LETTERS TO THE EDITOR

Alfuzosin-associated Dermatomyositis

Sir—Alfuzosin, a quinazoline derivative, is a selective antagonist of \( \alpha _1 \)-adrenoceptors. It causes a contraction of prostatic, prostatic capsule, proximal urethral and bladder base smooth muscle, thereby reducing the tone of these genitourinary structures. Consequently, elevated urethral tone, resistance and pressure, bladder outlet resistance and bladder instability, associated with benign prostatic hyperplasia (BPH), are reduced. Hence, alfuzosin can be considered effective in the symptomatic treatment of BPH. Adverse effects of alfuzosin have been evaluated in short- and long-term clinical trials. The most common side-effects seen in treated patients (usual daily dose 7.5–10 mg) were dizziness, headache, somnolence, diarrhoea, nausea, skin rash, asthenia and dry mouth. These side-effects were generally reported as mild and improved after cessation of therapy. No unexpected or serious adverse effects and discontinuations are significant in clinical trials [1–6]. Alfuzosin is available in most European and Asian countries, and registration applications have been submitted to other countries.

We recorded a probable alfuzosin-induced dermatomyositis in a man. This finding has not been previously reported for patients who have received alfuzosin for the treatment of BPH.

A 75-yr-old man was admitted to the hospital. His symptoms included a gradually increasing proximal upper and lower limb muscle pain and weakness during a 4 day duration, accompanied by facial rash and periangual lesions. Prior to his admission, he had been in his usual state of good health. He denied fever or weight loss, but he had noticed fatigue.

On admission, the patient appeared well. Muscle examination showed marked weakness involving the proximal limbs, with tenderness and swelling in deltoid, biceps and triceps areas. There was an erythematous rash with prominent oedema affecting malar areas and the bridge of the nose, periangual purpuric spots and erythematous plaques over the finger joints. The rest of the physical examination was normal.

Laboratory examination revealed a normal, complete blood count. The erythrocyte sedimentation rate (ESR) was 28 mm/h, creatine kinase (CK) was 2109 U/l (normal values 25–190 U/l), of which 100% was MM, lactate dehydrogenase (LDH) was 856 U/l (normal values 230–460 U/l), aldolase 24.5 U/l (normal values 0–7.5), serum aspartate aminotransferase (AST) 250 U/l (normal values 10–35 U/l) and alanine aminotransferase (ALT) 113 U/l (normal values 9–43 U/l). The rest of the biochemical tests, including gammaglutamyl transpeptidase (GGT) and alkaline phosphatase, were normal. The ANA was positive, with a titre of 1/80 with a speckled pattern. Anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP, anti-Jo-1 and anticardiolipin antibodies were negative. C3, C4 and thyroid hormones were within normal limits. Serological tests for HIV, Toxoplasma, cytomegalovirus, herpes virus and Epstein–Barr virus were negative. The evolution of analytical values is shown in Table I.

An electromyogram performed on the left side of the body showed an increase in the insertional activity of the muscle with numerous fibrillation potentials and positive sharp waves at rest. The motor units showed decreased amplitude and duration, and increased polyphasic potentials.

A magnetic resonance imaging (MRI) exploration showed findings consistent with inflammation of muscles, and a right deltoid muscle biopsy revealed an infiltrate of lymphocytes and plasma cells in the muscle and perimysial tissues with an occasional polymorphonuclear leucocyte. There was necrosis of muscle fibres with phagocytosis and regeneration.

An occult neoplasm was eliminated by performing X-ray films of the chest, urinalysis, ultrasonographic study of the abdomen, barium enema and gastroscopy. The patient has been receiving treatment with alfuzosin during the last year due to BPH. This drug was interrupted at admission; nonetheless, 3 days after there was no clinical or analytical improvement, so prednisone treatment was started at a dose of 1 mg/kg/day. On the following days, improvement in clinical and blood chemistry was found.

Several drugs have been described as causing agent-induced dermatomyositis (phenylbutazone [7], statins [8, 9], hydroxyurea [10], \( \tau \)-penicillamine [11, 12]). In this case, we have reported a new drug (alfuzosin) as a possible inducer of dermatomyositis. Alfuzosin is a quinazoline, \( \alpha _1 \)-adrenoceptor antagonist, which has been associated with an increase in ANA, e.g. with prazosin [13], although this report has been discussed [14]. Relevant information was found on Medline. The literature found was published between 1966 and 1997 on autoimmune syndrome (lupus erythematosus, dermatomyositis) induced by quinazoline. Only one report was found: a lupus erythematosus induced by doxazosin [15]. Nevertheless, an increase in ANA has been found in several cases [13, 16].

