Peripheral inflammatory arthritis in patients with chronic periaortitis: report of five cases and review of the literature

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Objectives. Chronic periaortitis (CP) is a rare disease with a potentially immune-mediated pathogenesis. The study aims to report the frequency and the clinical characteristics of peripheral inflammatory arthritis in a cohort of CP patients, and to review the literature regarding the association between arthritis and CP.

Methods. Forty-nine consecutive CP patients were seen at our department between 2000 and 2006; all of them underwent imaging (abdominal computed tomography and magnetic resonance imaging) and laboratory examinations, also including erythrocyte sedimentation rate, C-reactive protein and a panel of autoantibodies. The clinical history of the patients who developed peripheral inflammatory arthritis is reported in detail. A PubMed/Medline search without any date limits was performed for English-language articles reporting the association between CP and arthritis.

Results. Five of the 49 enrolled patients developed an inflammatory form of peripheral arthritis: three were diagnosed as having RA, one palindromic rheumatism and one acute reactive arthritis. In all but one case, arthritis became clinically overt months to years after the onset of CP, and its outcome was good, since almost all patients were asymptomatic at the end of follow-up. No patient suffered from ankylosing spondylitis. In the literature review, 20 cases of CP-associated arthritis were found, mainly in the form of case reports: 14 of them were spondyloarthropathies, whereas the remaining ones were RA, juvenile RA or undifferentiated arthritis.

Conclusions. Peripheral inflammatory arthritis, particularly RA or RA-like forms, may develop in CP patients. This overlap strengthens the hypothesis of an autoimmune origin of CP.

KEY WORDS: Retroperitoneal fibrosis, Inflammatory aneurysms, Rheumatoid arthritis, Autoimmunity, Antinuclear antibodies, Rheumatoid factor.

Introduction

Chronic periaortitis (CP) encompasses a group of rare diseases, whose common denominator is a retroperitoneal periaortic fibro-inflammatory tissue that frequently obstructs neighbouring structures [1, 2]. Histology shows a collagen-rich background and fibroblasts admixed with an inflammatory infiltrate consisting of lymphocytes, plasma-cells, macrophages and eosinophils [1, 3]. CP includes non-aneurysmal [i.e. idiopathic retroperitoneal fibrosis, (IRF)] and aneurysmal forms [i.e. inflammatory abdominal aortic aneurysm (IAAA), periaortic inflammatory retroperitoneal fibrosis] [2]. In some cases, it also involves the thoracic aorta, leading to mediastinal fibrosis [4].

CP frequently arises in patients with atherosclerosis. Antibodies to atherosclerotic plaque antigens (e.g. oxidized-low density lipoproteins and ceroid) are detectable at higher titres in CP patients than in controls, and adventitial lipid-laden macrophages are found in CP aortic specimens [1, 5], which is why CP was thought to be due to an inflammatory reaction to atherosclerosis. However, it may also occur in patients without evidence of atherosclerosis, and a number of findings such as the association with HLA-DRB1*03, the presence of systemic symptoms and the overlap with other autoimmune diseases, suggest that it may be driven by a systemic autoimmune process [4, 6, 7].

Several reports have described the association between CP and spondyloarthritis [8], whereas other types of arthritis appear to be exceedingly rare [9]. Here we report five cases of CP-associated peripheral inflammatory arthritis, selected from a cohort of 49 consecutive CP patients, and review the literature concerning the association between CP and arthritis.

Patients and methods

Between 2000 and 2006, 49 consecutive CP patients were seen at our department. CP was diagnosed by means of computed tomography/magnetic resonance imaging (CT/MRI); histological proof was available for 24 patients undergoing surgery for ureterolysis or aneurysmectomy. Each patient underwent laboratory tests including ESR, CRP, RF, ANA, anti-double stranded DNA (dsDNA), anti-extractable nuclear antigen, ANCA and anti-smooth muscle antibodies [7]. Anti-cyclic citrullinated peptide (CCP)-antibodies only became available in our central laboratory in May 2005. None of the patients had secondary forms of CP [4].

