Letters to the Editor

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Clinical improvement with infliximab in a child with amyloidosis secondary to familial Mediterranean fever

Sir, The most serious and fatal complication of familial Mediterranean fever (FMF) is amyloid A (AA) amyloidosis, usually affecting the kidneys, resulting in renal insufficiency progressing to end-stage renal disease. Amyloidosis may also affect the gastrointestinal tract, liver, spleen and other organs. Here, we present a case of FMF complicated by protracted arthritis, severe renal and gastrointestinal amyloidosis in which treatment with infliximab is associated with the clinical improvement of amyloidosis, in addition to complete resolution of protracted arthritis.

A 12-yr-old girl was admitted to the hospital with bloody diarrhea, vomiting, nephrotic syndrome, intermittent bilateral knee pain and swelling. Past medical history revealed recurrent attacks of abdominal pain and fever since the age of five. From 8 yrs of age, she had been suffering from recurrent arthritic attacks of the knees and ankles accompanied with fever and had been treated with antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and methotrexate with the presumed diagnosis of septic arthritis, acute rheumatic fever (ARF) and juvenile rheumatoid arthritis (JRA). She had worsened despite these therapies; 1 yr before her first admission, Mediterranean fever mutation test showed compound heterozygous for M694V/M680I mutations and colchicine therapy was started. However, she had discontinued the drug because of vomiting and diarrhea. Swelling of the lower extremities and face developed 3 months before her first admission. She was the second child of first degree cousins and she had no family history of FMF. On admission, she had pallor, oedema, marked ascites and protracted arthritis of the knees. Her height and weight values were below the third percentile for age and sex. She couldn’t walk. She had mild anemia, massive proteinuria and severe hypoalbuminaemia. Acute phase reactants were elevated, renal function tests and other biochemical parameters were normal. Renal, rectal and duodenal biopsies revealed AA amyloidosis confirmed by Congo red stain and by immunohistochemical staining. Colchicine 2 mg/day was restarted and naproxen therapy was commenced. However, she experienced no improvement in symptoms. She had no appetite and experienced a weight loss of 4 kg in a month because of recurrent abdominal pain, vomiting, diarrhea and associated fever. The requirements of hospitalization and albumin infusions increased. In November 2003, a trial of infliximab 3 mg/kg was initiated at 0, 2 and 6 weeks and then every 8 weeks. By the fifth dose of infliximab, the patient felt dramatically better (Table 1). Diarrhoea and arthritis improved significantly during the following months. She did not receive any albumin infusions after the onset of infliximab therapy. The patient was able to return to school after 2 yrs of disability secondary to arthritis and diarrhoea. After 22 months of therapy, gastrointestinal complaints resolved completely and protracted arthritis improved. She could walk and even run without any difficulty. In addition to these clinical findings laboratory markers improved markedly (Table 1).

Amyloidosis, the potentially lethal complication of FMF, is known to be prevented by effective dose regular colchicine therapy. However, it was unfortunately shown that the patients with severe nephrotic syndrome will progress to chronic renal failure, in spite of colchicine treatment [1,2]. There is still no alternative therapy to prevent this progression.

There have recently been several reports that anti-tumour necrosis factor (TNF) agents may affect amyloidosis in familial auto-inflammatory disease such as tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and other chronic inflammatory diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis [3-7]. Drew et al [3,4] reported clinical efficacy of etanercept in three patients with TRAPS and AA amyloidosis in two different reports. Elkayam et al [5] described a case of RA complicated by renal amyloidosis in which treatment with infliximab was associated with complete resolution of proteinuria and stabilization of amyloid deposits in 2002. Two preliminary studies from France and Spain indicated that anti-TNF therapy might be useful in amyloidosis secondary to inflammatory arthropathies [6, 7]. In addition, two recent reports have shown that anti-TNF therapies were used successfully in the patients with FMF and chronic arthritis [8,9]. Finally, Metyas et al [10] described the resolution of amyloidoid-related arthritis and an improvement of renal involvement in a patient with amyloidosis secondary to FMF with anti-TNF therapy. Our patient had amyloid deposition on biopsies obtained from gastrointestinal tract and kidney. Infliximab was started for protracted arthritis. While protracted arthritis resolved completely, her gastrointestinal symptoms due to

