values were significantly higher in the female subjects with osteophytes compared with those without any radiographic changes ($P = 0.05$, by Mann–Whitney $U$-test). More detailed analysis revealed that only TF osteophytes influence S-COMP levels. No correlation was found when the diagnosis was based solely on JSN. Our results are in accordance with the findings of Sharif et al. [3] that S-COMP is higher in men and in the case of TFOA. Our results, which are based on the subjects about 20 yrs younger than those in the material by Sharif et al., indicate that in some women, at least in early stage OA, the appearance of osteophytes involves increased S-COMP levels. Investigating subjects of the same age range as those in our study, Boegard et al. [7] found that TF osteophytes might be important signs of cartilage defects detectable by MRI. Therefore, being the expression of chondroneogenesis [8], osteophytes could be accompanied by cartilage damage not yet visible on plain radiographs. The possible link between S-COMP levels and osteophytes needs further investigation.

Also, the gender differences in COMP levels, which have not been taken account in the majority of studies, definitely require more attention. Up to now conflicting results have been published concerning gender differences [3, 9]. Nevertheless, both groups have stressed a significant increase in serum COMP levels at the age >65 yrs, especially in women. At present, we cannot exclude gender specific differences in development of early knee OA.

Our findings, based on the correlations between S-COMP levels and changes in the soft tissues confirm the standpoint that COMP is a more general marker of the joint tissues which might explain the finding that only S-COMP levels differentiated between the TF and PF OA groups, unlike other cartilage biomarkers (GAG, KS, YKL-40) [3]. Compared with other biomarkers, S-COMP might reflect better the changes in the joint as COMP consists of the contributions of different articular tissues.

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**Table 1. Comparison of S-COMP levels between the groups with and without radiographic and sonographic findings**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female With lesions</th>
<th>Female Without lesions</th>
<th>Male With lesions</th>
<th>Male Without lesions</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF osteophytes (by X-ray)</td>
<td>10.7</td>
<td>9.5</td>
<td>12.4</td>
<td>12.0</td>
<td>0.029</td>
</tr>
<tr>
<td>PF osteophytes (by X-ray)</td>
<td>9.8</td>
<td>9.8</td>
<td>11.9</td>
<td>12.2</td>
<td>0.343</td>
</tr>
<tr>
<td>Tibial osteophytes (by US)</td>
<td>12.8</td>
<td>9.7</td>
<td>13.0</td>
<td>11.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Femoral osteophytes (by US)</td>
<td>12.4</td>
<td>9.7</td>
<td>12.3</td>
<td>11.7</td>
<td>0.019</td>
</tr>
<tr>
<td>Meniscal changes (left, by US)</td>
<td>12.8</td>
<td>9.7</td>
<td>14.6</td>
<td>11.6</td>
<td>0.043</td>
</tr>
<tr>
<td>Meniscal changes (right, by US)</td>
<td>10.1</td>
<td>9.8</td>
<td>11.2</td>
<td>11.8</td>
<td>0.446</td>
</tr>
<tr>
<td>TF OA n = 40/18</td>
<td>10.2</td>
<td>9.3</td>
<td>12.4</td>
<td>12.0</td>
<td>0.045</td>
</tr>
<tr>
<td>PF OA n = 50/29a</td>
<td>9.8</td>
<td>9.8</td>
<td>12.0</td>
<td>12.2</td>
<td>0.551</td>
</tr>
</tbody>
</table>

Differences between groups by Mann–Whitney U-test. US, ultrasonography; F, female; M, male. Bold font style represents statistically significant difference between groups, $P < 0.05$.

Value for S-COMP levels are expressed in U/l.

*The number of females/males with lesions.

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**Herbal medicine** containing hidden prescription drugs

Sir, Patients may turn to herbal remedies if conventional treatment is perceived to have failed or causes an unwanted reaction. True herbal treatments can interact with standard medication but outcome may be dangerously unpredictable when ‘herbal’ treatments conceal prescription drugs with the potential to cause adverse effects or interact with medically
prescribed and over-the-counter products. Reactions may then be incorrectly attributed to prescribed drugs. We present three cases to highlight this problem.

Case 1

A Pakistani lady developed rheumatoid arthritis (RA) in 1993 at the age of 23, soon after coming to the UK. She was treated with anti-inflammatory drugs until referred to hospital in 1995, when sulphasalazine was added. In Autumn 1996, she started to take ‘herbal powders’, sent by her family in Karachi, when the joint pain worsened. However, despite routinely being asked about medication, she did not mention this at hospital visits until July 1997, when progressive synovitis led to discussion about alternatives to sulphasalazine. By then, she had been taking the ‘herbal’ powder daily in variable amounts mixed with food.

