LETTERS TO THE EDITOR

Digital Gangrene and Anticentromere Antibodies without Scleroderma

Sir—Takahashi et al. [1] recently reported on six cases with ulcers and gangrene in the extremities, but mild or no skin sclerosis, showing anticentromere antibodies (ACA) as the main finding.

A female patient with similar clinical characteristics has been attending our rheumatology unit. The patient, aged 39 yr, a mild smoker, not affected by diabetes or lipid metabolism abnormalities, was first admitted in February 1993. Her disease began at the age of 22 yr with Raynaud’s phenomenon. Ulcers and progressive gangrene requiring amputations of six fingers occurred between the ages of 34 and 38 yr, despite treatment with vasodilators, antiplatelet drugs and cervical sympathectomy.

During our follow-up, the patient experienced other severe ischaemic lesions, despite treatment with calcium channel blockers, aspirin, heparin, serial iloprost and prostanoiid infusions, prednisone (up to 20 mg daily) and a brief course of cyclophosphamide (100 mg daily). Amputation of the remaining fingers and the first left toe was inevitable. Vasculitis was observed in the s.c. tissue of an amputated finger (Fig. 1). We also recorded mat-like telangiectases on the face, lips and fingers, and thrombosis of the temporal branch of the retinal artery at the right eye. Over that time, skin sclerosis at any site, s.c. calcinosis, hypertrophy of the frenulum of the tongue, articular, muscular and tendinous manifestations, pulmonary bibasilar rales and heart murmurs were always absent.

In January 1998, pulses of the right and left posterior tibial and dorsalis pedis arteries were absent. Angiography showed significant narrowing of the right superficial femoral artery at the adductor hiatus, occlusion of anterior and posterior tibial arteries at both legs, and of the left peroneal artery. Multiple narrowings were observed in the remaining arterial branches of the lower limbs. The patient had no oesophageal complaints or X-ray abnormalities typical of systemic sclerosis (SSc).

High-resolution CT scan of the lungs showed no interstitial fibrosis. Pulmonary function tests revealed only markedly reduced diffusing capacity for carbon monoxide (DLCO) (36% of the predicted value). Nailfold capillary microscopy revealed microaneurysms, some capillary dilations, but no loop drop-out.

Laboratory studies revealed, over 5 yr, preserved renal and hepatic functions, normal blood cell counts, and normal serum complement and immunoglobulin levels. Serum cryoglobulins were never found. Indirect immunofluorescence test on HEp-2 cells always gave positive results with anticentromere staining pattern (titre ≥ 1:640). Antibodies to double-stranded DNA, RNP, Sm, SS-A, SS-B, topo-I and Jo-1 antigens were always absent. Antiphospholipid antibodies evaluated by ELISA showed normal levels of antiphospholipid antibodies (aCL) of the IgG class [normal value (n.v.) <10 GPL U/ml], but on some occasions raised levels of IgM aCL (ranging from 25 to 79 MPL; n.v. <10 MPL U/ml), IgM antiphosphatidylserine antibodies (25 MPS; n.v. <22 MPS U/ml) and IgM antibodies to β2-glycoprotein I (40 U; n.v. <7 U/ml). Lupus anticoagulant tests were negative. Levels of protein C, protein S and antithrombin III were normal. A test for activated protein C resistance was negative. Raised levels of Factor VIII-related antigen occurred in some instances.

Our patient does not fulfil the ACR criteria for classification of SSc [2] nor is she classifiable as ‘sine scleroderma SSc’ [3], because, although she presented ulcers at the fingertips, she has never showed by the onset of Raynaud’s phenomenon, skin sclerosis or pulmonary fibrosis over 22 yr. Moreover, no other organ system involvement was detected. On the other hand, she developed widespread vascular involvement of both medium and small vessels, as demonstrated by the presence of telangiectases, and by the occurrence of multiple digital amputations with findings of vasculitis in a small vessel. We believe that the reduced DLCO was also an expression of pulmonary vascular involvement independent of fibrosis. The main laboratory findings were persistently high titres of ACA and occasionally medium–high levels of IgM antiphospholipid antibodies. The striking link between ACA and Raynaud’s phenomenon is well known; in particular, the association between ACA and severe digital ischaemia has already been reported by others in SSc patients [4, 5]. The histological appearance of the vessel we observed is consistent with that by Takahashi et al. [1] and Herrick et al. [6] in their ACA-positive patients, and therefore the association ACA–vasculitis is confirmed. Moreover, the arteriographic changes

![Fig. 1. Intimal hyperplasia and infiltration of the media by mononuclear cells of a small artery from the left thumb (haematoxylin and eosin stain; original magnification ×125).](image)
found in large vessels are very similar to those described in ACA-positive patients [7, 8].

For these reasons, our patient seems to belong, with the ones reported [1], within a subset in the spectrum of scleroderma disorder recognizable by the occurrence of ACA and a serious vascular disease in the absence of skin and visceral fibrotic changes. Finally, the simultaneous occurrence of antiphospholipid antibodies and arterial occlusions is an additional and intriguing finding which recalls the rare association ACA–aCL–thrombosis reported in SSc patients [6, 9], but not observed by us in a recently evaluated large SSc series [10]. On this basis, we will take into account treatment with oral anticoagulants to reduce future ischaemic lesions and progression of the disease with some caution related to the co-existence of vasculitis.

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**Sternum Tumour Revealing a Chronic Myeloid Leukaemia**

SIR—Malignant sternum osteolysis, generally caused by multiple myeloma or metastatic cancer, is rarely an initial symptom that reveals a disseminated disease. We report an uncommon aetiology of an isolated sternum osteolytic lesion which revealed a localized worsening of an asymptomatic chronic myeloid leukaemia.