All patients initially received prednisone (1 mg/kg/day for the first month) and continued with tapering prednisone, tamoxifen and/or immunosuppressants, according to ongoing protocols. Remission of CP was defined as disappearance of symptoms, normalization of ESR and CRP and resolution of obstructive complications (e.g. hydronephrosis). The median follow-up was 36 months (range 12–117).

CP was associated with inflammatory arthritis in five patients, whose main findings are summarized in Table 1. The ARA-revised criteria [10] were used to diagnose RA.

Literature review

We searched PubMed/Medline without any date limits for English-language articles reporting the association between CP and arthritis and thus used the search terms ‘chronic periaortitis’, ‘retroperitoneal fibrosis’ or ‘inflammatory aortic aneurysm’, matched with ‘arthritis’, ‘spondyloarthropathy’, ‘spondylitis’ or ‘arthropathy’. Table 2 shows the main findings of the cases described in the literature [8, 9, 11–26].
TABLE 1. Main clinical and laboratory features of the five patients with CP-associated inflammatory arthritis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex, age (yrs)a</th>
<th>Type of CP</th>
<th>Type of arthritis</th>
<th>Time CP-arthritis (months)b</th>
<th>RFc</th>
<th>CP treatment</th>
<th>CP outcome</th>
<th>Arthritis treatment</th>
<th>Arthritis symptoms at last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 76</td>
<td>IAAA</td>
<td>Rheumatoid arthritis</td>
<td>+45</td>
<td>Pos.</td>
<td>Aneurysmectomy, PDN, TXF</td>
<td>Remission</td>
<td>PDN+MTX</td>
<td>Absent</td>
</tr>
<tr>
<td>2</td>
<td>F, 54</td>
<td>IAAA</td>
<td>Palindromic rheumatism</td>
<td>+35</td>
<td>Pos.</td>
<td>PDN</td>
<td>Remission</td>
<td>NSAIDs</td>
<td>Absent</td>
</tr>
<tr>
<td>3</td>
<td>M, 52</td>
<td>IRF</td>
<td>Reactive arthritis</td>
<td>+67</td>
<td>Neg.</td>
<td>PDN</td>
<td>Remission</td>
<td>NSAIDs+ antibiotics</td>
<td>Absent</td>
</tr>
<tr>
<td>4</td>
<td>F, 51</td>
<td>IRF</td>
<td>Rheumatoid arthritis</td>
<td>−120</td>
<td>Pos.</td>
<td>PDN (ureterolysis after relapse)</td>
<td>Relapse</td>
<td>MP+ HCO</td>
<td>Improved</td>
</tr>
<tr>
<td>5</td>
<td>F, 63</td>
<td>IRF</td>
<td>Rheumatoid arthritis</td>
<td>+22</td>
<td>Pos.</td>
<td>PDN</td>
<td>Remission</td>
<td>PDN+MTX</td>
<td>Improved</td>
</tr>
</tbody>
</table>

PDN, prednisone; TXF, tamoxifen; MP, methylprednisolone; NA, not available. aAt the time of diagnosis of CP. bTime interval between the diagnoses of CP and arthritis; ‘+’ and ‘−’, respectively indicate that CP preceded or followed the onset of arthritis. cAssessed at onset of arthritis.