Figure 1 shows how the powder was normally supplied wrapped in newspaper, whose print suggests Chinese origin. Analysis showed it to contain phenylbutazone with no evidence of other active agent or heavy metal.

She was advised to stop taking the powder and started methotrexate in September 1997 with good response until July 2002, when taking 15 mg/week with folic acid, prednisolone 5 mg/day and occasional naproxen. Synovitis then progressed, and she mentioned that her family had again sent herbal medicine, this time in the form of powder and tablets (Fig. 2). She admitted to have stopped methotrexate for a month and had been taking this ‘herbal’ treatment alone with good effect. Analysis showed that the light brown pellets contained paracetamol, ibuprofen, indomethacin and diazepam. The others were inert and no heavy metals were present. Advice was again given about the dangers of unknown ‘herbal’ treatment.

Case 2

An Indian lady developed RA in 2001 at the age of 25, and started treatment with sulphasalazine and low-dose prednisolone. After 2 yrs, she was well and prednisolone was withdrawn. She then admitted to taking sulphasalazine only intermittently and was keen to stop altogether. There was no synovitis, and the erythrocyte sedimentation rate and C-reactive protein were normal. Gradual dose reduction was planned but she was lost to follow-up.

On return in late 2004, she had recurrent synovitis and had restarted both prednisolone and sulphasalazine with little beneficial effect. Alternatives were discussed and only then did she mention the ‘herbal’ powder sent by her mother from India over the previous year (Fig. 3). She was taking one teaspoon twice a day with benefit. She commented on weight gain and appeared cushingoid, compared with the previous year. We thus suspected that the powder contained a corticosteroid, and analysis showed the presence of prednisolone, diclofenac and paracetamol; there were no heavy metals.

Case 3

This 30-yr-old Indian lady moved to the UK in January 2005 and gave a 4-yr history of joint pain and swelling. She was found to have seronegative erosive RA. She was expecting to conceive, and therefore, disease-modifying anti-rheumatic drugs were avoided and arthritis was controlled with low-dose prednisolone. She mentioned that she had also been taking a ‘herbal’ powder from India for many years and had found it helpful.

A sample was sent for analysis, and she was advised to stop taking the powder pending the results as the content was unknown and was potentially harmful when planning to conceive. Analysis showed the powder to contain phenylbutazone and diclofenac with traces of prednisolone and paracetamol. No heavy metals were present.

She was last seen in September 2005, when taking prednisolone 7.5 mg daily and still three doses per week of the powder.

Analysis for pharmaceuticals (600 compounds) was performed in all cases by the dissolution of the material in methanol followed by high-performance liquid chromatography coupled...
with diode-array detection. Separate investigation for ‘heavy metals’ (53 elements) was carried out by inductively coupled plasma mass spectrometry following digestion in nitric acid.

Discussion

How often ‘herbal’ compounds which conceal active ingredients are used in the UK is unknown, but we have no reason to believe that these cases are unique. The powders and tablets described here were purchased openly by relatives, and our patients believed that because the treatments had been branded ‘herbal’, they were benign and could be taken with prescribed drugs. For the same reason, they also felt they did not need to mention them at hospital visits or to GPs, who were also unaware. Patients may also not tell physicians about alternative treatments for the fear of a negative reaction.

Fortunately, none of our patients came to harm, but doctors and pharmacists should be aware that even true herbal treatments may not be benign. They may interact with conventional drugs [1], and cause hepatotoxicity [2]. In our patients, adverse reactions could have occurred due to the prescription drugs hidden in their ‘herbal’ mixtures, for example renal impairment or peptic ulceration with indomethacin or diclofenac, and marrow aplasia with phenylbutazone. As importantly, the hidden anti-inflammatory drugs could reduce renal clearance and increase toxicity of prescribed drugs such as methotrexate. Two of our patients also took occasional over-the-counter paracetamol and ibuprofen as well as these ‘herbal’ treatments containing the same or similar compounds which could result in overdose.

Gertner et al. [3] described five patients with arthritis taking ‘herbal’ remedies, all of which were found to contain mefenamic acid and diazepam. In these cases, serious complications did arise including massive gastrointestinal bleeding and benzodiazepine toxicity. A recent article also urged caution after ‘natural dietary acid’ and diazepam. In these cases, serious complications did arise.

