 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.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-Bœckh-Behrens et al. 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. Nevertheless, it is interesting to note that some autoimmune diseases, including scleroderma, SS, and primary biliary cirrhosis, are fetal anti-maternal chronic graft versus host disease (GVHD),

We are able to comment on our previous paper. We were concerned that the pathogenic process in SS is not similar to that in chronic GVHD. In this regard, donor cell microchimerism is often seen in patients with SS who were previously pregnant. In contrast, blood cells in patients with SS and those with chronic GVHD have been totally replaced by donor derived cells. Because of the exceedingly low ratio of non-host to host cells in women with SS, it is believed that the pathogenic process in SS is not similar to that in chronic GVHD. In this regard, donor cell microchimerism 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 to 100 peripheral blood nucleated cells—i.e., that is, at least 10 times more frequent than the ratio in women with SS who have sons.

Our recent electron microscopic analysis of lachrymal gland biopsy specimens from patients with SS and those with chronic GVHD after haemopoietic stem cell transplantation clearly indicated a substantial difference in pathogenic processes between these two disease conditions. T cells were mainly detected in the periductal area, and some T cells had infiltrated into the ductal epithelia through disrupted basal laminae in patients with chronic GVHD. In patients with SS, the T cells were diffusely found in both acinar and periductal areas, but scarcely detected in the ductal epithelia. T cells which had infiltrated into the ductal epithelium in chronic GVHD were CD4+ 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-Bœckh-Behrens and those of our study do not exclude the possibility that microchimerism has a role in the pathogenesis of SS. The presence of a small population of non-host cells would not evoke a putative GVHD mechanism itself, but would result in induction and/or promotion of autoimmunity. For example, non-host cells could differentiate into immune regulatory cells, thereby disregulating the immune system under certain exiguous conditions, such as concurrent infection. Because persistent fetal microchimerism is common in normal women, further work should aim at functional studies of immune cells originating from fetal cells in patients with SS and from healthy women who were previously pregnant.

M KUWANA
Institute for Advanced Medical Research, Keio University School of Medicine, Japan

I TODA
Department of Ophthalmology, Tokyo Dental College, Japan

Correspondence to: Dr M Kuwana, Institute for Advanced Medical Research, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

kuwanam@sc.i-tec.keio.ac.jp


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 of standard treatment is restricted to only a few cases, the exact role of C1q adsorption within the multimodal treatment of SLE needs to be evaluated in controlled studies.

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 13.8×10^11/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. 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 be aware of treatment related malignancy in patients receiving this agent related leukaemia. 

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 IU/ml)</td>
<td>64</td>
<td>29</td>
</tr>
<tr>
<td>C1c* (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.

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

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 myelo-suppression develops, we should discontinue CYC, as soon as possible, to avoid the risk of developing treatment related leukaemia.

Figure 1 Bone marrow findings in November 1988.

Atrophoderma and juvenile idiopathic arthritis

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

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

CASE REPORT

A 13 year old girl was referred by her general practitioner with a four month history of joint swelling and stiffness. The symptoms were mainly of the small joints of the hands and wrists. She also had early morning stiffness of the same joints and of the neck. On initial examination she was noted to have a diffuse purple, slightly atrophic patch on her lower back, which was symmetrical and pear shaped. The patch measured 22×15 cm and showed subtle features of dermal atrophy with more visible vascular marking than in the surrounding skin (fig 1). Her musculo-skeletal examination showed swelling with synovial thickening of all the proximal interphalangeal and distal interphalangeal joints with some metacarpophalangeal joints affected also. The rest of the systemic examination was normal. Her baseline haematology, including an erythrocyte sedimentation rate of 8 mm/1st h (normal <10), and biochemistry, including C reactive protein ≤5 mg/l (normal ≤6), were within normal limits. Antinuclear antibody was positive at 1 in 100 dilution and extractable nuclear antigen was negative. 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.