TABLE 2. Clinical findings of the cases reported in the English-language literature of chronic periaortitis associated with inflammatory arthritis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex, age (yrs)b</th>
<th>Type of CP</th>
<th>Type of arthritis</th>
<th>Time CP-arthritis (yrs)b</th>
<th>HLA-B27</th>
<th>RF</th>
<th>Arthritis treatment</th>
<th>CP treatment</th>
<th>Arthritis outcome</th>
<th>CP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hisson and Freimanis [12]</td>
<td>M, 64</td>
<td>IRF</td>
<td>SA</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Ureterolysis</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Wackman et al. [13]</td>
<td>F, 7</td>
<td>IRF+MF</td>
<td>JRA</td>
<td>−1</td>
<td>Pos.</td>
<td>NA</td>
<td>NA</td>
<td>Aspirin</td>
<td>Steroids</td>
<td>Stable</td>
</tr>
<tr>
<td>Goldbach et al. [15]</td>
<td>F, 34</td>
<td>MF</td>
<td>SA</td>
<td>0</td>
<td>Pos.</td>
<td>NA</td>
<td>Indomethacin</td>
<td>Ureterolysis</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Solomon and Maurer [16]</td>
<td>M, 51</td>
<td>IRF</td>
<td>SA</td>
<td>−20</td>
<td>Pos.</td>
<td>NA</td>
<td>Steroids</td>
<td>Ureterolysis</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Wicks et al. [17]</td>
<td>F, 72</td>
<td>IRF</td>
<td>SA</td>
<td>0</td>
<td>Neg.</td>
<td>NA</td>
<td>Steroids</td>
<td>Ureterolysis</td>
<td>Steroids</td>
<td>Remission</td>
</tr>
<tr>
<td>Reilly and Moran [18]</td>
<td>M, 64</td>
<td>IRF</td>
<td>SA</td>
<td>−30</td>
<td>NA</td>
<td>NA</td>
<td>Irradiation</td>
<td>Steroids</td>
<td>Remission</td>
<td>Improved</td>
</tr>
<tr>
<td>Delia Ghi and Ghi [19]</td>
<td>F, 63</td>
<td>IRF</td>
<td>SA</td>
<td>−35</td>
<td>Neg.</td>
<td>Neg.</td>
<td>NSAIDs</td>
<td>Ureterolysis</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Tsai et al. [9]</td>
<td>F, 13</td>
<td>IRF</td>
<td>JRA</td>
<td>−10</td>
<td>Neg.</td>
<td>NA</td>
<td>Aspirin</td>
<td>Steroids</td>
<td>Improved</td>
<td>NA</td>
</tr>
<tr>
<td>Boonen et al. [20]</td>
<td>M, 42</td>
<td>IRF+MF</td>
<td>Unclassified</td>
<td>NA</td>
<td>Neg.</td>
<td>NA</td>
<td>NSAIDs</td>
<td>Ureterolysis</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Leblanc et al. [8]</td>
<td>M, 7</td>
<td>IRF</td>
<td>SA</td>
<td>−6</td>
<td>Neg.</td>
<td>NA</td>
<td>Steroids, D-PCM</td>
<td>Ureterolysis</td>
<td>Arthralgia</td>
<td>Remission</td>
</tr>
<tr>
<td>Wendling et al. [21]</td>
<td>M, 66</td>
<td>IAAA</td>
<td>SA</td>
<td>−3</td>
<td>Neg.</td>
<td>NA</td>
<td>MTX</td>
<td>NA</td>
<td>NA</td>
<td>Remission</td>
</tr>
<tr>
<td>Bezza et al. [22]</td>
<td>M, 52</td>
<td>IRF</td>
<td>SA</td>
<td>0</td>
<td>Pos.</td>
<td>NA</td>
<td>NSAIDs</td>
<td>Steroids</td>
<td>Remission</td>
<td>Improved</td>
</tr>
<tr>
<td>Takagi et al. [23]</td>
<td>F, 66</td>
<td>IAAA</td>
<td>SA</td>
<td>0</td>
<td>Pos.</td>
<td>Neg.</td>
<td>NSAIDs</td>
<td>Aneurysmectomy</td>
<td>Remission</td>
<td>Remission</td>
</tr>
<tr>
<td>Haug et al. [24]</td>
<td>NA</td>
<td>IAAA</td>
<td>RA</td>
<td>0</td>
<td>Pos.</td>
<td>NA</td>
<td>NA</td>
<td>NSAIDs</td>
<td>Steroids</td>
<td>NA</td>
</tr>
<tr>
<td>Haug et al. [25]</td>
<td>NA</td>
<td>IAAA</td>
<td>RA</td>
<td>0</td>
<td>Pos.</td>
<td>Pos.</td>
<td>NSAIDs</td>
<td>Steroids</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lemke et al. [26]</td>
<td>M, 61</td>
<td>IRF+ thoracic periaortitis</td>
<td>RA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Remission</td>
<td>Remission</td>
<td></td>
</tr>
</tbody>
</table>

