

## 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.<sup>1</sup> 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,<sup>2</sup> comparing radiographic and sonographic imaging of MCP joints in patients with rheumatoid arthritis (RA) supports this impression. The same study observed magnetic resonance imaging (MRI) changes corresponding to specific sites at selected radiograph-negative joints that had sonographic erosions, and found (depending 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,<sup>3</sup> (median age (range) 48 (23-78) years; eight female; 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 ultrasound (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 for ease of transducer access, as well as early, characteristic, and/or representative involvement by RA erosions: ulnar head/styloid; radial head/styloid; 2nd MCP joint (ulnar aspect); 3rd proximal interphalangeal joint (ulnar and radial aspect); 1st MTP joint (medial aspect); and the 5th MTP joint (lateral aspect). All four limbs were examined and to ensure comparability of sites, only bone lesions in the coronal plane were considered. All sites were examined in longitudinal and transverse planes in joint extension, and were classified as erosive, if they had at least one "break" in the cortical contour, visible in both planes and

**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)

Site	Radiography (%)	Ultrasound (%)
Ulnar head/styloid	4 (13)	7 (23)
Radial head/styloid	2 (7)	3 (10)
2nd MCP* joint	0	11 (37)
3rd PIP* joint: radial aspect	0	7 (23)
3rd PIP* joint: ulnar aspect	0	6 (20)
1st MTP* joint	1 (5)	7 (35)
5th MTP joint	6 (20)	15 (50)
Total	13 (7)	56 (28)

\*MCP = 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.

associated with an irregular floor. The latest available posteroanterior x ray of hands and feet (median time interval preceding ultrasound (range) 3 (0-18) months) was assessed for the presence of erosions at corresponding sites by a radiologist with a special interest in musculoskeletal imaging (DG), who was unaware of the sonographic findings. The 1st MTP joint was excluded from the analysis wherever the radiograph showed osteoarthritic change, because sonographic assessment for erosions was felt to be unreliable.

A total of 13 sites (in seven subjects) had radiographic erosions; all except for one ulnar site were identified by ultrasound. Sonography detected a total of 56 erosive sites (in 11 subjects)—that is, four times as many as radiography.

Two patients without radiographic erosions at the study sites had erosions elsewhere in the radiographs of their hands and feet, but both had erosive sites on ultrasound. Table 1 shows the frequency of radiographic and sonographic sites with erosions. Figure 1 shows an example of a sonographic erosion at the 5th MTP joint that was not seen on radiography.

Recently a Dutch study of patients with early RA, followed up radiographically for six years, found the 5th MTP joint to be the most common hand or foot joint affected by erosions at baseline, as well as by new and progression of erosions in the first and fifth year of follow up.<sup>5</sup> Although our study is limited by lack of data on sonographic reliability or corroborative MRI imaging, its findings add support to the notion that the rheumatoid 5th MTP joint is probably the most common site of sonographic as well as radiographic erosions. This offers yet further potential for earlier diagnosis and treatment of erosive arthritis, justifying more studies into the diagnostic specificity of sonographic erosions of this and other MTP joints.

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### 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.<sup>1-3</sup> Last generation broad band linear transducers (10-22 MHz) have an axial resolution power lower than 0.03 mm, and even minimal cortical defects of small joints can be clearly depicted.

We agree with Dr Klocke and colleagues that the 5th metatarsophalangeal (MTP) joint is the most common site of sonographic erosion in patients with RA. In our daily practice sonographic assessment of the 5th MTP joint and second metacarpophalangeal joint is included in the baseline approach to patients with RA.

We think that a few points need additional emphasis. Firstly, close sonographic monitoring of early erosion could have an interesting role for a better understanding of disease progression and efficacy of treatment. Secondly, latest generation power Doppler equipment may offer some additional information about the perfusional status of synovial membrane and pannus.<sup>4</sup>

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## Corticosteroid injection for the treatment of carpal tunnel syndrome

We read with interest the article by O'Gradaigh and Merry on a comparison between low and high dose, and short and long acting corticosteroids in the treatment of carpal tunnel syndrome.<sup>1</sup> 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.<sup>2</sup> Failure to detect statistical difference does not imply equivalence. A large scale, probably multi-centre, 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,<sup>3</sup> 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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## 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