A 48-yr-old man was hospitalized for a rapidly enlarging painful sternum swelling. The remainder of the clinical examination was normal, with no spleno-megaly or adenopathy. There was no weight loss or fever and the general state of the patient’s health remained good. Skeletal X-rays showed a sternum osteolysis with cortical break (Fig. 1) and the body scan confirmed this sole abnormality. The red blood cell (5.45 \( \times \) 10\(^{12} \)/l ) and platelet (488 \( \times \) 10\(^{9} \)/l ) counts were at the upper limit of normal. The white blood cell count was normal (6.5 \( \times \) 10\(^{9} \)/l ) apart from basophil (0.72 \( \times \) 10\(^{9} \)/l ). The basophilia was suggestive of a myeloproliferative disease, even though the remainder of the biological data were within the limits of the normal range, in particular the kidney function and calcium (2.36 mmol/l) and alkaline phosphatase (151 IU/l) evaluations. Bone marrow aspiration showed a hypercellular marrow with an increased number of myeloid precursors at all stages of development and numerous megakaryocytes. The existence of a Philadelphia chromosome [translocation (9; 22)] confirmed the diagnosis of chronic myeloid leukaemia. A bone marrow aspiration in the sternum lesion

**Fig. 1.**—Sternal osteolysis with cortical break (X-ray).
showed lymphoblastic cells corresponding to localized blast crisis. The sternum pain was reduced with paracetamol. Despite chemotherapy with doxorubicin, cyclophosphamide, vincristine and methylprednisolone, the disease progressed with the appearance of circulating lymphoblast cells. The patient died 2 months after diagnosis, caused by an intra-cerebral haemorrhage, with a refractory generalized worsening of the chronic myeloid leukaemia.

Sternum tumours are generally caused by metastatic cancer, multiple myeloma or plasmacytoma. This case report of an isolated osteolytic sternum lesion revealing the localized blast crisis of an asymptomatic chronic myeloid leukaemia is very rare. If skeletal manifestations are well known complications of chronic myeloid leukaemia, they are usually late and associated with generalized worsening [1]. However, discovery of this disease prior to the diagnosis of a bony lesion is uncommon. Few cases have been reported in the literature [1–3]. In each case, evolution was rapidly fatal because of generalized acutization, despite chemotherapy in two cases [1, 2]. These clinical findings have a very poor prognosis and may suggest the use of more intensive chemotherapy. In our patient, we found that worsening was initially localized in the sternum tumour, and later became generalized. It is possible that localized radiotherapy may have delayed evolution to blast crisis [2], and therefore have improved the poor prognosis. This proposal warrants further confirmation.

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Unusual Occurrence of Acute Low Back Pain in a Patient with Ruptured Urachal Cyst

Sir—Low back pain is a common health problem. Almost 90% of patients suffer back pain caused by mechanical reasons. The remaining 10% of adults with back pain suffer the symptom as a manifestation of one of over 70 non-mechanical illnesses that may be associated with back pain [1]. We discuss a 17-yr-old male patient whose precipitating event of low back pain was a physical task; however, the complete clinical history spoke against a mechanical reason for back pain.

Except for congenital cheilognathopalatoschisis, the patient was always healthy. Three weeks before admission, he had lifted a heavy load. The next morning, he awoke with fever up to 40°C and chills. A mild pain in the suprapubic region with bilateral radiation toward the sacrum was initially present. During the following days, a severe, diffuse low back pain radiating to the upper medial parts of both legs and a waddling gait developed. The high fever persisted for 2 days and then gradually decreased. All the same, the patient continued to have severe fatigue. He lost his appetite and 7 kg of his body weight. Night sweating and more frequent micturition with no burning, pain, hesitancy or urgency were also present. NSAIDs brought a little pain relief, but no improvement of other symptoms.

He was referred to the department of rheumatology 3 weeks after the first symptoms due to acute low back pain and waddling gait. The active movement of hip joints was decreased, while passive movements were still preserved. The gluteal muscles, abductors of both legs and quadriceps muscles were painful to palpation. The neurological examination disclosed weakness and atrophy of the gluteus medius muscles. The straight leg raising test was bilaterally positive at 80°. Tests for sacrococcygeal joint tenderness, lumbar spine flexion and abdominal examination were normal.

Abnormal laboratory findings included a white blood cell count of 12 × 10⁹/l, ESR 75 mm/h and CRP 91 mg/l. Serum electrolyte levels, urinalysis, tests of hepatic and renal function, blood and urine cultures, plain radiographs of axial skeleton and colonoscopy were normal. Abdominal ultrasound revealed a non-homogeneous collection 6.4 × 5.2 cm between the urinary bladder and abdominal surface of the rectus abdominis muscle. CT of the abdomen showed a thickened anterior wall of the urinary bladder, and a mass between the urinary bladder and the rectus abdominis muscle. The mass extended bilaterally around the urinary bladder (Fig. 1A), and a mild upper urinary tract dilatation. CT of the abdomen showed a thickened anterior wall of the urinary bladder, and a mass between the urinary bladder and the rectus abdominis muscle. The mass extended bilaterally around the urinary bladder (Fig. 1B). Labelled leucocyte scan showed diffuse aggregation in the pelvis without persuasive evidence of localized infection. Electromyography (EMG) revealed complete bilateral paralysis of the gluteus medius muscle with neither voluntary nor spontaneous activity. No EMG abnormalities were found in other muscles.

Based on the presented data, we concluded that the cause of the patient’s disease was a rupture of a urachal cyst. No therapy was prescribed. The symptoms gradually disappeared within the next 3 weeks. On discharge from hospital, ESR was 26 mm/h, CRP <3 mg/l and white blood cell count 6.6 × 10⁹/l. Seven weeks after the first symptoms, EMG and abdominal ultrasound were completely normal.