aAt the time of onset of CP. bTime interval between the diagnoses of CP and arthritis; ‘+’ and ‘−’, respectively indicate that CP, respectively, preceded or followed the onset of arthritis. cAssociated with SAPHO syndrome. SA, spondyloarthritis; MF, mediastinal fibrosis; D-PCM, D-penicillamine; NA, not available.

Case reports

Case 1

In October 2000, a 76-yr-old man was admitted to our department because of fatigue and lumbar pain. He had undergone surgery for IAAA, 1 yr earlier. Upon admission, serum creatinine was 1.9 mg/dl, ESR 40 mm/I h, CRP 26 mg/l (normal <5 mg/l) and ANA were positive (titre 1/80). CT demonstrated progressive periaortic fibrosis encasing both ureters with resulting hydro-nephrosis that required ureteral stents. Prednisone therapy led to disease remission within 1 month and creatinine decreased to 1.5 mg/dl. Prednisone was changed to tamoxifen; as CT showed shrinkage of the periaortic tissue, the ureteral stents were removed whereas tamoxifen was withdrawn after 8 months.

The patient returned to our hospital in July 2003, complaining of a 2-month history of symmetric polyarthritis involving the wrists, the metacarpal-phalangeal and the proximal interphalangeal joints, the shoulders and knees. Morning stiffness lasted at least 90 min. Physical examination revealed swelling and tenderness of the involved joints, and bilateral wrist flexor tenosynovitis. X-rays showed periarticular soft tissue swelling and juxta-articular osteoporosis of the proximal interphalangeal joints and carpal bones. ESR was 106 mm/I h, CRP 60 mg/l, and ANA titre 1/320; RF was 31 IU/ml (negative <15 IU/ml). RA was diagnosed, and treatment with methylprednisolone (16 mg/day) and methotrexate (10 mg/week) induced rapid clinical improvement. Steroids were withdrawn 6 months later, and methotrexate continued until July 2005. At the last visit (April 2006), the patient was asymptomatic and no longer taking any drugs.

Case 2

In October 2000, a 54-yr-old woman was admitted to our department because of hypogastric and lumbar pain. ESR was 15 mm/I h and CRP 20 mg/l; ANA (1/160) and anti-smooth muscle antibodies (1/160) were also positive.

CT showed a 4 cm-wide IAAA. Prednisone therapy induced disease remission, and was stopped after 9 months.

In September 2003, the patient reported episodes of arthritis with morning stiffness of about 1 h duration, initially involving the small joints of the hands and subsequently migrating to the elbows and metatarsal-phalangeal joints. The duration of the attacks was 1–2 days, and their frequency fortnightly. ESR and CRP were high, and RF positive (198 IU/ml). A radiogram of the involved joints was normal. Palindromic rheumatism was diagnosed; the patient continued taking NSAIDs during the attacks and no progression to RA was observed during the following 2 yrs.

Case 3

In April 2001, a 58-yr-old man was admitted to our department because of perineal pain and left-sided varicocele. In December 1995, he had received a diagnosis of IRF and had undergone bilateral ureterolysis.
Upon admission, ESR and CRP were high (48 mm/Ih and 41 mg/l, respectively), autoantibodies were negative. Prednisone therapy rapidly led to disease remission, and 1 month later it was changed to tamoxifen. Two months later, the patient presented with acute arthritis involving the left elbow, which was markedly swollen and tender; he also reported self-limiting diarrhoea 3 weeks prior to the arthritis attack. CRP was again high and RF negative. Synovial fluid and stool cultures were negative, but serum antibodies to Salmonella were positive. Although tamoxifen-induced arthritis was also considered, diagnosis of reactive post-infectious arthritis seemed more likely. NSAIDs and amoxicillin plus clavulanic acid induced symptom remission within a few weeks and, 2 months later, no signs of joint inflammation were observed.

