LETTERS

Hug(h)e(s') ears: an unusual presentation of antiphospholipid syndrome

A 49 year old white man presented with extensive deep vein thrombosis and reported a number of recent transcient ischaemic episodes. He was diagnosed three years previously with primary antiphospholipid antibody syndrome (APS), having had an ischaemic episode, raised anticardiolipin antibodies (IgG aCL 37 u/ml, normal <20), absence of clinical or serological evidence of systemic lupus erythematosus, etc, and was taking aspirin 75 mg daily. He also had an IgM κ paraprotein (5.3 g/l). On this occasion, IgG aCL was at the upper limit of normal, lupus anticoagulant was present (dilute Russel viper venom ratio 1.67, normal 0.81–1.19). Thrombophilia screen, including functional protein C and free protein S, was otherwise normal. Initially heparinised, he was started with warfarin treatment, target international normalised ratio (INR) 3.0 to 3.5. Three weeks later, he developed chest/flank pain and dyspnoea (pO2 7.96 kPa, pCO2 3.83 kPa, pH 7.46), severe thrombocytopenia (15×10^9/l), raised erythrocyte sedimentation rate (122 mm 1st h) and C reactive protein (319), and abnormal liver fuction tests. Haemoglobin, white cell count, blood film, and renal function were normal, INR 3.45, ANA, ENA and ANCA negative. Ventilation perfusion scan confirmed pulmonary embolus. Thrombocytopenia was treated with intravenous immunoglobulin (0.4 g/kg (40 g)/ day for five days). On the third day, he developed painful, swollen, tender indurated dark red ears (fig 1), with similar lesions on both cheeks. Biopsy showed extensive vascular thrombosis, with low grade vasculitis felt to be secondary to the thrombotic process (fig 2). Warfarin treatment was resumed while heparinised (target INR 3.0–3.5, maximum platelet count 103×10^9/l). After discharge, twice weekly INR remained 2.9–3.6, platelet count falling gradually to 64×10^9/l. Two days after this blood check, he developed headaches and vomiting, lost consciousness overnight, and died en route to hospital. Necropsy revealed subdural haemorrhage, haemorrhagic infarction of the left adrenal gland, thrombi of various ages in the periadrenal fat and in both lungs, infarction and haemorrhage in the right adrenal gland and in the myocardium.

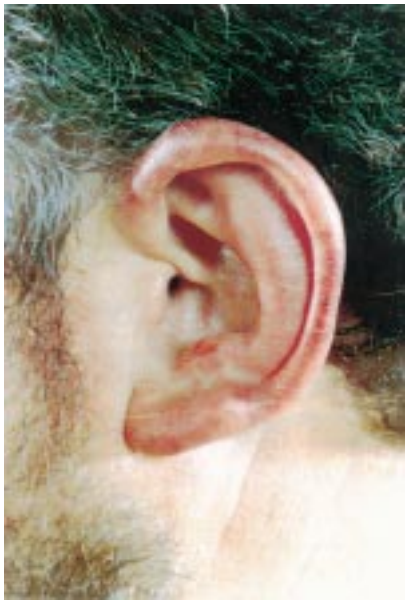

Figure 1 Swollen tender indurated red ear and adjacent skin (day 2).

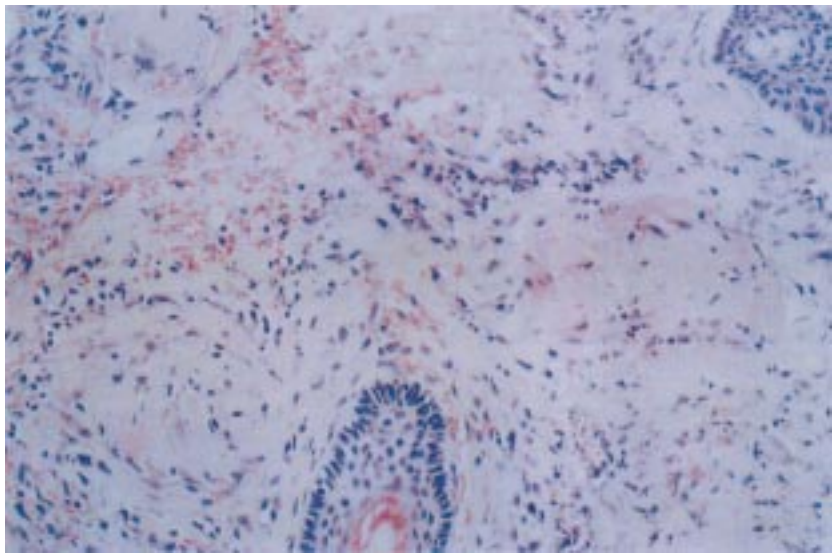

Figure 2 Section of dermis showing recent and organising thrombi in several vessels, erythrocyte extravasation, and focal inflammatory cell infiltration (haematoxylin and eosin × 210).