Table 1

	A versus C	B versus C	A versus B	D versus C	D versus E
Difference	0.61	0.58	0.03	0.67	0.05
95% CI	0.42 to 0.80	0.38 to 0.77	-0.20 to 0.26	0.44 to 0.89	-0.024 to 0.34

who improve in the control and treatment groups (table 1). The 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 cannot be replicated in humans. This study was not primarily established to compare adverse effects, and we would agree that the sample was too small to detect an uncommon side effect. 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 would have been found to be more effective but for a type II error. On the contrary, we have explained in our article how the lower dose may be sufficient to treat all steroid-responsive carpal tunnel syndrome. Those who suggest rejecting our findings, and continue to use other treatments, must (a) indicate why a higher dose or longer acting steroid should be better (bearing in mind the absence of any data to support this); (b) justify the clinical relevance of any small difference that might have been missed in this study; (c) justify the possible increased risk of (nerve) toxicity, however small—*primum non nocere*.

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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).<sup>1</sup> 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<sup>2</sup> who fulfilled four or more of the diagnostic criteria for SS proposed in 1993 by the European Community Study Group. All 20 female patients analysed for the presence of fetal microchimerism were also classified as having definite SS according to the San Diego criteria. A PCR was performed that could detect one male cell in a background of  $5 \times 10^5$  female cells. The

amount of genomic DNA used in the PCR reaction was 3 µg, and more than five samples were tested for each woman. Eighteen healthy Spanish women (mean age 48.7 years (range 32-65)) who had male children comprised the control group. Using this method, we found no Y chromosome-specific DNA in either patients or controls.

Clinical manifestations of Sjögren's syndrome, as those of other autoimmune diseases such as systemic sclerosis, polymyositis, or primary biliary cirrhosis, are similar to those of chronic graft versus host disease. Microchimerism of fetal cells has been investigated in patients with systemic sclerosis by both quantitative and non-quantitative methods, the results being controversial.<sup>3-5</sup> It has also been investigated in primary biliary cirrhosis and inflammatory myopathies by non-quantitative methods, yielding negative or non-conclusive results.<sup>6-7</sup> Our 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.<sup>8-10</sup>

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## Authors' reply

We read with interest this letter by Mijares-Boeckh-Behrens *et al* commenting on our previous paper.<sup>1</sup> 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.<sup>1</sup> Nelson raised the fascinating possibility that some autoimmune diseases, including scleroderma, SS, and primary biliary cirrhosis, are fetal anti-maternal chronic graft versus host disease (GVHD),<sup>2</sup> though this theory is still controversial.<sup>3</sup>

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<sup>3</sup> 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 microchimerism is often seen in patients who received solid organ transplantation, but these patients rarely develop chronic GVHD.<sup>4</sup> The ratio of non-host to host cells in patients receiving liver transplants is shown to be more than one to 10<sup>4</sup> peripheral blood nucleated cells<sup>5</sup>—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.<sup>6</sup> T cells were mainly detected in the periductal area, and some T cells had infiltrated into the ductal epithelia through disrupted basal laminae in patients with chronic GVHD. In patients with SS, the T cells were diffusely found in both acinar and periductal areas, but scarcely detected in the ductal epithelia. T cells which had infiltrated into the ductal epithelia in chronic GVHD were activated CD8+ cytotoxic T cells, indicating that T cell invasion leads to the destruction of the ductal epithelium (Ogawa Y, Kuwana M, manuscript in preparation). Based on this finding, chronic GVHD in the lachrymal gland can be simply explained by an allo-immune response to the ductal epithelium by donor-derived T cells. On the other hand, a recently proposed pathogenic process in SS described an inappropriate apoptosis in lachrymal epithelial cells as the initial phase, followed by lymphocyte infiltration and autoimmune aggregation, resulting in further glandular destruction.<sup>7</sup>

However, the results of Mijares-Boeckh-Behrens and those of our study<sup>1</sup> 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 disrupting the immune system under certain exogenous conditions, such as concurrent infection. Because persistent fetal microchimerism is common in normal women, further work should aim at functional studies of immune cells originating from fetal cells in patients with SS and from healthy women who were previously pregnant.