Urachal anomalies are rare clinical entities. Among them, cysts are the most frequent form of abnormality in adults [2, 3]. If the cyst remains uninflamed or does...
not enlarge to a size causing mechanical symptoms, it usually remains undetected or is found only incidentally [4]. However, acute symptoms may be generated by the rupture of the uninfected urachal cyst or diverticulum following a manoeuvre that increases intra-abdominal pressure [5].

The principal abnormal finding in our case was a mass between the rectus abdominis muscle and the dome of the urinary bladder, demonstrated by both abdominal ultrasound and CT. This mass represents, according to diagnostic criteria, urachal remnants with an accuracy approaching 100% with regard to diagnosis of a cyst [2, 6]. The enlarged but asymptotic urachal cyst ruptured due to increased intra-abdominal pressure during the lifting of a heavy load. Following the rupture, the fluid from the cyst also spread toward the subperitoneal and retroperitoneal space of the pelvis, which in turn caused inflammation with consequent soft-tissue swelling. Since the inflammation was aseptic, it spontaneously regressed after resorption of the cyst’s contents. The bilateral paresis of gluteus medius muscles can therefore be explained by mechanical compression of superior gluteal nerves following soft-tissue swelling in the foramen suprapiriforme. Since the compression was not extreme, only reversible demyelination of nerve fibres without axonal degeneration appeared. The swelling of retroperitoneal soft tissue also caused a mild reversible upper urinary tract dilatation.

This is a case of referred low back pain caused by inflammation in the lower abdomen and pelvis due to rupture of a urachal cyst, but an even more unusual feature of the case is the waddling gait as a sign of bilateral involvement of the superior gluteal nerve. This has not been reported before in association with a ruptured urachal cyst.

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Cerebral Calcification in a Patient with Systemic Lupus Erythematosus and a Monoclonal IgG Reactive with Glial Fibrillary Acidic Protein

Sir—We describe a female patient with systemic lupus erythematosus (SLE), ulcerative colitis, an anti-glia fibrillary acidic protein (anti-GFAP) antibody, cerebral calcification and anosmia, who did not have a clinical history of SLE central nervous system (CNS) involvement.

The patient was diagnosed with SLE in 1980 at the age of 33 yr. Her disease was well controlled with the combination of hydroxychloroquine and a short course of low-dose oral steroid.

Symptoms of ulcerative colitis developed in 1987, and in 1989 a panproctocolectomy was performed for failed medical treatment.

In 1993, an IgG kappa paraprotein (~2–3 g/l) was detected in the serum. Investigations excluded myeloma, but a skull radiograph showed a large amount of calcification overlying the fronto-parietal region (Fig. 1), which had not been present radiographically in 1980. Calcium, phosphate, serum parathyroid hormone, lead levels and carboxyhaemoglobin were all within normal limits. Computed tomography (CT) and
blotting against cultured rat astrocytes indicated reactivity of the patient’s IgG with two proteins of ~50 kDa. With human brainstem tissue extracts, four major proteins of 40–50 kDa were demonstrated. The same proteins were reactive with a mouse monoclonal anti-GFAP antibody. There was no evidence of intrathecal complement activation; the IgG/albumin ratio was not supportive of intrathecal synthesis of the paraprotein, indicating transfer across the blood brain barrier (BBB). [Details of laboratory techniques can be obtained on request from the authors.]

On direct questioning, the patient complained of headaches and a reduction in taste and smell, but was unsure how long these symptoms had been present. There was no other history of neuropsychiatric disease. Neurological examination revealed anosmia, but taste sensation was intact; the remainder of the examination was normal.

The patient was started on 40 mg of prednisolone because of concerns that these findings represented an episode of cerebral lupus. The headaches resolved, but the anosmia remains unchanged. The dose of prednisolone has gradually been reduced to 1 mg daily, with no change in symptoms for 4 yr.

Brain calcification is not a common finding in SLE, and has only been reported following episodes of cerebral lupus [1–4]. The patient described does not have a clinical history of cerebral lupus, and the only neurological abnormality is anosmia, which, as an isolated abnormality, has not to our knowledge been described in cerebral lupus. It is interesting to speculate that the anti-GFAP antibody may be responsible for the patient’s anosmia because olfactory glia contain GFAP and these cells are certainly likely to be important in the support of the primary olfactory sensory cells. However, without further evidence, this is highly speculative and it is possible that the defect arises from vascular damage.

The high titre and the light chain restriction of the anti-GFAP IgG antibody in the serum and CSF are consistent with this anti-GFAP antibody being identifiable as the IgG paraprotein present in her serum. SLE was diagnosed >10 yr before the detection of the paraprotein, which would be compatible with its induction being secondary to SLE. Symmetrical, non-arteriosclerotic, slowly progressing brain calcification has been reported in a patient with an IgM paraprotein [5]. Since astrocyte processes normally wrap around the small blood vessels in the brain and are intimately associated with BBB function, it is possible that the calcium deposition is a consequence of altered astrocyte metabolism due to the high-titre anti-GFAP antibody leading to a BBB alteration, and an increased influx of calcium.

In summary, the anti-GFAP antibody in the patient’s serum and CSF may have been induced by the lupus, although the patient did not have a clinically identifiable episode of cerebral lupus. The high titre and binding properties of the anti-GFAP antibody present may have resulted in the cerebral calcification and anosmia found, although this is speculative.
We are grateful to Dr. James Robertson for allowing us to report on his patient. We are also grateful to Dr. Susan Walker and Dr. Alison Green for help with the CSF samples.