This could be considered catastrophic antiphospholipid syndrome, though the fatal event was in fact haemorrhagic. The return of near normal platelet numbers may have precipitated the thromboses of his ears, though he was moderately thrombocytopenic when many of the thrombotic events identified at postmortem examination probably occurred.

Thrombocytopenia occurs in about 23% of APS patients.[1] aCL antibodies have been reported in autoimmune thrombocytopenic purpura (ITP),[2] but immunosuppressive treatment restores platelet numbers and reduces platelet associated immunoglobulin without reducing the aCL titre,[3] suggesting specific antiplatelet antibodies in APS, distinct from those in ITP. Platelet activation is suggested as an initial event triggered by antiphospholipid antibodies,[4] and severe thrombocytopenia ($<50 \times 10^9$/l) may in fact be protective against thrombotic events. The Italian Registry of Anti-Phospholipid Antibodies[5] have found a thrombosis risk (without treatment) of 32% in patients with moderate thrombocytopenia ($50–100 \times 10^9$/l) compared with 40% in APS patients without thrombocytopenia, and only 9% in severely deficient patients, data confirmed in a prospective study.[6]

Warfarin treatment (INR >3.0) considerably reduces the risk of recurrent thrombosis.[7 8] One review reports nine episodes of haemorrhage (no deaths or permanent sequelae), six of which were associated with excessive anticoagulation; warfarin was resumed without complication in six of the seven patients involved.[9] None the less, Galli *et al*[10] urge caution, as the incidence of bleeding complications in these patients exceeds that of patients on a similar level of anticoagulation for prosthetic heart valves. Though moderate thrombocytopenia does not modify their anticoagulation policy, they do not recommend anticoagulation for severely thrombocytopenic patients.

The IgM paraprotein is of interest in light of reports of lupus anticoagulant activity associated with a number of IgM monoclonal gammopathies.[11] However, in the cases described, the incidence of thrombosis was considerably lower than that seen in APS, and our patient had positive IgG aCL antibodies in addition to the lupus anticoagulant.

This is the first case of bilateral thrombosis of the ears reported in APS (Hughes' syndrome), hence the quasi-eponymous title. It also highlights the Scylla and Carybdis of coexistant severe thrombocytopenia and thrombophilia. We must continue to protect our patients as best as possible, according to the available evidence, remembering that hard cases make poor laws.

We thank Professor R Ball for assistance with figure 2.

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Effect of hormone replacement therapy on bone density in a patient with severe osteoporosis caused by anorexia nervosa

Osteoporosis is a recognised complication of anorexia nervosa, in part because of oestrogen deficiency.[1] Data on the effect of oestrogen supplementation in osteoporotic patients with anorexia nervosa are limited. The effect of oestrogen supplementation on bone density in a patient with severe osteoporosis because of anorexia nervosa is reported.

The patient presented at the age of 26 years with a history of intermittent back pain and kyphosis. Her menarche was at the age of 13 years when she weighed 53 kg. At that time she developed a restrictive eating habit but continued to menstruate until the age of 19 years when she became amenorrhoeic and weighed 32 kg. Although she received psychological support her weight only improved temporarily. She remained underweight at 41 kg for the two years preceding presentation. The patient admitted to drinking minimal amounts of milk, although did have yoghurts regularly. The only exercise she did was walking as part of daily activities. There was no history of binge eating or vomiting and she denied laxative, diuretic, alcohol or drug abuse.

On examination her height was 1.57 m, weight 41 kg (body mass index 17). Her sclera were normal and joint hypermobility and excessive skin laxity were not found. She had a kyphosis with spinal tenderness on percussion and reduced spinal movements. General examination was normal. Investigations showed normal full blood count, biochemistry including serum calcium, phosphate, alkaline phosphatase, and thyroid function. Serum oestradiol was 55 pmol/l (range 120 to 570), luteinising hormone 0.5 IU/l (range 1 to 10), follicle stimulating hormone 4.6 IU/l (range 1 to 8), and testosterone 0.4 nmol/l. Radiographs showed multiple vertebral fractures of her thoracic spine but her lumbar spine was normal. Biochemical markers of bone turnover, parathyroid hormone, and vitamin D levels were not measured. Bone mineral density (BMD) was measured using a Lunar DPX densitometer and showed severe osteoporosis with a lumbar spine (L2 to L4) BMD of 0.36 g/cm^2 (T score −7.0, Z score −6.2) and femoral neck BMD of 0.51 g/cm^2 (T score −3.9, Z score −3.38).