In our case, the quick response to corticosteroids
induced by quinazoline. The diagnosis of causes other than pharmacological ones. Therefore, we recommend that clinical signs of patients who have been treated long term with quinazoline be monitored for possible autoimmune syndrome induced by quinazoline.

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Cavitary Lung Tuberculosis in a Rheumatoid Arthritis Patient Treated with Low-dose Methotrexate and Steroid Pulse Therapy

Sir—Rheumatoid arthritis (RA) patients are frequently treated with immunosuppressive agents and steroids, which may increase the risk of opportunistic infections. Corticosteroid pulse therapy (CPT) produces relatively mild side-effects [1, 2] and the infection rate during low-dose methotrexate (MTX) ranges from 0 to 27%, with an increased risk soon after the onset of therapy [3]. Several pathogens have previously been reported in RA patients treated by CPT and low-dose MTX. We report a case of upper lobe cavitary tuberculosis (TB) in a patient with RA under this treatment.

In 1991, M.M., a white female aged 40 yr who had been suffering from RA since 1988, first came to our clinic. She had previously undergone treatment with NSAIDs, low-dose steroids (LDS) (prednisone 5 mg daily), hydroxychloroquine and oral gold salts, but with poor response. Diagnosis of RA was confirmed, according to the 1987 ACR criteria; she had acute arthritic symptoms, rheumatoid nodules, serum IgM factor and decreased levels of complement fractions. Diagnosis of RA was confirmed, according to the 1987 ACR criteria; she had acute arthritic symptoms, rheumatoid nodules, serum IgM factor and decreased levels of complement fractions.

In December 1994, the patient complained of a persistent cough, with little sputum and no fever. Radiographic changes of the joints. Total oral prednisolone i.v. daily was administered, with a to avoid high-dose oral steroids, a 3 day course of CPT (1 g methylprednisolone) was followed by a clinical remission; 10 days later, 4 mg methylprednisolone daily were administered.

In January 1994, arthritic flare-up was associated with phenylbutazone therapy. J Rheumatol 1987;14:397–8.

In September 1994, active arthritis reappeared: methylprednisolone 8 mg daily was administered, without clinical improvement. To obtain a prompt resolution of symptoms and to avoid high-dose oral steroids, a 3 day course of CPT (1 g methylprednisolone i.v. daily) was followed by a clinical remission; 10 days later, 4 mg methylprednisolone daily were administered.

In December 1994, the patient complained of a persistent cough, with little sputum and no fever; increased sedimentation rate and normal white cell count were found. Chest X-ray and tomography revealed right upper lobe cavitation and contralateral nodules (Fig. 1), without evident clinical signs on physical chest examination. Any past history of TB was excluded. Direct microscopic examination of the sputum revealed the presence of Mycobacterium tuberculosis (MT) and sputum cultured for acid/alcohol-fast bacilli grew MT. This confirmed the diagnosis of TB and definitively excluded other forms of nodular lung lesions such as malignancy and rheumatoid pulmonary involvement.
MTX was stopped and steroids were tapered off, while rifampicin 600 mg, ethambutol 1.5 g and isoniazid 300 mg daily were started immediately. Determination of drug susceptibility revealed the efficacy of all three. After 6 months, rifampicin was suspended, while ethambutol and isoniazid were continued for a further 3 months.

X-ray control after 5 months showed complete resolution of the cavitation with residual contralateral calcified nodules, confirmed later by radiographic controls.

In the following years, M.M. started parenteral gold salts, but suffered from severe articular damage and leucocytoclastic vasculitis together with mixed cryoglobulinaemia, and underwent three surgical prostheses. Class II HLA determination revealed the presence of DR4 antigen.

This is a case of RA in a middle-aged woman who developed a cavitary TB after low-dose MTX and CPT. We chose this therapy to obtain prompt control of the flare-up of arthritis, sparing high-dose oral steroids, and to achieve clinical remission by MTX alone.