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Biochemical investigations were as follows: transaminase levels normal, lactate dehydrogenase (LDH) 969 IU/l (normal 100–450), creatinine 142 IU/l (normal 100–145), aldolase 8.2 IU/l (normal 2.0–5.8). There was an increased level of platelet-associated IgG (PA-IgG, 156.4 ng/10⁷ cells, normal 8–25). Rheumatoid factor, antinuclear antibody, anti-DNA, anti-RNP, anti-Sm, anti-SSA/Ro, anti-SSB/La, anti-
scl-70, anti-Jo-1 antibodies, Coombs’ test and anti-
myeloperoxidase neutrophil cytoplasmic antibody were all negative or normal. Serum immunoglobulins and complement levels were normal. Circulating immune complexes were not detected. Serological evidence of recent viral infection was not found. An intensive search for an occult malignancy was performed without any positive findings. The results of bone marrow aspiration showed a normal nucleated cell count, but there was an increase in megakaryocytes (150/μl). Mature-looking histiocytes (1.6% of all nucleated cells) sometimes demonstrated haemophagocytosis (Fig. 1). Malignant cells were never detected. Thus, as we found no causative disorders except DM of HS, the diagnosis of HS based on DM was made. During the first week of admission, pancytopenia progressed (leucocyte

Fig. 1.—Haemophagocytosis in bone marrow. The mature-looking histiocytes with many vacuoles showed phagocytosis of mature granulocytes, platelets and erythrocytes. (May–Giemsa stain; the bar indicates 10 μm.)

Haemophagocytic Syndrome in a Patient with
Dermatomyositis

Sir—Haemophagocytic syndrome (HS) is character-
ized by the proliferation of reactive or neoplastic
histiocytes which exhibit phagocytosis of haemato-
poietic elements. Reactive HS has been reported to be
associated with infection, malignancies or autoimmune
disorders [1–4]. Here we describe a patient with derma-
tomyositis (DM) who developed HS during the course
of her disease. To our knowledge, this is the first report
on HS associated with DM.

A 48-yr-old woman was admitted to our hospital in
December 1996 with 3 months duration of low-grade
fever, itchy erythematous eruptions on her posterior
neck, hands and feet, swelling of fingers and periorbital
rash. She did not have muscular weakness or muscle
enzyme elevation. Heliotropic rash on her eyelid and
Gottron’s sign on her proximal interphalangeal and
metacarpophalangeal joints were evident. Skin ulcers
were present at the metacarpophalangeal joint on the
left second finger and on the right elbow. She was
diagnosed as a case of DM without overt muscle
involvement.

After admission, her body temperature rose to
38.5°C and pancytopenia developed. Splenomegaly or
lymphadenopathy was not evident. Complete blood
count revealed a leucocyte count of 3500/μl, mild
anaemia and a platelet count of 51 × 10³/μl. Serum
iron, ferritin and haptoglobin levels were normal.
The erythrocyte sedimentation rate was 28 mm/h.

1. Nordstrom DM, West SG, Andersen PA. Basal ganglia calcifica-
tions in central nervous system lupus erythematosus. Arthritis
2. Anderson JR. Intracerebral calcification in a case of systemic
lupus erythematosus with neurological manifestations. Neuro-
3. Raymond AA, Zariah AA, Samad SA, Chin CN, Kong NC.
Brain calcification in patients with cerebral lupus. Lupus
P, Vega Astudillo A, Garcia Puig J. Massive cerebral calcification
in systemic lupus erythematosus: report of an unusual case. Lupus
5. Nishiyama K, Honda E, Mizuno T, Sakua M, Kawakami H. A
case of idiopathic, symmetrical non-arteriosclerotic, intra-cerebral
calcification (Fahr’s disease) associated with M-proteinemia, fol-
lowed by multiple myeloma. Rinsho Shinkeigaku–Clin Neurol

Haemophagocytic Syndrome in a Patient with Dermatomyositis

Sir—Haemophagocytic syndrome (HS) is characterized by the proliferation of reactive or neoplastic histiocytes which exhibit phagocytosis of haematopoietic elements. Reactive HS has been reported to be associated with infection, malignancies or autoimmune disorders [1–4]. Here we describe a patient with dermatomyositis (DM) who developed HS during the course of her disease. To our knowledge, this is the first report on HS associated with DM.

A 48-yr-old woman was admitted to our hospital in December 1996 with 3 months duration of low-grade fever, itchy erythematous eruptions on her posterior neck, hands and feet, swelling of fingers and periorbital rash. She did not have muscular weakness or muscle enzyme elevation. Heliotropic rash on her eyelid and Gottron’s sign on her proximal interphalangeal and metacarpophalangeal joints were evident. Skin ulcers were present at the metacarpophalangeal joint on the left second finger and on the right elbow. She was diagnosed as a case of DM without overt muscle involvement.

After admission, her body temperature rose to 38.5°C and pancytopenia developed. Splenomegaly or lymphadenopathy was not evident. Complete blood count revealed a leucocyte count of 3500/μl, mild anaemia and a platelet count of 51 × 10³/μl. Serum iron, ferritin and haptoglobin levels were normal. The erythrocyte sedimentation rate was 28 mm/h.