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## LETTERS TO THE EDITOR

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### 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).<sup>1–3</sup> C1q deficiency and the presence of C1q autoantibodies are associated with increased disease activity in SLE.<sup>1</sup> Therefore, C1q is a promising candidate for adsorption of pathogenetic relevant molecules from the plasma of patients with SLE. A C1q immunoadsorbent was developed in 1990<sup>4</sup> and has been used in several patients.<sup>5</sup>

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, polyarthritis, and lupus nephritis (histological membranous glomerulonephritis, WHO Va), as well as laboratory abnormalities, led to the diagnosis, SLE.<sup>6</sup> 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) no remission of the cutaneous 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 adsorbents (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 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 50 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 no relapse 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 immunoadsorbents (MIRO adsorbents) 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.<sup>5</sup> Moreover, additional molecules, such as fibrinogen, are bound by the collagen-like region of C1q.<sup>5</sup> As fibrinogen decreased to <0.8 g/l in our patient during treatment, the plasma volume had to be slightly reduced. Other possible side effects, such as marked thrombocytopenia or anaphylactic reactions according to an increased bradykinin 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 manifestations as an immune complex disease.<sup>7</sup> However, the

Table 1 Serological parameters

Parameter	Before C1q immunoadsorption	After 12 C1q immunoadsorptions
Antinuclear antibodies (negative)	1/2560	1/2560
Anti-dsDNA (<20 IU/ml)	38	20
C1q autoantibodies (<20 U/ml)	54	29
CIC* (IgM) (<55 µg/ml)	108	83
C3c* (0.9–1.8 g/l)	0.50	0.58
C4* (0.1–0.4 g/l)	0.05	0.03

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

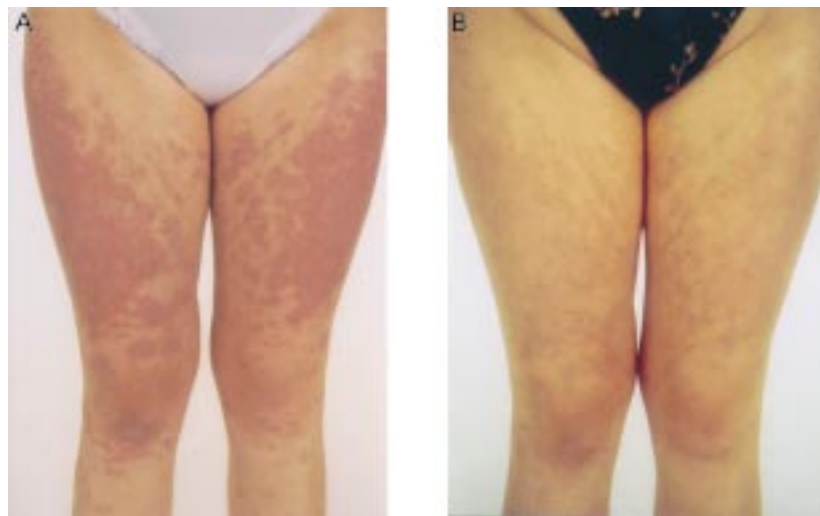


Figure 1 Discoid rash of both femurs (ventral side) before C1q immunoadsorption (A). After 12 C1q immunoadsorptions the rash resolved completely (B).

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,<sup>8</sup> the exact role of C1q adsorption within the multimodal treatment of SLE needs to be evaluated in controlled studies.

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## 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),<sup>1,2</sup> though treatment related malignancies have been recorded.<sup>3,5</sup> Among treatment related malignancies, the development of erythroleukaemia has been rarely reported.<sup>6</sup> 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  $13.8 \times 10^{10}/l$ . 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-Huët 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,<sup>1,2</sup> 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.<sup>7</sup> CYC is a highly carcinogenic agent and induces renal cancer, bladder cancer, MDS, and myelogenous leukaemia.<sup>3–11</sup> CYC related second malignancies in WG have also been reported,<sup>3–7,11</sup> 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  $-5/5q-$ ,  $-7/7q-$ ,<sup>10</sup> 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