Irrespective of treatment, the susceptibility to common infections of patients with RA does not seem to have increased [4]. Nevertheless, these patients are frequently treated with immunosuppressive agents and, among these, CPT and low-dose MTX have been associated with an increased risk of opportunistic infections [1–4]. No case of TB was reported before 1995 during low-dose MTX [3] and CPT; only three other cases of cytomegalovirus infections, one of Pneumocystis carinii pneumonia and one of herpes zoster have been reported since then [5–9]. TB infection has been reported in three rheumatic patients who underwent low-dose MTX and were affected by diseases different from RA [3, 10].

In conclusion, this case underlines the necessity of close monitoring for severe opportunistic infections in rheumatoid patients during treatment with CPT and MTX, particularly those with an aggressive disease or with its markers.

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Fig. 1.—Chest X-ray revealing right upper lobe cavitation and contralateral nodules.
Similar Response of Adrenocorticotrophic Hormone, Cortisol and Prolactin to Surgery in Rheumatoid Arthritis and Osteoarthritis

Sir—Studies by Chikanza et al. [1] showed a diurnal cortisol rhythm which was at the lower limit of normal in patients with rheumatoid arthritis (RA) and a failure to increase cortisol levels following surgery. They also found increased levels of prolactin in patients with RA and an abnormal increase in prolactin levels after surgery [2]. They conclude that in RA a defective hypothalamic-pituitary-adrenal axis response and excessive prolactin reaction lead to a pro-inflammatory hormonal status which might play a role in the pathogenesis of RA [3]. The aim of this study was to confirm these findings.

Nine patients with rheumatoid factor-positive RA and 10 patients with osteoarthritis (OA) who needed total knee or hip replacement were studied. Seven RA patients were using disease-modifying anti-rheumatic drugs (DMARDs). All OA patients, and all but one RA patients, were treated with NSAIDs. At 7:30 a.m. before surgery, and on the following 4 days, blood was collected for the determination of plasma adrenocorticotropic hormone (ACTH), plasma cortisol and serum prolactin levels.

There was no significant difference in age (RA: mean [s.e.m.] 63.3 [3.5] yr, OA: 66.4 [2.1 yr]). Mean ESR in RA patients was 25.6 [3.4] mm/h. Before surgery, plasma cortisol levels in patients with RA and in patients with OA were 0.48 [0.04] μmol/l and 0.58 [0.04] μmol/l, respectively (Fig. 1A). Following surgery, no significant changes were found either within or between groups. Before surgery, ACTH levels were in the normal range, both in the RA patients (6.7 [1.3] pmol/l) and the OA patients (5.32 [1.2] pmol/l) (Fig. 1B). The first day after surgery, a comparable decrease was seen in both groups with a return to pre-operative levels in the following days. There were no significant differences in prolactin levels before surgery between both groups nor were there any significant changes after surgery (not shown).

These observations are in disagreement with the study of Chikanza et al. [1, 2]. Firstly, we found higher levels of cortisol in both RA and OA patients. This might be related to the fact that in our study patients’ blood was drawn at 7:30 a.m. and in Chikanza’s study at 9:00 a.m. Before surgery, in our patients cortisol levels were in the upper range of normal and we attributed this to stress in anticipation of the operation; perhaps the patients in the study of Chikanza had received more sedative drugs as pre-medication than the patients in our study. Another explanation could be the influence of anti-rheumatic therapy on the HPA axis. In the study by Chikanza et al., the diurnal rhythm of cortisol was studied in 10 patients with active RA, 10 patients with non-inflammatory arthritis (NIA) and in 10 patients with osteomyelitis (OM); whereas all patients with RA were treated with NSAIDs, only five of the NIA and none of the OM patients were. Nine RA patients were also treated with a DMARD. The RA patients showed the lowest cortisol values, the NIA patients higher values and the OM patients the highest values. The high cortisol values of the OM patients are to be expected because of their active inflammation, but one would expect the same values in the RA patients with a comparable degree of inflammation. The fact that this was not found might suggest a hypothalamic defect, but might also be the result of the use of NSAIDs and/or DMARDs. One of the possible mechanisms by which cytokines may activate the HPA axis is through the synthesis of prostaglandins, which stimulate the secretion of corticotrophin releasing hormone (CRH) [4–6]. Studies in animals have shown that the effect of cytokines on