Biochemical investigations were as follows: transaminase levels normal, lactate dehydrogenase (LDH) 969 IU/l (normal 100–450), creatine kinase 142 IU/l (normal 100–145), aldolase 8.2 IU/l (normal 2.0–5.8). There was an increased level of platelet-associated IgG (PA-IgG, 156.4 ng/10⁷ cells, normal 8–25). Rheumatoid factor, antinuclear antibody, anti-DNA, anti-RNP, anti-Sm, anti-SSA/Ro, anti-SSB/La, anti-scl-70, anti-Jo-1 antibodies, Coombs’ test and anti-myeloperoxidase neutrophil cytoplasmic antibody were all negative or normal. Serum immunoglobulins and complement levels were normal. Circulating immune complexes were not detected. Serological evidence of recent viral infection was not found. An intensive search for an occult malignancy was performed without any positive findings. The results of bone marrow aspiration showed a normal nucleated cell count, but there was an increase in megakaryocytes (150/μl). Mature-looking histiocytes (1.6% of all nucleated cells) sometimes demonstrated haemophagocytosis (Fig. 1). Malignant cells were never detected. Thus, as we found no causative disorders except DM of HS, the diagnosis of HS based on DM was made. During the first week of admission, pancytopenia progressed (leucocyte

Fig. 1.—Haemophagocytosis in bone marrow. The mature-looking histiocytes with many vacuoles showed phagocytosis of mature granulocytes, platelets and erythrocytes. (May–Giemsa stain; the bar indicates 10 μm.)
count 2800/μl, haemoglobin level 9.7 g/dl, platelet count 27 × 10^9/μl). Sixty milligrams per day of oral prednisolone was started. High fever, leucocytopenia and anaemia resolved rapidly, but thrombocytopenia only insufficiently. Methylprednisolone pulse therapy (1 g/day for 3 days) was introduced twice, and an increase in the platelet count to around 170 × 10^9/μl, as well as a decrease of LDH and PA-IgG, occurred. However, skin ulcers worsened. Skin ulcer biopsy revealed the presence of vasculitis with mononuclear cell infiltration around s.c. vessels and occlusion of the lumens. Monthly i.v. pulse cyclophosphamide (IVCY) was prescribed and the ulcers gradually disappeared.

In addition, the platelet count increased further. She is now in good condition with oral prednisolone and IVCY once every 3 months.

Pancytopenia, especially thrombocytopenia due to HS was the most critical problem in our patient. Kumakura et al. proposed a disease entity of ‘autoimmune-associated haemophagocytic syndrome (AAHS)’ which includes ‘acute lupus HS’ [1, 3]. The pathogenesis of AAHS could be explained by autoantibody-mediated [3], immune complex-mediated [1] or cytokine-mediated mechanisms [4, 5]. Firstly, autoantibodies may react to blood cells, resulting in haemophagocytosis by stimulated histiocytes through the Fcγ receptor, mainly in the bone marrow [3, 7]. This is supported by the existence of PA-IgG in some patients [3] and the proposed mechanism in experimental autoimmune neutropenia [6]. Secondly, blood cells sensitized by immune complexes may be phagocytosed by histiocytes via complement – complement receptor interaction. Lastly, uncontrolled production of inflammatory cytokines may activate histiocytes.

In our case, the autoantibody-mediated mechanism is favoured, since she had elevated serum PA-IgG, normal levels of serum complements and circulating immune complexes.

Immunosuppressive agents including corticosteroids are recommended for the treatment of AAHS. Although acute lupus HS often shows a rapid response to steroid therapy [1], the effectiveness of corticosteroid therapy has not been firmly established in patients with AAHS. Some cases are reported to be resistant to corticosteroid or even more intensive therapies [3]. In our case, an improvement in platelet count did occur when methylprednisolone pulse therapy and IVCY were prescribed.

In this patient, we cannot definitely determine whether she had so-called amyopathic DM [8] or only a low-grade inflammatory process of DM. In addition, skin ulceration caused by vasculitis is relatively rare in adult-onset DM [9, 10]. Further studies are necessary to determine whether skin ulceration or a normal creatinine kinase level can be defined as a dependent risk factor in DM.

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Successful Treatment with Antithymocyte Globulin and Cyclosporin A of a Severe Aplastic Anaemia Associated with an Eosinophilic Fasciitis

Sir—A 60-yr-old man developed progressive skin tightness of both his forearms and his legs. His personal history revealed ulcerative and haemorrhagic rectocolitis 30 yr previously. Physical examination showed an induration of his limbs, his abdominal wall and the superior part of his back. The hands and the face were not affected. Peripheral blood eosinophilia was noted (1000/mm³). Biopsy of the deep fascia showed oedema and lymphocytic inflammation of the fascia, and confirmed the diagnosis of eosinophilic fasciitis (EF). He received corticosteroids without improvement. Three months later, a pancytopenia appeared. The blood count noted an aregenerative anaemia (Hb: 7.6 g/dl), a leuconeutropenia (WBC: 2.9 × 10⁹/l; polynuclear neutrophils: 0.7 × 10⁹/l) and a severe thrombocytopenia (platelets: 30 × 10⁹/l). His treatment did not include any drug with haematopoietic toxicity. The diagnosis of severe aplastic anaemia (SAA) was made after examination of aspirated bone marrow which showed a hypoplasia. Renal and hepatic function was normal. Corticosteroids were not effective. Treatment with cyclosporin A (CsA) associated with antithymocyte globulin was begun and induced progressive improvement. He received antithymocyte globulin (300 mg/day) for 5 days and CsA (4 mg/kg/day) for 1 yr (CsA serum level: 200 ng/ml). His transfusion requirements decreased and he required no further transfusion 4 months after the beginning of his treatment. After 9 months, his peripheral blood examina-
tion was considered as normal. Two years later, without treatment, the blood examination remained normal and the skin was almost completely normalized.

