Some reports noted an anti-CCP serum level reduction after the introduction of DMARDs, with a titre that however did not decrease under positive threshold [10].

Almost all authors considered the option of a possible overlap disease with RA. Despite that it cannot be confirmed whether anti-CCP antibodies have any pathogenic role in PsA; based on analysis of results of those and previous reports, we may consider that their presence seems predominantly related with a symmetric polyarticular pattern with erosive evolution.

Rheumatology key message

- Anti-CCP showed a low prevalence in PsA, mostly related with symmetric polyarticular pattern.

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Letters to the Editor

Pericardial effusions on anti-TNF therapy for rheumatoid arthritis—a drug side effect or uncontrolled systemic disease?

Sir, A 48-yr-old male diagnosed with seropositive erosive RA in 1993 was first treated with SSZ, and then MTX. He developed extra-articular features including rheumatoid nodules (1997), acute pericarditis (1998), bilateral pleural effusions (1999), sensory peripheral neuropathy (2005), and in 2006 pyoderma gangrenosum (PG), whilst taking oral MTX 15 mg/week, HCQ 400 mg/day and prednisolone 7.5 mg/day. Treatment was escalated to subcutaneous MTX 20 mg/week, HCQ 400 mg/day, prednisolone 50 mg/day and topical tacrolimus, but ulcers on both lower limbs failed to heal and he developed digital vasculitis and livedo reticularis.

Tests demonstrated a leucocytosis (13.2 × 10⁹/l) with normal inflammatory markers. Immunology showed ANA weak positive, pANCA positive (anti-MPO negative), anti-cyclic citrullinated peptide (CCP) positive. Chest X-ray showed chronic pleural thickening with normal heart size. DAS28 score was 2.72 but clinical opinion from peer group rheumatologists and dermatologist was that anti-TNF therapy was appropriate treatment for the PG. He commenced pulsed i.v. infliximab 3 mg/kg (250 mg) but his second dose was omitted as he developed Gram-negative cellulitis at the site of PG ulcers.

On week 4, 1 day after second dose of infliximab, he was admitted with a 2-week history of increasing breathlessness on exertion: echocardiography showed large circumferential pericardial effusion (3 cm posterior, 1.7 cm anterior) with right ventricular diastolic collapse and he was transferred to a cardiac surgery centre. A pericardial drain was inserted, which drained 800 ml of blood-stained fluid. Cytology and culture of the fluid were negative; it was therefore felt to be a reactive effusion. Prednisolone was increased to 60 mg daily, continuing MTX and HCQ.

In spite of this, the effusion reaccumulated on two further occasions, each time necessitating insertion of a drain, and then formation of a pericardial window. Following these surgical procedures he was commenced on 3 months of pulsed i.v. cyclophosphamide 500 mg fortnightly, and reducing doses of prednisolone. He was then recommenced on MTX 15 mg weekly together with ciclosporin 50 mg b.d. His ulcers healed and arthritis remained well controlled with no further pericardial effusions. Prednisolone was reduced to 10 mg within 6 months when tests showed normocytic anaemia (Hb 11.9 g/dl, MCV 84.0 fl), normal inflammatory markers (ESR 3, CRP 3), DAS28 2.94 and repeat ANA negative.

Following the index case, the BSR Biologics Register was searched for patients with RA who had developed pericardial effusions whilst on anti-TNF therapy. The consultants involved were individually contacted and a total of seven further cases were identified in which significant pericardial disease had occurred. The details of these cases are displayed in Table 1.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Disease duration</th>
<th>Exposed to TNF inhibitor</th>
<th>Duration of exposure</th>
<th>Onset of effusion</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>15 yrs</td>
<td>ETN</td>
<td>12 mos</td>
<td>Week 4</td>
<td>PTI</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>20 yrs</td>
<td>MTX + ETN</td>
<td>18 mos</td>
<td>Week 2</td>
<td>PTI</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>M</td>
<td>10 yrs</td>
<td>MTX + ETN</td>
<td>6 mos</td>
<td>Week 1</td>
<td>PTI, PG</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>5 yrs</td>
<td>MTX + ETN</td>
<td>9 mos</td>
<td>Week 3</td>
<td>PTI, PG</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>15 yrs</td>
<td>MTX + ETN</td>
<td>12 mos</td>
<td>Week 5</td>
<td>PTI, PG</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>F</td>
<td>20 yrs</td>
<td>MTX + ETN</td>
<td>18 mos</td>
<td>Week 4</td>
<td>PTI, PG</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>M</td>
<td>10 yrs</td>
<td>MTX + ETN</td>
<td>12 mos</td>
<td>Week 1</td>
<td>PTI, PG</td>
</tr>
</tbody>
</table>

All patients in the series had seropositive erosive RA. Their pericardial effusions frequently occurred within the first 4 months, as in our case, with one case each at 7, 12 and 13 months of therapy. There were two males and five females, average age 64.6 yrs, mean length of disease 20.3 yrs. Five patients needed surgical intervention for effusions with or without tamponade. One patient was continued on anti-TNF therapy and in four it was re-started at a later date after resolution of the acute phase: in two of these, pericarditis or other systemic disease re-occurred.

In the index case, the temporal link between commencing infliximab and the onset of pericardial effusion suggests a causative association, although mild sub-clinical pericardial involvement is common in RA with an incidence of 30% in one post-mortem series [1].

There is growing evidence for the use of biologics in treating systemic features of RA [2] and also PG [3], but these patients are at risk of developing infective complications. Septic pericardial effusions have been reported, one in a distributor of farm equipment who developed peptostreptococcal pericarditis with a purulent effusion on infliximab [4] and also a patient on etanercept with MTX who developed purulent pericarditis due to methicillin-sensitive Staphylococcus aureus [5].

Patients on anti-TNF therapy occasionally develop features of drug-induced lupus [6, 7] and also cutaneous or systemic vasculitis (including scleritis, mononeuritis multiplex and central nervous system vasculitis) [8]. Thirty-five patients on either etanercept or infliximab were reported to the FDA Adverse Event System due to skin lesions typical of leucocytoclastic vasculitis [9]. Other systemic symptoms were common and one patient had pericarditis. Of these, 22 improved after stopping anti-TNF therapy: six of nine relapsed on re-challenge.
A non-infective pericardial effusion could be due to a paradoxical flare of systemic rheumatoid secondary to anti-TNF therapy. Amongst 107 patients treated with infliximab, a flare of systemic features was found in three cases manifesting as polyarthritis, fever and raised acute-phase reactants although none with significant pericardial disease [10].

Thus, patients on anti-TNF may develop infective pericarditis, cutaneous vasculitis and drug-induced lupus. Although in the index case the pericarditis seemed to have been provoked by the biologic therapy, it seems most likely that this occurred due to inadequate control of systemic disease, or a flare of extra-articular rheumatoid disease. Caution should be exercised in seropositive RA patients with prior pericarditis and a baseline echo as well as chest X-ray should be requested. Cyclophosphamide and rituximab should be seen as possible alternatives in these patients.

**Rheumatology key message**

- Caution needed using anti-TNF in RA patients with previous pericarditis.

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