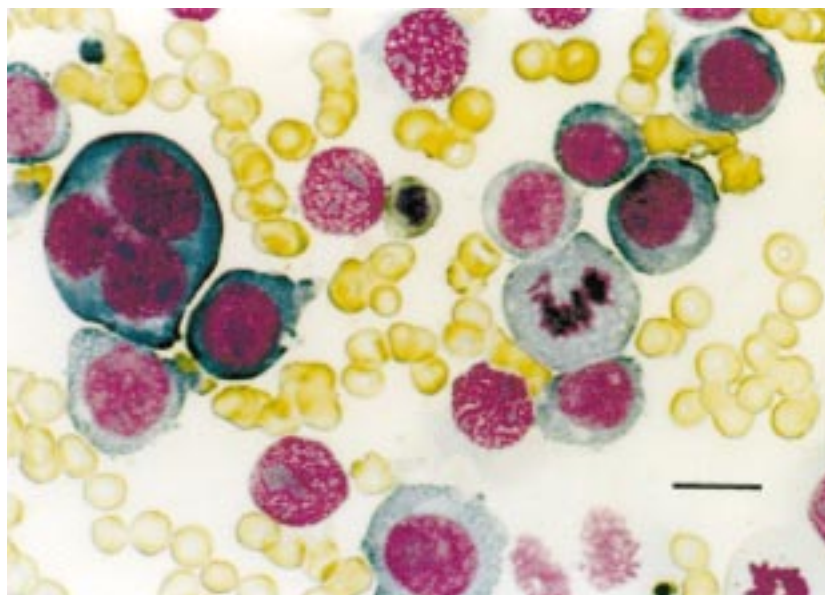


Figure 1 Bone marrow findings in November 1988.

drug, especially when a cumulative dose of more than 10 g is given.<sup>11</sup> 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 development of treatment related leukaemia.

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



Figure 1 Symmetrical, pear shaped, slightly atrophic patch on the lower back.

Idiopathic atrophoderma, as described by Pasini and Pierini, is a distinctive form of dermal atrophy seen particularly in children and younger people.<sup>4</sup> 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 22x15 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 <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 9x10 cm.

## 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.<sup>5-6</sup> The cause remains uncertain although infective agents, particularly *Borrelia burgdorferi*, have been implicated in few reports.<sup>7</sup> 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 so far of an 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. Joint symptoms in a child with APP 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.<sup>8</sup> 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.

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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 recognised indications of anti-tumour necrosis factor  $\alpha$  treatment, indicating that these diseases may have important mechanisms in common, at least in part, through the contribution of the Th1/Th2 cytokine balance.<sup>1-3</sup> The classical improvement of 75% of patients with RA during pregnancy suggests that pregnancy is a natural situation where this balance is modified.<sup>4-5</sup> 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 colonoscopy showed an inflammation of the whole colon consistent with UC. She was treated with mesalazine, 3 g/day, and steroids, 1 mg/kg/day. No improvement was seen and the patient went to hospital for parenteral nutrition. After three weeks there was a major improvement, she had a normal colonoscopy and went home.

Two weeks later, she was sent back to the hospital after a major relapse with massive bloody diarrhoea, abdominal pain, and rapid weight loss. Laboratory investigations showed erythrocyte sedimentation rate 32 mm/1st h, C reactive protein 89 mg/l, haemoglobin 90 g/l, leucocytes 12 600/ $\mu$ l, 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. Histological analysis of the colon showed a diffuse inflammation of the colon with an infiltration of the mucosa and lamina propria with lymphocytes, plasma cells, and granulocytes.

When first seen for arthritis, she had a very active, distal, and symmetrical arthritis affecting mostly hands and feet, with severe synovitis. She had pain at night and morning stiffness of at least one hour. A Rose-Waaler test was positive 1/128, antinuclear antibody negative, and HLA A3/A24 B7/B38 DRB1\*0101/DR14 DQ5. Foot x rays showed bilateral erosions of the fifth metatarsophalangeal joints. 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.<sup>6-9</sup>

Here, both RA and UC were poorly active or inactive during pregnancy with 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 flare 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.<sup>3</sup> 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.

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## 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



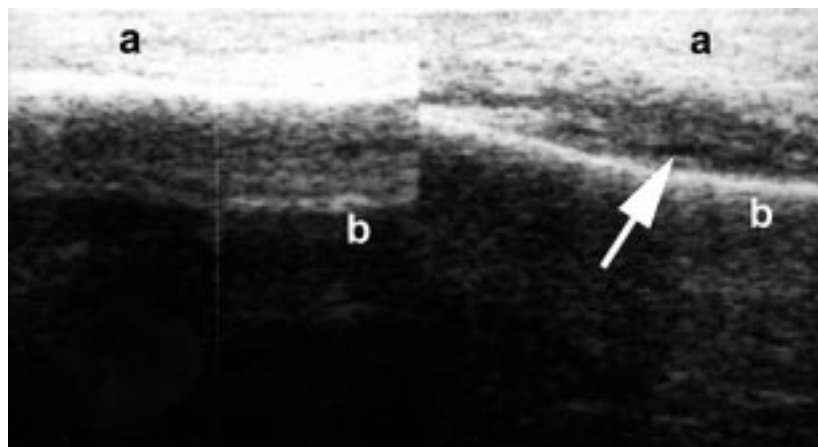


Figure 1 Ultrasonography of the distal pretibial region: the normal right leg (left) and echo-poor areas (arrow) in the left leg (right). a = position of the transducer at the skin surface; b = bone of the tibia.