EF is a rare connective tissue disorder. It is characterized by stiffness, painful swelling and induration of the skin and soft tissues of the extremities and trunk associated with an eosinophilia. Fascia-muscle biopsy reveals thickened fascia with lymphocyte infiltration, sometimes with eosinophil cells. Clinical features of a connective disorder are not characteristic, but cases of associated systemic manifestations such as arthritis, thyroid disorders, inflammatory bowel disease, hepatitis and pericarditis were occasionally reported. Thus, EF is sometimes associated with other autoimmune diseases: ulcerative colitis [1] as in our patient, Hashimoto’s thyroiditis [2], sarcoidosis [3], etc. Its aetiopathogenesis is still unknown, but the lymphocytic infiltration and the partial response to corticotherapy argue for an immunological disorder.

Interestingly, the haematological complications of EF can be serious and are noted in 10% of the 200 observations reported in the literature [2]. SAA is the most frequent complication [2]. The prognosis of SAA associated with EF has generally been poor. A few observations have reported a role for immunosuppressive treatment [4] which is another argument for an immunological aetiology of EF and SAA. Thus, two patients had prompt and complete remission of both EF and SAA [5]; one received a combination of CsA and antithymocyte globulin, and the second a bone marrow transplant. We report, here, the second case of long-term cure of both SAA and EF with this immunosuppressive combination (CsA and antithymocyte globulin).

The cure of our patient with this immunosuppressive treatment may be due to the early treatment of the aplastic anaemia before complete aplasia. We emphasize the importance of regular blood examinations in patients with EF.

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Aortitis in Relapsing Polychondritis

Sir—Relapsing polychondritis (RP) is characterized by recurrent and ultimately destructive inflammatory episodes of cartilaginous structures. We report two cases of RP with involvement of the aorta. We would like to point out that such aortitis may occur subclinically, accounting for otherwise unexplained inflammation parameters. The cases also illustrate that aortitis may occur even in patients receiving therapy and that the response to immunosuppression is often unpredictable.

Case 1 was a 28-yr-old female who was admitted with a 4 week history of weight loss (7 kg) and strong periumbilical pain. We noted a saddle nose and a soft, pliable deformation of her left ear without signs of active inflammation. The right ear, in contrast, was red, tender and swollen at the pinna, but not at the lobule. A biopsy showed chondrocyte degeneration with infiltration of lymphocytes, macrophages and plasma cells. There was diffuse tenderness over the costal margins at anteroposterior compression of the chest. Cardiovascular examination was without abnormalities, except for a murmur in the epigastrium. The ESR was 94 mm and the CRP was 174 mg/l (normal up to 5 mg/l). Interestingly, the complement breakdown product C3d was elevated (20 mg/l; normal: <10 mg/l), but CH50 measurements were normal. CT and MRI imaging revealed aortitis with concentric thickening of the periaortal connective tissue, extending from the distal aortic arch to the proximal abdominal aorta (Fig. 1). Aortography showed a normal vascular tree. A leucocyte-labelled scintigram confirmed the inflammatory nature of the periaortal tissue. Transesophageal echocardiography excluded valvular abnormalities and aortic dissection. Oral prednisolone and cyclophosphamide pulse therapy (1200 mg i.v., triweekly) was instituted. The abdominal and auricular symptoms subsided within 2 months, and NMR imaging revealed substantial improvement, but no resolution of the aortic infiltrate. New nasal and costal chondritis, bilateral knee pain and episcleritis could not be prevented. After a total dose of 10.2 g of cyclophosphamide, a regimen of prednisolone (15 mg/day), cyclosporin A (175 mg/day) and methotrexate (12.5 mg weekly) was prescribed, but there was no satisfactory response. Finally, clinical remission was achieved with daily prednisolone (8 mg), azathioprine (100 mg), and the CRP decreased from 205 mg/l to 3 mg/l. Ten months later, the patient was readmitted with a CRP of 179 mg/l, a normal C3d and
no signs or symptoms of chondritic lesions. While a CT scan failed to detect any abnormalities, MRI revealed no signs of chondritic lesions. While a CT scan failed to detect any abnormalities, MRI revealed aortitis from the aortic arch to the descending portion of the aorta. The steroid was increased to 40 mg and azathioprine was replaced by methotrexate (12.5 mg weekly). Two weeks later, the CRP had normalized.

According to the literature, the most frequent aortic lesion in RP is valvular insufficiency, secondary to loss of the elastic tissue of the aortic ring with dilatation (in 4–9% of the patients [1–4]. Aneurysms of either the thoracic or the abdominal aorta occur in 4% and are caused by disruption of elastic fibres [1–4]. Dissection and rupture of the aneurysms can ensue [1].

Only a few anecdotal communications guide the therapy of aortic involvement in RP [1, 5, 6] and controlled therapeutic trials have not been carried out. It is known that corticosteroids and cyclophosphamide are able to decrease the frequency, duration and severity of flares, but may not be able to stop disease progression in severe cases [6]. Many manifestations of RP, including aortitis, were reported to be refractory or develop during such therapy despite disease remission in other organs [3, 5]. Drugs reported to be beneficial in milder disease are cyclosporin A, dapsone and methotrexate, but they may also prove to be ineffective [1, 7]. Successful surgical resection of aneurysms and heart valve replacement has been documented, but inflammation can recur adjacent to grafts [3]. Because of the unpredictable clinical response, an exact prognosis of RP is difficult to establish. A total of 86% of the patients embark on a relapsing and 14% on a progressive clinical course controlled therapeutic trials have not been carried out. It is known that corticosteroids and cyclophosphamide are able to decrease the frequency, duration and severity of flares, but may not be able to stop disease progression in severe cases [6]. Many manifestations of RP, including aortitis, were reported to be refractory or develop during such therapy despite disease remission in other organs [3, 5]. Drugs reported to be beneficial in milder disease are cyclosporin A, dapsone and methotrexate, but they may also prove to be ineffective [1, 7]. Successful surgical resection of aneurysms and heart valve replacement has been documented, but inflammation can recur adjacent to grafts [3]. Because of the unpredictable clinical response, an exact prognosis of RP is difficult to establish. A total of 86% of the patients embark on a relapsing and 14% on a progressive clinical course
respectively. Because aortic lesions are among the leading causes of death in RP, we recommend considering aortic involvement in any patient with RP and suggest early treatment. Using MRI, aortic involvement may be diagnosed before the onset of dilatation. Complement tests are of no diagnostic value [6].