She underwent psychiatric assessment but declined help. After some discussion, with an emphasis on the severity of her osteporosis, she agreed to take hormone replacement therapy (HRT) and calcium. She was treated with oestradiol valerate 2 mg and norethisterone acetate 1 mg (Kliofem) with calcium 500mg (Calcichew) daily. Over the following year her lumbar spine BMD increased from 0.36 g/cm^2 to 0.51 g/cm^2 (a gain of 38%), but her femoral neck BMD remained unchanged (fig 1). The DXA scan lumbar spine images and L2-L4 area remained similar in all three scans suggesting that the increase in lumbar spine BMD was not resulting from incident lumbar vertebral fracture. After one year she discontinued treatment because she felt bloated. Her lumbar spine BMD has declined since this point. During the period of time that she was taking HRT and calcium no other drugs were given and the patient made no changes in lifestyle. Her weight increased by 2 kg and her height remained stable.

The patient presented in the case report is interesting for a number of reasons including the large increase in lumbar spine BMD because of the effect of HRT. Caution has to be used in the way this increase in lumbar spine BMD is interpreted as the extreme severity of the patients osteoporosis emphasises the percentage increase because of a denominator effect. However, in terms of outcome, her BMD has increased by over 2 standard deviations over a short time course, representing a potential fracture reduction of about fourfold (though this inference is based on data from postmenopausal women).

Oestrogen replacement to increase BMD seems reasonable in amenorrhoeic women with osteoporosis secondary to anorexia nervosa. However, an open randomised controlled study of comparing no treatment with either HRT (Premarin 0.625 mg and Provera 5 mg) or the combined oral contraceptive pill (ethinyl estradiol 35 µg) concluded that oestrogen supplementation did not prevent progressive bone loss.[2] A subgroup of six patients with initial body weights of less than 70% of ideal did however show a small increase in BMD (4.4%). The lack of treatment response when compared with the patient reported could reflect differences in the type, dose, and frequency of delivery of the oestrogen or alternatively the type and dose of progestogen. For example, norethisterone is known to have oestrogenic and androgenic properties in addition to being progestogenic.

The magnitude of the increase in lumbar spine BMD suggests that there is more than filling in of the remodelling space, and possibly an anabolic effect of oestrogen is being seen, as suggested in recent studies of postmenopausal women.[3 4] The lack of increase in femoral BMD is worthy of comment. It is well recognised that different parts of the skeleton and different bone envelopes differ in their response to hormones such as oestrogen. Thus the femoral neck, which is predominantly cortical bone, is likely to be affected differently by oestrogen compared with the spine, which is predominantly trabecular bone. In addition increased skeletal loading may be required to facilitate the maximum effect of oestrogen at certain skeletal sites such as the hip.

Although restoration of normal body weight and menses may partially restore BMD in anorexic patients with osteoporosis, the findings in the patient reported suggest that oestrogen supplementation should not be neglected. Further studies are required to determine the most effective HRT regimen, combined with appropriate changes in exercise and weight gain in this group of patients.

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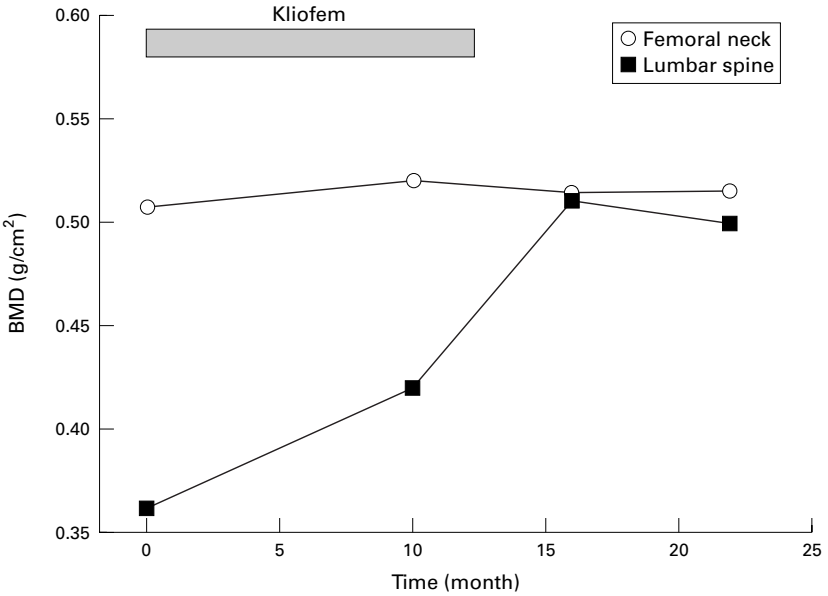

Figure 1 Change in bone mineral density with hormone replacement therapy.