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Colchicine</th>
<th>2003 September</th>
<th>2003 October</th>
<th>Colchicine plus infliximab</th>
<th>2004 June</th>
<th>2005 October</th>
<th>2006 February</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>26.5</td>
<td>22.5</td>
<td>22.5</td>
<td>29</td>
<td>33</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9.1</td>
<td>8.3</td>
<td>8.3</td>
<td>10</td>
<td>11</td>
<td>11.5</td>
<td>11.5</td>
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<tr>
<td>ESR (mm/h)</td>
<td>113</td>
<td>118</td>
<td>118</td>
<td>77</td>
<td>11</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>2.4</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>39</td>
<td>44</td>
<td>44</td>
<td>50</td>
<td>40</td>
<td>43</td>
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</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>1</td>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>1.1</td>
<td>0.8</td>
<td>0.8</td>
<td>1.8</td>
<td>2.9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>T Protein (g/dl)</td>
<td>4</td>
<td>3.9</td>
<td>3.9</td>
<td>4.3</td>
<td>5.4</td>
<td>5.8</td>
<td>5.8</td>
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<td>T Cholesterol (mg/dl)</td>
<td>489</td>
<td>510</td>
<td>510</td>
<td>200</td>
<td>130</td>
<td>115</td>
<td>115</td>
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<tr>
<td>Proteinuria (mg/m²/h)</td>
<td>407</td>
<td>436</td>
<td>436</td>
<td>200</td>
<td>40</td>
<td>45</td>
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amyloidosis disappeared. Moreover, her proteinuria decreased and the requirement of albumin infusion therapy disappeared. Her quality of life clearly improved after the use of infliximab treatment.

Although the results of our patient yield a promising role of infliximab treatment in FMF-associated amyloidosis, further clinical studies are necessary to elucidate the long-term safety and efficacy of this treatment.

The authors have declared no conflicts of interest.

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Associations between cartilage oligomeric matrix protein and several articular tissues in early knee joint osteoarthritis

Sir. Knee osteoarthritis (OA) involves different joint tissues. Nevertheless, main focus has been placed on the changes in articular cartilage. Therefore, components of the cartilage have been studied thoroughly as progression markers for early stage OA [1, 2]. Recently, with the help of the whole panel of cartilage biomarkers, Sharif et al. [3] found that only serum cartilage oligomeric matrix protein (S-COMP) levels differentiated between the subsets of tibiofemoral (TF) and patellofemoral (PF) OA, being higher in the former subset.

However, it is not clear which structural changes are related to high levels of biomarkers in knee OA. S-COMP is not an entirely cartilage-specific macromolecule but is also found in tendons, ligaments, menisci and synovium [4]. Usually, the radiographic diagnosis of OA is a combination of joint space narrowing (JSN) and/or presence of osteophytes. To the best of our knowledge, the relationship between S-COMP and the above mentioned features of OA have not been investigated separately. We made an attempt to investigate what kind of knee-joint structures might be associated with increased levels of S-COMP in subjects with early knee OA.

A population-based cohort of 158 subjects, aged 32–55 (mean 45) yrs, with chronic knee pain (>3 months) and/or other knee joint limitations was examined clinically and radiologically. The study was approved by the Ethical Committee of Human Research, Tartu University. From each subject written, informed consent for participation was obtained according to the Declaration of Helsinki. Among them, 99 (63%) were women and 59 (37%) were men. Serum levels of COMP were measured by ELISA (AnaMar Medical, Uppsala, Sweden).

The radiographs from both knee joints were performed in a standing frontal antero-posterior position for the assessment of the TF joints and in a lying position, with the knee joint in 60° flexion, for PF joints. The radiographs were graded independently by two radiologists for osteoarthritic changes (presence of JSN and/or osteophytes) according to the grading system (grades 0–III) of Nagaosa et al. [5].

Fifty-five (34%) individuals in the study group had knee-joint symptoms but no radiographic findings, 85 (53%) were diagnosed with knee OA grade I, among them 20 with only tibiofemoral OA, 35 with only patellofemoral OA and 30 had both knee joint compartments affected in combination. Twenty-one subjects (13%) had OA grade II or III, predominantly in the PF region. Radiographic findings of osteophytes and JSN were distributed in the OA group as follows: one-third had only osteophytes, another third had only JSN and the rest had both simultaneously.

The knees were examined ultrasonographically using a multi-frequency linear 7.5 MHz probe. The presence of osteophytes, thickness of tendons, PF cartilage, meniscal changes and synovial effusion was assessed according to the EULAR guidelines [6] and graded in 0/1 scale.

For statistical evaluations non-parametric methods (Spearman’s rank correlations, Mann–Whitney U-test) were used. P-values < 0.05 were considered significant.

S-COMP median values for male and female subjects were 12.0 and 9.8 U/l, respectively, P = 0.0001. Data demonstrated obvious gender differences with regard to associations between the S-COMP levels and the other parameters (Table 1). S-COMP values correlated with age only in female subjects (r = 0.284, P = 0.004). Additional investigations showed that the S-COMP