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.<sup>1</sup> 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 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 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  $14.5 \times 10^9/l$ . Rheumatoid factor and antinuclear antibodies were negative. Antineutrophil cytoplasmic antibodies, p type, were positive 1/320.

Repeat blood cultures were negative. Joint and bone x ray examinations of the lower legs were normal.

Sonographic examination of the distal pretibial region was performed before specific clinical symptoms of PG were present. The left ankle showed fluid between the tendon apparatus and the periosteal bone, and the arthritis seemed to have disappeared. The right ankle seemed normal (fig 1).

In addition, technetium bone scintigraphy disclosed a remarkably increased uptake of the isotope in the soft tissues of the lower legs, especially at the left medial site. The bones and joints of the lower legs showed a normal uptake. In the meantime the areas of striking blue colour correlating with the aforementioned findings had evolved into ulcers around both ankles.

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,<sup>2</sup> synovitis of the hip joint,<sup>3</sup> and chronic shoulder complaints.<sup>4</sup>

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<sup>1</sup>—according to today's nomenclature, diffuse idiopathic skeletal hyperostosis (DISH).<sup>2</sup> 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.<sup>3</sup> Systematic studies of OPLL began in Japan 25 years ago. A varying proportion of patients with DISH have OPLL, and vice versa.<sup>3,4</sup> However, recent observations indicate that cervical OPLL may be fairly frequent in ankylosing spondylitis.<sup>5</sup>

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 of DISH, a suspicion of genetic predisposition. Although several authors found an increased frequency of HLA-B27 among their patients with DISH, most papers did not confirm it.<sup>2</sup> This discrepancy might partly be accounted for either by coincidence of DISH and ankylosing spondylitis, or by difficulties in differentiating between these two disorders.<sup>6,7</sup> OPLL, similarly to DISH, seems to have some associations with low glucose tolerance and obesity.<sup>4</sup> Attention has also focused on the role of bone formation promoting factors in OPLL.<sup>8</sup>

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 junction.<sup>9</sup> However, as far as we know, no investigation of this type has been so far performed in patients with DISH.

As the common clinical and metabolic features of OPLL and DISH can suggest their common aetiopathogenesis, a genotyping study on the COL 11 A2 gene was done in a group of 60 Czech patients with DISH. Diagnosis of DISH was based on the x ray changes on the spine. Sixty healthy Czech blood donors were controls. Genotyping was performed in DNA samples, 200 ng each, extracted from peripheral blood leucocyte cells. Polymorphism at intron 6 (-4) in the COL 11 A2 gene was determined by mutagenically separated polymerase chain reaction (PCR).<sup>10</sup> 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

Table 1 Intron 6 (-4) allele frequency

	T	A	Total
DISH (No (%))	75 (66)	39 (34)	114
Non-DISH (No (%))	74 (63)	44 (37)	118
Total	149	83	232
$\chi^2$	0.239		
Odds ratio	1.143		

distinct genotypes and water as negative control were included. Comparison of the genotypic frequencies of single variants was made by contingency  $\chi^2$  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,  $\chi^2=0.296$  (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).<sup>1-4</sup> Few observations of vasculitis occurring immediately after massive inhalation of a presumed antigen have been published.<sup>2</sup> 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 mononeuritis multiplex in the left peroneal nerve upon clinical examination. The erythrocyte sedimentation rate was 72 mm/1st h, white blood cell count was  $16.12 \times 10^9/l$ ,<sup>3</sup> with 1870 eosinophils, serum creatinine 170  $\mu\text{mol/l}$ ; 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 patchy necrotising glomerulonephritis. 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  $\mu\text{mol/l}$ . 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 dermal-hypodermal junction with mononuclear cell and eosinophil infiltrates in the artery walls without leucocytoclastic or necrotising vasculitis. Ulnar artery biopsy showed complete occlusion of the artery lumen without evidence of vasculitis. CSS

was diagnosed and prednisone was prescribed, which was progressively tapered over 18 months. Eight years later, the patient remains well.