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Gertner et al. [3] described five patients with arthritis taking ‘herbal’ remedies, all of which were found to contain mefenamic acid and diazepam. In these cases, serious complications did arise including massive gastrointestinal bleeding and benzodiazepine toxicity. A recent article also urged caution after ‘natural dietary supplements’ purchased over the Internet for treatment of erectile dysfunction were found to contain concealed phosphodiesterase inhibitors that are potentially harmful to patients also taking nitrates [4].

We have no way of knowing whether relative quantities of each drug varied from batch to batch or if true herbal compounds were also present, but this is the first time to our knowledge that herbal remedies have been shown to contain the mixtures of the prescribed medication we identified. There is an urgent need for the development of pharmacovigilance for ‘herbal’ medicines [5], and shops selling these should be regulated in a similar fashion to those dispensing recognized pharmaceutical products [6]. Methods are available for the analysis of adulterants in herbal medicine [7] and should routinely include tests for heavy metal contaminants, not found in our cases but they are regular constituents of Indian [8] and Chinese [9] remedies. Public awareness could be increased by posters in the waiting areas of clinics. Drug information leaflets, such as those produced by the Arthritis Research Campaign, could also useful carry a warning of the possible interactions between prescribed drugs and true or adulterated herbal treatments as well as with ‘over-the-counter’ remedies. Clinicians need to be vigilant, and should routinely enquire about ‘herbal’ treatments when taking a medical history [10].

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Adalimumab-associated pulmonary fibrosis

Sir, A small number of reports have implicated infliximab as an aetiological factor in the development of lung inflammation and fibrosis in patients with rheumatoid arthritis [1–5]. Etanercept has also been suggested to have been the cause of acute lung injury in one case in which non-caseating granulomas and birefringent particulate material were identified in transbronchial biopsy specimens [6]. Anti-tumour necrosis factor (TNF)-α drugs are being used with increasing frequency in the treatment of severe resistant rheumatoid arthritis. Current practice in most units is to perform a chest radiograph prior to commencing TNF blockade, primarily to rule out tuberculosis [7].

We report the case of an otherwise well 76-yr-old female patient with severe rheumatoid arthritis who was being treated with adalimumab and methotrexate. She had never smoked. Seropositive rheumatoid arthritis was diagnosed in 2003 and treatment with methotrexate was commenced within 6 months of diagnosis. She was tolerating a weekly dose of 22.5 mg of methotrexate, along with sulphasalazine 1G b.d. and hydroxychloroquine 200 mg o.d., but was still experiencing articular symptoms. In 2005, it was decided to commence adalimumab instead of sulphasalazine and hydroxychloroquine, whilst continuing methotrexate. A chest radiograph was performed prior to starting adalimumab and was reported as entirely normal. She had no respiratory symptoms.

Initially there was a marked symptomatic improvement in her arthritis. However, within 10 weeks of starting adalimumab, she developed progressive shortness of breath on exertion. She was treated initially by her primary care physician for pulmonary oedema and a chest infection with no improvement and an echocardiogram showed good left ventricular function. Two weeks after the onset of shortness of breath, she deteriorated and became dyspnoeic at rest and was admitted to the hospital, requiring high-flow oxygen. Clinically, there were signs of pulmonary fibrosis. A high resolution CT scan of the lungs showed extensive confluent reticular and honeycomb shadowing in a basal and posterior distribution (Figs 1 and 2). Lung function tests showed a carbon monoxide transfer factor (TLco) which was 30% of that predicted. Bronchoscopy was performed and the lavage showed a mixed infiltrate of alveolar macrophages with some lymphocytes and neutrophils. Culture for tuberculosis and analysis for Pneumocystis jiroveci and viruses were negative. Methotrexate and adalimumab were both discontinued and the patient was treated with oral prednisolone following which there was some improvement and she was discharged to receive home oxygen therapy.

She was reviewed in clinic after a month and, in view of a further deterioration, it was decided to commence treatment with pulsed intravenous cyclophosphamide. However, prior to starting this treatment, she was readmitted to hospital with a mild intercurrent chest infection and unfortunately, because of her very poor respiratory reserve, the infection proved fatal.

As far as we are aware, pulmonary fibrosis has not been reported previously in association with treatment with adalimumab. In this case, there are similarities with those which appear to link lung injury with infliximab treatment. While a cause and effect relationship cannot be proved, this case suggests that caution should be exercised with all of the anti-TNF drugs when treating rheumatoid patients who have pre-existing lung disease. Continuing vigilance is necessary as our experience in using these agents grows.

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