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Fig. 1.—Cortisol (A) and adrenocorticotrophic hormone (ACTH) (B) levels in patients with RA (—) and OA (– – –). Values were taken at 7:30 a.m. on day 0 (day of surgery) and on days 1–4 after surgery. Values are the mean ± S.E.M.
CRH release could be antagonized by blocking the cyclooxygenase pathway and thereby prostaglandin synthesis by NSAIDs [7, 8]. Through this mechanism, NSAIDs might cause a decreased cortisol response. In the study of Chikanza et al. [1, 2], the reactions to surgery were studied in 10 patients with RA, nine with OA and 10 with OM. Before surgery, cortisol levels were similar in RA and OA, but higher in OM patients (not using NSAIDs). After operation, RA patients showed no increased cortisol levels, whereas OM and OA patients did. This difference after surgery cannot be explained by the use of NSAIDs as this was comparable in RA and OA. A possible influence of DMARDs on the HPA axis cannot be excluded.

Secondly, we did not observe higher levels of prolactin before the operation in patients with RA nor an excessive secretion after surgery. This might be explained by a difference in disease activity, as illustrated by the ESR: mean [s.d.] 25.6 [10.3] vs 56.9 [18] mm/h in the study by Chikanza et al. However, our findings of normal prolactin levels in RA are in agreement with recent studies in which no significant difference was found in prolactin levels between patients with RA and controls [9, 10].

In conclusion, we found neither a defective response of the pituitary–adrenal axis nor an excessive prolactin secretion in patients with RA. We therefore question the existence of a defective hypothalamic response in patients with RA and suggest that a possible influence of NSAIDs on the HPA axis should be considered. This study was supported by a grant from ‘Het Nationaal Reumafonds’ of The Netherlands.


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Re: Management of Idiopathic Carpal Tunnel Syndrome

Sirs—The survey by Pal et al. [1] revealed an interesting variation in the management of idiopathic carpal tunnel syndrome (ICTS) by British rheumatologists, but the guidelines proposed by the authors are untenable. ICTS is one of the commonest and simplest conditions that we are asked to treat. It is primarily a clinical diagnosis based principally on a suggestive history, and perhaps reinforced by one or more physical signs. Neurophysiological assessment is superfluous in most cases and is potentially misleading. Steroid injection of the carpal tunnel is easy to perform, usually rapidly effective and has a low complication rate. It can also serve as a specific and sensitive diagnostic test for the condition. Failure of response indicates either an incorrect diagnosis or median nerve compression of a degree which is unmanageable to local steroid therapy. In the latter situation, the physical signs should be unequivocal and the diagnosis readily confirmable by electromyography (EMG) and nerve conduction studies (NCS) prior to surgery. The false-negative rate for EMG and NCS in the diagnosis of ICTS is unknown, but milder or intermittent cases of median nerve compression may not be associated with a measurable slowing of sensory nerve conduction velocity, the minimum diagnostic criterion for CTS [2].

Apart from further increasing the demand on an already overburdened service, insisting on neurophysiological verification of the diagnosis of ICTS prior to treatment may deny patients a very simple, safe and effective treatment, or at least delay it for weeks or months. Phalen [3] considered that ‘electrodiagnostic studies surely are not necessary in every patient with carpal tunnel syndrome’ and that a good response to a local steroid injection ‘provides excellent confirmation of the diagnosis’. A pragmatic policy is to reserve EMG and NCS for cases in which there is reasonable doubt about the diagnosis, or where conservative treatment has proved ineffective [4].

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Binding Feet, the Living Legacy of the Ching Dynasty (1644–1912), China

Sir—A 97-yr-old Chinese lady has had bindings of her forefeet since childhood (Fig. 1). The small toes were purposely fused in extreme flexion. Other deformities include dystrophic toe nails, loss of medial arch support, ankle valgus and displaced heel pad. In motion, she practically walks on her buried small toes, although she still retains remarkably good ankle flexion and extension. Ironically, the practice of bindings was the privilege and class symbol of the ladies of wealthy and aristocratic families of the Ching Dynasty (1644–1912), China. The gait, which is small-stepped and shifting, is intended to be graceful and genteel. Such small feet, known as the 'the three inches of the golden lily', are rarities and seldom seen nowadays.

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Fig. 1.—(a) Standing view, both feet. (b) Dorsal surface, apparent missing small toes. (c) Volar surface of left foot, showing extreme flexion of small clawed toes. (d) Volar surface of left foot, close-up view, in plantar flexion. (e) Lateral view of left foot, displaced heel pad, apparent missing toes.