Book review

Oxford Textbook of Rheumatology. 2nd ed. Edited by P J Maddison, D A Isenberg, P Woo, D N Glass. (Pp 2208; £195). Oxford: Oxford Medical, 1998. ISBN 0-19-262697-3.

First time around, I must confess to having purchased "The Other" rheumatological tome—that is, Klippel and Dieppe (KD), attracted by its user friendliness and liberal use of eye catching coloured diagrams, tables, and photographs in contrast with the more monochrome first edition of the *Oxford Textbook of Rheumatology* (OTR). It was therefore with interest that I agreed to review the second edition of the OTR to see whether I would change my allegiance!

The two main differences from the first edition, immediately evident from even the most cursory of glances of the textbook are as follows:

(1) The second edition of the OTR is dramatically more colourful with numerous colour photographs. Furthermore, the tables and line diagrams have improved both quantitatively and qualitatively as well as acquiring colour themselves, somewhat reminiscent in appearance and style of KD (fig 1). An infectious side effect of healthy competition, I suspect! This is most obvious in such chapters as "The skin", which is now very visual, having previously only had a few photographs in a section distant from the actual text. The chapter on the eye has similarly benefited from colour processing as has the chapter on rehabilitation of children, which is now a sheer delight to read.

(2) The cushingoid-like weight gain! The 57% increase in pages is approaching the number that requires a government health warning for all those readers with weak backs and/or biceps musculature! The third edition is likely to require a tripartite division.

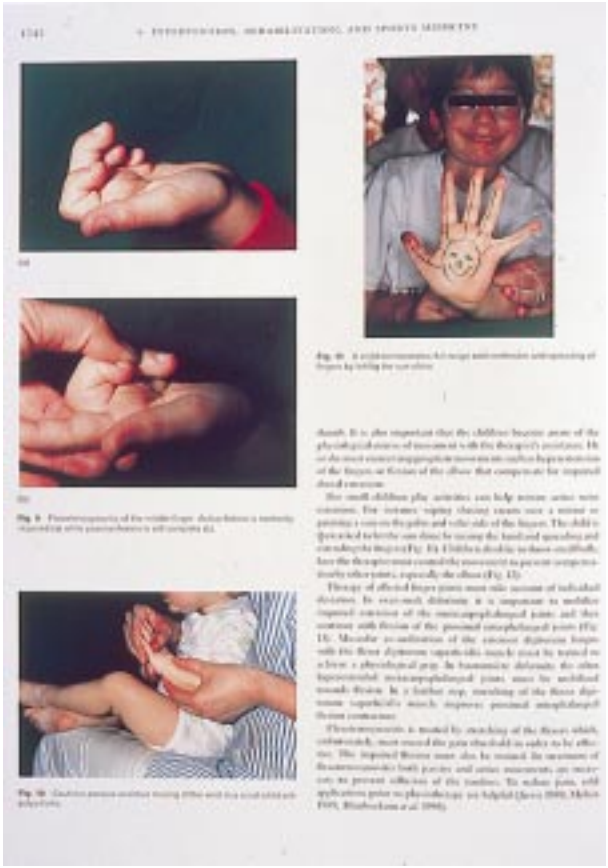

Figure 1 Representative page from the Oxford Textbook of Rheumatology (p1742).

The comprehensive text and liberal use of illustration will, without doubt, meet the needs of, and attract a wide target audience, defined by the editors as "trainees, full-time clinicians and academic rheumatologists." There is a happy, balanced marriage between the scientific and clinical components of the text, with the complicated aspects of each explained with welcome clarity. An evidence-based approach is frequently used with summary tables of the available evidence from trials and studies accompanied by more extensive referencing than in the first edition. There are no major omissions, with this edition seeing the welcome arrival of several new chapters including psychological issues in rheumatic diseases, outcome assessment, sports injuries, osteomyelitis, the neurophysiology of pain, and a much improved, well illustrated chapter on injection therapy.

Most of the disease specific chapters in volume 2 have a similar structure, for example, epidemiology, clinical features, etc, which is particularly useful and educational for those in training. The "Practical Problem" sections of KD however have no equivalent in the OTR and may represent an area worthy of thought for the next edition, useful for both trainees and trainers alike. Most chapters do however have "Points to Remember" lists. These are sadly not universal.

