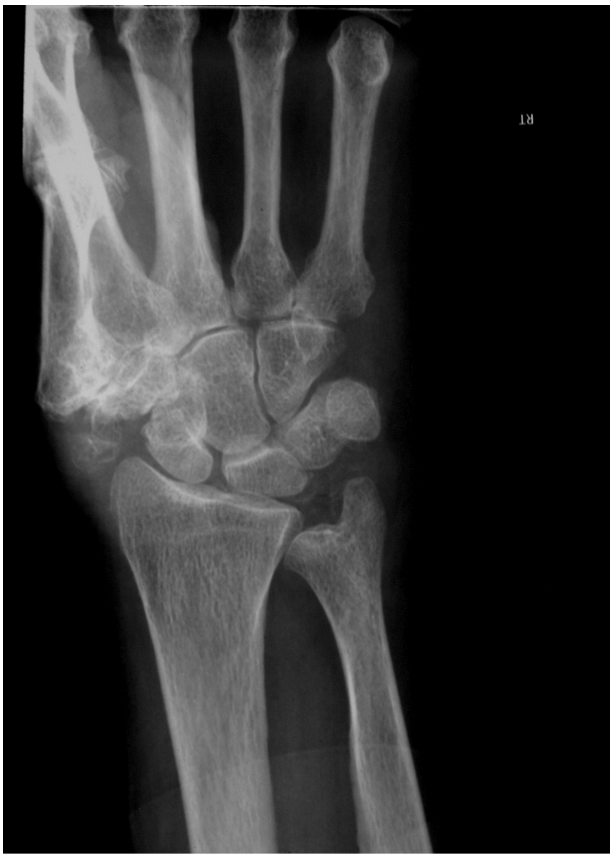

FIG. 1. Wrist X-ray illustrating chondrocalcinosis in the triangular fibrocartilage, which is typical for pseudogout.

sodium, and her wrist symptoms subsided. She went on to complete her course of anti-tuberculous therapy, and her neck pains and abnormal neurology resolved.

Discussion

Anti-tuberculous chemotherapy-induced crystal arthropathy is a rare and poorly recognized adverse effect of pyrazinamide and ethambutol. A metabolite of pyrizinamide, pyrinazoic acid, inhibits the renal tubular secretion of uric acid and ethambutol reduces its renal clearance. The resulting hyperuricaemia can give rise to arthralgias and very rarely an arthritis. Khanna *et al.* [1] prospectively studied 134 patients with pulmonary TB, and only one patient of the 71 cases receiving ethambutol developed arthritis with one other complaining of arthralgias. In 60 of the 134 cases, ethambutol was replaced with thiacetone, and none of these patients had any rise in their serum urate or musculoskeletal symptoms. To date, only four cases of ethambutol-/pyrazinamide-induced gout have been reported in the English literature [1–4]. No cases of pseudogout associated with TB chemotherapy have been reported, although one case reports the concomitant occurrence of TB septic arthritis within a pseudogout tophaceous nodule [5].

This is the first reported case of concomitant gout and pseudogout induced by TB chemotherapy. The case highlights the rarely reported musculoskeletal side effect of anti-tuberculosis treatment and the importance of joint aspiration and careful analysis of joint fluid. Such rare cases may become more prevalent in the future with the resurgence of *M. tuberculosis*, and the rheumatologist needs to be alert for the occurrence of these adverse events.

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Uterine artery Doppler in predicting pregnancy outcome in women with connective tissue disorders

SIR, We read with great interest the article by Le Thi Huong *et al.* [1] on the second trimester Doppler ultrasound as best predictor of late pregnancy outcome in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).

The authors prospectively examined 100 high-risk pregnancies and concluded that Doppler examination and history of thrombophlebitis were independent predictors of fetal and neonatal death in SLE and APS pregnancies progressing beyond 22 weeks. Infact, six out of eight fetal/neonatal deaths and other major and minor obstetric complications occurred in patients with abnormal second trimester Doppler ultrasound.

In order to investigate the role of uterine Doppler ultrasound abnormalities as a risk factor for adverse pregnancy outcome, we have prospectively followed 40 pregnancies in 40 patients with SLE and other connective tissue diseases including vasculitis: six patients were affected by APS, nine patients by SLE, 12 patients by undifferentiated connective tissue disorder (UCTD), three patients by Behçet's disease (BD), four patients by scleroderma (Scl) and five patients by Sjögren's syndrome (SS).