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Infection with an Unenveloped DNA Virus (TTV) Associated with Non-A to G Hepatitis in Patients With Rheumatoid Arthritis

Sir—Recently, an unenveloped, single-stranded DNA virus (TTV) has been discovered, in association with post-transfusion hepatitis of non-A to G aetiology [1, 2]. DNA of TTV is detected in nine of the 19 (47%) patients with fulminant non-A to G hepatitis and 41 of the 90 (46%) patients with chronic cryptogenic liver disease. It is detected in liver from some patients with chronic non-A to G hepatitis, in levels from 10 to 100 times higher than in the corresponding sera, thereby suggesting that TTV may be replicating in the liver. TTV resembles parvoviruses, among animal viruses, in its morphology and genetic structure, and is excreted into the stool for possible faecal–oral transmission.

Since infection with human parvovirus B19 is implicated in the induction of polyarthritis, which closely resembles rheumatoid arthritis (RA) [3], 46 patients with RA in Japan were tested for TTV DNA. All RA patients fulfilled the revised criteria for the classification of RA proposed by the American Rheumatism Association. Overall, TTV DNA was detected in 12 (26%) patients with RA; the prevalence was significantly higher (P < 0.02, Fisher’s exact probability test) than that (12%) in healthy blood donors in Japan. The prevalence of TTV DNA in RA patients was much higher than those of ongoing infection with hepatitis B (2%), C (0%) and G (2%) viruses. Persistent hepatitis C virus infection causes a wide spectrum of extrahepatic manifestations, including porphyria cutanea tarda, cryoglobulinemia, vasculitis with monoclonal rheumatoid factor, and polyarthritis. Hepatitis B virus also causes polyarthritis. However, in our series, the prevalence of these three hepatitis virus infections did not exceed that in the general population in Japan.

Table I compares various features between the 12 RA patients with TTV DNA and the remaining 34 who were without detectable TTV DNA in serum. None with TTV DNA had a history of blood transfusion. There were no differences in the clinical features listed in the table between the two groups of patients, except for the prevalence of rheumatoid factor (RF); it was significantly less frequent in the patients with TTV DNA than in those without. RF is also reported less frequently in the patients with RA associated with parvovirus B19 [4]. Of the seven patients without RF, five (71%) were positive for TTV DNA, which is more frequent than in seven of the 39 with RF (18%) (P < 0.01, Fisher’s exact probability test).

Although viral antigens are demonstrated in synovial membranes of affected joints in parvovirus-associated polyarthritis, arthritis is usually self-limited and subsides along with the elimination of the virus by the immune system. The localization of parvovirus-like particles in RA, but not osteoarthritis synovia is suggested [5]; these particles do not cross-react with antibodies to parvovirus B19, however. Thus, it would be worthwhile to survey further the association of TTV with RA, and search for TTV DNA in synovial membranes from RA joints.

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TABLE I
Comparison of the patients with rheumatoid arthritis who did and did not have TTV DNA in serum

<table>
<thead>
<tr>
<th>Feature</th>
<th>Positive (n = 12)</th>
<th>Negative (n = 34)</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.3 ± 14.2</td>
<td>53.8 ± 14.5</td>
<td>NS‡</td>
</tr>
<tr>
<td>Female</td>
<td>9 (83%)</td>
<td>30 (88%)</td>
<td>NS§</td>
</tr>
<tr>
<td>Duration of RA (yr)</td>
<td>7.3 ± 6.0</td>
<td>7.9 ± 5.2</td>
<td>NS§</td>
</tr>
<tr>
<td>Stage of RA†</td>
<td>3.1 ± 0.8</td>
<td>3.4 ± 0.7</td>
<td>NS‡</td>
</tr>
<tr>
<td>RF (%)</td>
<td>58.3</td>
<td>94.1</td>
<td>P &lt; 0.01§</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0</td>
<td>5 (15%)</td>
<td>NS§</td>
</tr>
<tr>
<td>HBsAg</td>
<td>0</td>
<td>1 (3%)</td>
<td>NS§</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>HGV RNA</td>
<td>0</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>18.8 ± 6.6</td>
<td>22.6 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>13.8 ± 8.7</td>
<td>18.5 ± 14.8</td>
<td>NS</td>
</tr>
<tr>
<td>IgG (mg/100 ml)</td>
<td>1787 ± 638</td>
<td>1769 ± 515</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/100 ml)</td>
<td>2.92 ± 2.1</td>
<td>1.83 ± 2.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

HBSAg, hepatitis B surface antigen; HCV, hepatitis C virus; HGV, hepatitis G virus; ALT, alanine aminotransferase (normal range: 7–43 IU/l); AST, aspartate aminotransferase (12–32 IU/l); CRP, C-reactive protein; NS, not significant.

*TTV DNA was determined by polymerase chain reaction (PCR) with semi-nested primers with NG059 (sense: 5'-ACA GAC AGA GGA GAA GCC AAC ATG-3') and NG063 (antisense: 5'-CTG GCA TTT TAC CAT TTC CAA AGT TGG ATA GAC TGG-3') [9] in the first round, and with NG061 (sense: 5'-GGC ATG YTR TGG ATA GAC TGG-3' (Y = T or C; R = A or G)) and NG063 for 25 cycles with the same conditions in the second round [2]. The size of the first-round PCR was 286 bp, and that of the second-round PCR was 271 bp.