Fairburn and Kidd, when reviewing the first edition of OTR (Ann Rheum Dis 1995;54:23–4), commented that the placing of the chapter on rehabilitation at the end of the book may reinforce the inferiority of rehabilitation as an aspect of rheumatological care, especially to the younger, less experienced readership. Sadly, both rehabilitation chapters (adult and children) remain at the end of the book and are not actually cross referenced in some of the relevant specific disease chapters, for example, rheumatoid arthritis, systemic onset and pauciarticular juvenile chronic arthritis.

There are some potentially confusing chapter arrangements, for example, rheumatoid factor positive polyarthritis is included under the heading of rheumatoid arthritis and although it is similar to adult rheumatoid arthritis, some may think it preferable to be seen as distinct from adult rheumatoid arthritis in view of the differences in general management of childhood arthritides.

Overlap and repetition is almost unavoidable in such large textbooks with multi-authorship. Cross referencing is prevalent but not universal (see above). There are some minor areas of overlap, for example, role of diet in inflammatory arthritis (sections 1.3.6 and 3.5.3) but perhaps the most obvious major area is the overlap and repetition in the regional problems. Whereas the regional upper limb problem section (1.2.2.1) includes anatomy and clinical aspects, the soft tissue rheumatism chapter includes pathogenesis as well as the same clinical aspects. My personal opinion is that in this most important area for the "jobbing rheumatologist", the division is to the detriment of the impact of this section of the text. KD certainly wins hands down for its regional pain section in comparison in this regard.

In my reviewing process, I tried to think of some practical questions for which a clinician may use the book as a source for quick reference. Useful summary algorithms/sections were readily available for most conditions. Similarly, a useful algorithm is given for management of septic arthritis in childhood though not for adulthood. The algorithm for management of rheumatoid arthritis unfortunately is somewhat confusing (and incomplete in my copy), compounded by the fact that the order of drugs discussed in the algorithm, table, and text is inconsistent.

This second edition therefore now compares well with the competitors, having been significantly improved upon the previous edition. The competition between the large rheumatology tomes is obviously proving beneficial and long may it continue—it is the readership who will benefit. As my nearest university library has neither the first or second edition of either the OTR or KD, I would recommend all libraries to have both. I wonder when the CD-ROM of this edition is planned!

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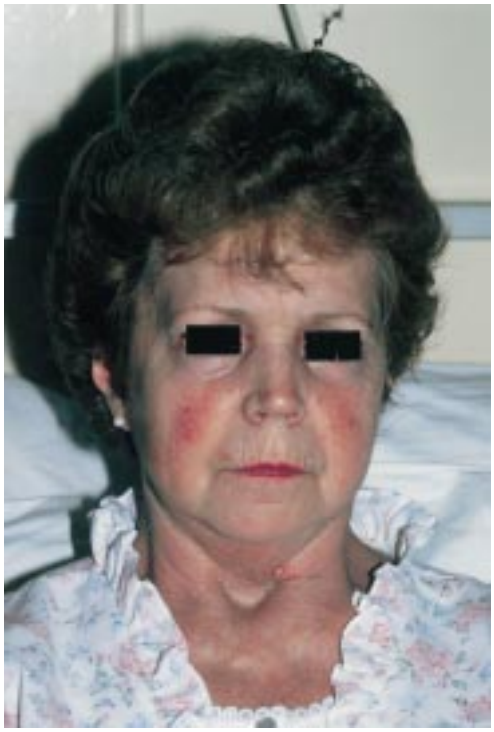
Unusual and memorable

Series editor: Gary D Wright

This 58 year old woman has a history of seropositive rheumatoid arthritis for 25 years. Her disease was controlled with 50 mg sodium aurothiomalate every three weeks for the past 21 years. Recently she had noticed a change in her skin colour.



On examination she had slate grey pigmentation over her face, neck, and hands, most marked in the periorbital region. There was no history of amiodarone ingestion. There was no history of respiratory disease and arterial blood gases were normal. She did not have haemochromatosis.

Chrysiasis secondary to longstanding sodium aurothiomalate treatment was first described in 1928.[1] It is a photodependent pigmentation resulting from aurosomes gathering in light exposed regions.

The phenomenon is dose dependent, the severe form being reported after a cumulative dose of 263 mg/kg of sodium aurothiomalate.[2] This woman had a cumulative dose of 787 mg/kg. It is a benign condition but has a high potential for misdiagnosis if unrecognised.

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