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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-nuclear tumour factor (ANF) 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 became 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 high fever associated with massive bloody diarrhoea, abdominal pain, and rapid weight loss. Laboratory investigations showed erythrocyte sedimentation rate 32 mm/1st h, CRP reactive protein 89 mg/l, haemoglobin 90 g/l, leucocytes 12 900/μl, and serum albumin 21 g/l. Despite being treated with steroids intravenously and cyclosporin, with some effect on arthritis, the colitis continued to deteriorate and a total colectomy with ileostomy was performed. Pathological analysis of the colon showed a diffuse inflamma-
tion 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/DRD4 DQ5. Foot x rays showed bilateral erosions of the fifth metatarsophalangeal joint. No sacroiliitis was found and the lumbar spine was normal. Treatment with methotrexate 7.5 mg, then 15 mg/week intramuscularly and salazopyrine 3 g/day associated with calcium, vitamin D, and pamidronate was begun. The treatment was not completely effective. UC is commonly associated with arthritic manifestations, and differential diagnosis between RA and UC associated arthritis can be difficult. In this patient the diagnosis of RA was made according to the 1987 American Rheumatism Association criteria with a DR1 genotype. The diagnosis of UC was made on the basis of the clinical course, endoscopic findings, and colon pathology. A bibliographic search showed that only a few cases of associations between RA and CD or UC have been described, and the influence of pregnancy on the association of RA and UC has never been seen before.

Here, both RA and UC were poorly active or inactive during pregnancy. 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 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. 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.

F BOYER
E FONTANGIES
P MOISSEC
Departments of Immunology and Rheumatology, Hôpital Edouard Herriot, Lyon, France

Correspondence to: Dr P Moissec, Clinical Immunology, Unit, Department of Rheumatology and Rheumatology, Hôpital Edouard Herriot, 69437 Lyon Cedex 03, France
moissec@laennec.univ-lyon1.fr


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 polyarthritis.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. Of the patients 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 discouloration. 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, a moderate perivascular lymphocytic and histiocytic infiltrate without nodules 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. There has already been established in patients with, for example, poptliteal cysts,2 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 Berlijnseweg,
8901 BR Leeuwarden
The Netherlands
p.m.houtman@xxs.nl

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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).5 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.6 Systematic studies of OPLL began in Japan 25 years ago. A varying proportion of patients with DISH have OPLL, and vice versa.7 However, recent observations indicate that cervical OPLL may be fairly frequent in ankylosing spondylitis.8

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 hyperretinoi- aemia. This suggests, together with an occasional familial incidence, a genetic contribution to this condition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm this. The 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 some associations with low glucose tolerance and obesity.9 Attention has also focused on the role of bone formation promoting factors in OPLL.10

Recently, Japanese authors discovered a predisposing locus for OPLL through linkage analysis of 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 junction.11 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 control subjects. 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).12 Detection of the intron (−4) allele, 16T and 16A primers, together with the common complementary strand primer G72, were used. In each PCR reaction, control DNAs of three known
distinct genotypes and water as negative control were included. Comparison of the genotyptic frequencies of single variants was made by contingency χ² test.

In conclusion, results of analysis of intron 6 (−4) polymorphisms in the COL 11 A2 gene in Czech patients with DISH do not agree with data from Japanese patients with OPLL. However, the principal question of possible genetic relations between DISH and OPLL warrants further study, using a broader spectrum of genotyping and larger cohorts of patients.

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

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</td>
<td>75 (66)</td>
<td>39 (34)</td>
<td>114</td>
</tr>
<tr>
<td>Non-DISH</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 foot drop, which was found to be due to mononucleosis multiplex in the left peroneal nerve upon clinical examination.

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 (case 2), flour (case 3), or pigeons 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 mononucleosis multiplex in the left peroneal nerve upon clinical examination. ANCA were not tested.

We propose that major antigenic differences between the two cases were due to the difference in antigen exposure.

References

1. Restnick D, Nishimoto G, Rogers J, et al. Bronchial allergic aspergillosis involving CSS, and Oritz 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. In patients, the occurrence of vasculitis may reflect hypersensitivity to the inhaled antigen, because they had daily professional exposure or contact with diesel fumes (case 1), harvest grain dust (case 2), flour (case 3), or pigeon and/or cereal dust (case 4) and because mass-
patients, to systemic dissemination and the acute onset of vasculitic 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  

L MOUTHON  
UNEDITED  
UFR-SMBH Léonard de Vinci,  
Bobigny, France  

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

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

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

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>Interval 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 for 15 months.

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 chills, arthralgias without arthritis, malaise, and abdominal pain with diarrhea. Severe leukocytosis (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; antineuclear 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 genetic analysis (kindly performed by Dr Joos Frenkel) showed the presence of mutations in our patient. Combined treatment with colchicine and a non-steroidal anti-inflammatory drug is suggested in order to fulfi l 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.

Non-steroidal anti-inflammatory drugs in the treatment of hyper-IgD syndrome

Hyper-IgD syndrome (HIDS) is due to mutations of the gene coding for mevalonate kinase, an enzyme that has a pivotal role in the synthesis of isoprenoids and cholesterol.

Are DISH and OPLL genetically related?

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

Ann Rheum Dis 2001 60: 902-903

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