**Case 3:** A 53 year old woman who worked in a bakery for 30 years had had asthma for 20 years, with skin tests positive 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 mononeuritis 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 pigeons. These signs regressed after oral prednisone treatment, but 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 and medium sized vessels, without fibrinoid necrosis. Prednisone (1 mg/kg/day) was prescribed, then tapered and discontinued when all symptoms resolved. After one month, the same symptoms reappeared after another exposure to pigeons. A chest roentgenogram showed extensive bilateral basal nodules, and pulmonary biopsy disclosed vasculitic lesions, with fibrinoid necrosis of arteriole and venule walls. Despite 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 rarely been identified; we have noted that onset is sometimes associated with desensitisation, vaccination, exposure to various drugs or environmental substances, or too rapid steroid tapering.<sup>4</sup> In case 4 (previously published<sup>2</sup>), the abundance of actinomycetes in pneumocystis might suggest that they caused the vasculitis.

Stephens *et al* described bronchoallergic aspergillosis evolving to CSS,<sup>5</sup> and Orrids *et al* reported a case of CSS induced by free base cocaine.<sup>6</sup> Some drugs have been associated with the occurrence of CSS, particularly recently zafirlukast.<sup>6</sup> 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.<sup>7,8</sup> In our 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 pigeons 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



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

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## 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.<sup>1</sup>

Table 1 Therapeutic regimens followed sequentially and the clinical responses detected

	Duration of fever (days)	Intercritical period (days)	Months of treatment	Flare ups (n)
No treatment	4 (2)	17 (8.2)	5	7
Colchicine	4 (1)	33 (25)	15	15
Prednisone	1 (1)	14 (6)	5	9
Naproxene	1 (1)	18 (7)	7	9

So far, there is no consensus about how HIDS should be treated. Here we report our experience with a child with HIDS treated with different drug regimens.

The child was born 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 diarrhoea. Severe leucocytosis (up to  $39 \times 10^9/l$ ) and acute phase reactant positivity (C reactive protein 2.9 mg/l; normal values <4 mg/l) were also detected. An abdominal echo scan disclosed enlarged mesenteric lymph nodes, as well as thickened and hyperaemic colonic walls.

Common causes of infections were ruled out; antinuclear antibodies, complement fractions, adenosine-deaminase, lymphocyte subpopulations, and in vitro lymphocyte proliferation to antigens and mitogens were in the normal ranges. The commonest mutations (met 680 ile, met 694 val, met 694 ile, val 762 ala) known to occur in the Italian population at exon 10 of the pyrin gene<sup>2</sup> were absent. When our patient was 3 years old, frankly increased IgA plasma concentrations (9.39 g/l) and IgD plasma concentrations at the upper level of normal (98 IU/l, normal values below 100 IU/l) were found. At the same time, the presence of mevalonic acid and its metabolites in urinary samples was shown by gas chromatography and mass spectrometry; moreover, blunted mevalonate kinase synthesis in cultured skin fibroblasts (5.3 pmol/min/mg *v* controls 144 (67), kindly performed by Dr Wanders) was detected. A genetic analysis (kindly performed by Dr Joos Frenkel) showed the presence of mutations in both alleles of the mevalonate kinase gene—that is, alanine at position 148 into threonine; isoleucine at position 268 into threonine. On the basis of this a diagnosis of HIDS was proposed.<sup>3</sup>

Because a randomised trial of treatment was refused by our patient's parents, a cycle of treatment with colchicine (1 mg/day) was given for 15 months.<sup>4</sup> During this period the intercritical periods were longer; however, some side effects occurred such as recurrent abdominal pain and skin rash. When the diagnosis of HIDS was suggested, the patient was treated with a single dose (12.5 mg) of prednisone at the beginning of the flare up episodes. Fever promptly receded and the other symptoms (abdominal pain, diarrhoea,

etc) were milder or absent. Notably, the fever remained periodical. To avoid the possible side effects of long term administration of steroids, we decided to treat the patient with the non-steroidal inflammatory drug, naproxene, given in single dose (250 mg) at the beginning of the flare ups.

Intriguingly, its therapeutic effect was dramatic; fever suddenly disappeared and related symptoms were well tolerated. Table 1 summarises the therapeutic regimens given sequentially and the clinical responses detected in our patient.

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 fulfil 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.

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