†The stage of RA was determined according to Steenbrocker et al. [6]. Statistical analysis was performed using either the Mann–Whitney U-test (‡) or Fisher’s exact probability test (§).


**Outcome in Systemic Vasculitis**

Sir—The recent review of systemic vasculitis by Boki et al. [1] highlights some of the problems associated with the classification of vasculitis. Although, in their review, polyarteritis nodosa (PAN) is subclassified into classical PAN and microscopic polyangiitis (MPA), this separation is largely ignored in the article and, as a result, the clinical and therapeutic data are more difficult to interpret. As has been clearly demonstrated, hepatitis B-associated PAN is a very separate entity both in clinical pattern and response to treatment. Indeed, antiviral therapy, coupled with steroids and plasma exchange, are the ideal treatment for this disease [2]. There is no mention of the use of these treatment regimens in the four patients with PAN.

The outcome analysis is based on a non-randomized study looking at pulse vs continuous cyclophosphamide therapy using the requirement for change in therapy as the main end point. We would argue very strongly that this is an inappropriate end point, and in our own recently published controlled study of pulse vs continuous treatment no significant differences between treatments could be found [3]. In our own prospective study, alteration to therapy was allowed and recorded since the study was based on an intention to treat. This is often required in more widespread clinical practice. Escalation of therapy was necessary in 31 out of the total of 54 patients, and this applied to both the pulse and continuous arms. Remission rates, treatment failure, death and relapse were similar in both groups.

A randomized study is clearly the most appropriate way of assessing the effect of any drug regimen. Treatment-related toxicities are a growing concern with cyclophosphamide and in our study [3] these were largely confined to the group on continuous cyclophosphamide. The authors’ conclusions on overall morbidity and mortality are again slightly hampered by their grouping since a previous study of systemic vasculitis [4] has suggested very significantly improved survival in patients with (classical) PAN as compared with MPA.

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Sensorineural Hearing Loss, Iritis and Ankylosing Spondylitis

Sir—We have recently reported a case of Takayasu’s arteritis with sensorineural hearing loss and inflammatory eye disease [1]. Relapses in hearing were successfully treated with i.v. steroids, prostaclin and aspirin on one occasion, and i.v. steroids and cyclophosphamide on another, remission being maintained with methotrexate and low-dose prednisolone. We wish to describe a patient with a sensorineural hearing loss, iritis and ankylosing spondylitis (AS), and discuss treatment.

A 41-yr-old man with AS, presented in August 1993 with bilateral iritis, treated successfully with steroid and mydriatic eye drops, and then in October 1993 with 6 weeks of worsening bilateral hearing loss and tinnitus. His AS had begun when he was aged 18 yr. Previous episodes of peripheral inflammatory arthritis had been treated with sulphasalazine between 33 and 37 yr. In March 1993, active wrist and ankle synovitis had led to sulphasalazine being recommenced and indomethacin 100 mg o.d. being started. He had previously used naproxen and phenylbutazone. He had bilateral sacroiliitis on plain radiograph, was positive for B27 on HLA typing and was seronegative for RF. On examination, he had loss of the lumbar lordosis, limited lumbar spine flexion and right knee synovitis. The cardiovascular and respiratory systems, eyes and outer ears were normal. Investigations revealed a haemoglobin of 10.2 g/dl with normal white cell and platelet counts. The urea and electrolytes, calcium, and liver function tests were normal. The ESR was 81 mm/1 h and there was a polyclonal increase in immunoglobulins: IgG 19.80 g/l (6–16), IgA 5.38 g/l (0.75–4), IgM 3.07 g/l (0.25–2). ANA and ANCA were not measured. Pure tone audiometry revealed bilateral sensorineural hearing loss worse in the left ear. Magnetic resonance imaging of the posterior fossa was normal.

In November 1993, indomethacin was discontinued and prednisolone 30 mg daily commenced, being reduced to 5 mg daily by December 1993. Right, but not left, ear hearing improved (Fig. 1). In September 1996, worsening hearing in the right ear led to an increase in the prednisolone dose to 60 mg daily and the hearing improved (Fig. 1). Over the next 2 months, the prednisolone dose was reduced to 12.5 mg daily. In June 1997, further hearing loss in the right ear resulted in an increase in prednisolone to 25 mg daily. With no improvement after 6 weeks, prednisolone was increased to 50 mg daily. There was no improvement and the steroid dosage was gradually reduced. He remains with significant hearing impairment.

Conductive hearing loss in association with AS has been reported previously [2]. A letter describing auditory findings in 94 ears from 48 patients states that ‘sensorineural hearing loss was found more frequently in patients with AS than in the control population’, although the data are not presented [3]. To our knowledge, there has been only one other report of sensorineural hearing loss in one of a group of six patients with AS in whom auditory assessment was carried out [4]. This patient was taking ototoxic drugs at the time of audiometric examination. Although sensorineural hearing loss is a recognized complication of non-steroidal anti-inflammatory drugs (NSAIDs) [5], we feel that in our patient it related to inflammatory disease, rather than drug toxicity, as in 1993 it coincided with an increase in activity of inflammatory joint and eye disease, and when hearing deteriorated in 1996 and 1997 the patient was not taking NSAIDs. This case highlights that sensorineural deafness may be a rare complication of AS. The response to steroids implicates an inflammatory process in the pathophysiology of the deafness. The early use of more aggressive immunosuppressive therapy, as in our recently reported case with sensorineural hearing loss [1], may have prevented the profound deafness seen in this patient with AS.

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