The second trimester fetal Doppler ultrasound examination was abnormal in 14 pregnancies: in 45% of the SLE patients (four out of nine), in 67% of the APS patients (four out of six), in 75% of patients with BD (three out of four) and 100% of the Scl patients. Out of 14 pregnacies, 11 were complicated by premature deliveries associated, with pre-eclampsia in four cases and with premature membrane ruptures (PROM) in the other four. There was one delivery of a growth-restricted liveborn (intrauterine growth retardation, IUGR). Only two of these 14 pregnancies progressed until the end of the third trimester and delivered spontaneously. The mean gestational age at delivery was 35 weeks, the mean birth

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weight was 2142 g and the mean APGAR scores at 5 and 10 min were, respectively, 8 and 8.

All the 26 patients with a normal arterial uterine Doppler ultrasound examination at the second trimester delivered uneventfully. There was only one premature delivery due to PROM in an SLE patient. The mean gestational age at delivery was 39 weeks, the mean birth weight was 3200 g and the mean APGAR scores at 5 and 10 min were, respectively, 9 and 10.

Although literature data addressing the role of uterine artery Doppler screening as predictor of poor outcome are contradictory [2–7], in agreement with Le Thi Huong *et al*.'s [1] result, our study confirms how pregnancy outcome of patients with abnormal uterine waves is worse when compared with a woman with normal Doppler. In fact, abnormal Doppler velocimetry was related to an increased prevalence of PROM, IUGR, maternal and perinatal complications (low birth weight and low APGAR score). Not surprisingly, due to the important role of vascular damage, apart from APS and SLE patients, Scl and BD patients were at very high risk as well.

In contrast to Le Thi Huong *et al*. [1] data and probably due to the lower number of patients examined, Doppler abnormalities were not associated with an increased rate of neonatal or fetal death.

In conclusion, it is our opinion that Doppler velocimetry should be considered as a reliable and useful tool to identify SLE and other CTD patients at higher risk in order to start a proper therapy.

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Successful treatment with leflunomide of arthritis in systemic sclerosis patients

Sir, Systemic sclerosis (SSc) is a connective tissue disease clinically characterized by different degrees of skin fibrosis and visceral organ involvement [1]. Joint involvement with severe synovitis during SSc is relatively uncommon. About 11% of SSc patients present with arthritis at disease onset [2], usually characterized by mono-oligoarthritis, responsive to steroid therapy [3].

In some patients, arthritis is more aggressive; it can become erosive, simulating classical rheumatoid arthritis [1, 2]. Since leflunomide has been usefully employed in rheumatoid arthritis and other autoimmune systemic diseases [4–6], we undertook a preliminary investigation of the efficacy of this drug in patients with SSc complicated by active arthritis.

Three women with SSc, classified according to preliminary ACR criteria [7], were treated with leflunomide at the standard dosage of 20 mg/day (Table 1). In all patients arthritis had been unresponsive to other therapeutic attempts, including steroids, methotrexate, cyclosporin A and D-penicillamine. In two patients (cases 1 and 3) the articular involvement was asymmetrical and non-erosive, whereas the third (case 2) showed symmetrical and erosive polyarthritis with the presence of serum rheumatoid factor. This patient may be better classified as SSc/rheumatoid arthritis overlap syndrome. In no case was renal and/or hepatic involvement observed before or after the treatment. Leflunomide was well tolerated in all cases; only one patient developed moderate diarrhoea, which disappeared with the reduction of the leflunomide dosage to 20 mg every other day, without any relapse of arthritis. After few weeks of treatment, we observed resolution in cases 1 and 2 and a significant improvement in articular involvement in case 3, with normalization of inflammatory parameters; these variations remained stable after 1 yr of follow-up (Table 1).

No significant modifications were observed for skin and visceral organ involvement in two of the three patients. Only one showed a reduction in the modified Rodnan skin score (from 25 to 14 after 1 yr of treatment) and a mild increase in lung carbon monoxide diffusion capacity (case 3).

Besides rheumatoid arthritis, leflunomide has been reported to be useful in some autoimmune diseases, such as systemic lupus erythematosus, Sjögren's syndrome and Wegener's granulomatosis [4–6]. Leflunomide is an isoxazole derivative with immunomodulating activity; it inhibits T-activated lymphocyte replication and reduces some cytokines, particularly IL-2 and TNF-α, that are probably involved in the early stages of scleroderma [8–10]. Many studies suggest that lymphocytes and cytokines play an important role in the pathogenesis of SSc; in particular, high levels of IL-2 and/or IL-2 receptor are observed in the early stages of the disease [9, 10]. According to its pharmacological activity, leflunomide could be usefully employed in SSc, particularly in patients with severe articular involvement.

In our patients, leflunomide was able to improve SSc-associated arthritis; it was well tolerated and in one case its efficacy persisted despite dosage tapering. Moreover, other SSc organ involvement remained stable in two cases, while skin sclerosis improved in the other one. On the whole, these data suggest the possible use of this drug in the SSc. This is the first study focusing on leflunomide in the treatment of SSc-associated arthritis; its actual efficacy should be ascertained in controlled trials including larger patient populations.

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