Tamoxifen was withdrawn in February 2002. The follow-up continued until May 2005, and no articular manifestations were reported.

Case 4
In April 2001, a 51-yr-old woman was referred to our department because of suspected IRF. RA had been diagnosed based on symmetric polyarthritis involving the metatarsal joints, the small joints of the hands and knees, positive RF and radiographic evidence of bone erosions adjacent to the metatarsal–phalangeal joints, 10 yrs earlier. Good control of arthritis had been achieved with short methylprednisolone courses.

On admission, she was taking no drugs and complained of abdominal pain and fatigue. Abdominal sonography showed left-sided hydronephrosis, and CT disclosed IRF enveloping the left ureter. CRP levels were high (20 mg/l), whereas ESR and serum creatinine were normal; ANA were positive (1/640) and RF high (55 IU/ml). The patient also complained of bilateral knee pain, but physical examination and X-rays were unremarkable.

A ureteral stent led to the resolution of the hydronephrosis, and treatment with prednisone induced IRF remission, which was also demonstrated by CT. The ureteral stent was removed after 6 months of steroid therapy that was continued for another 3 months. Two months after steroid withdrawal, the patient complained of metatarsal and knee pain; physical examination disclosed bilateral knee swelling and stress pain of the metatarsal–phalangeal joints. Treatment with salazopyrin and NSAIDs promptly induced disappearance of arthritis symptoms. In April 2005, the patient spontaneously stopped salazopyrin and, during the following months, reported subcontinuous hip pain.

Case 5
In February 2003, a 63-yr-old woman was admitted to our department because of lumbar and abdominal pain. Serum creatinine was 8.1 mg/dl, ESR 100 mm/Ih and CRP 182 mg/l and ANA were positive (1/320). MRI disclosed IRF with bilateral ureteral involvement, which required stent placement; creatinine normalized (1.1 mg/dl). Prednisone therapy was started and after 4 months MRI showed a shrinkage of the IRF, so the ureteral stents were removed and the patient continued steroid tapering for another 4 months. Steroid withdrawal, however, was followed by enlargement of IRF and relapsing hydronephrosis. Surgical ureterolysis was thus performed and another 8-month prednisone course was administered.

Two months after treatment withdrawal, the patient reported joint pain and swelling symmetrically involving the wrists, the metacarpal–phalangeal and proximal interphalangeal joints. Despite NSAID administration, the pain and swelling progressed to involve both elbows, the left ankle, right knee and shoulder. Laboratory tests demonstrated high ESR (60 mm/Ih), CRP (66 mg/l) and RF levels (81.8 IU/ml) and positive anti-CCP antibodies (50 IU/ml, negative <25 IU/ml). RA was diagnosed; treatment with methylprednisolone (initial dose, 16 mg/day) and hydroxychloroquine (400 mg/day) led to the disappearance of the arthritis symptoms. Five months later, steroids were withdrawn, but left ankle arthritis relapsed and low-dose methylprednisolone was resumed. In December 2006, the patient was asymptomatic.

Discussion
We identified five of 49 consecutive CP patients who also had peripheral inflammatory arthritis: three developed RA, one palindromic rheumatism and one reactive arthritis. In all but one case, the arthritis became clinically overt months to years after CP, although the administration of steroids for CP may have accounted for a delay in its onset. The clinical course of arthritis was benign and quite atypical if compared with classical RA cases, since most patients remained asymptomatic even after treatment withdrawal.

These findings broaden the spectrum of diseases associated with CP, and further support the view that autoimmune mechanisms contribute to its pathogenesis [27] and that it may be a systemic disorder. However, since RA has a prevalence of 1% in the general population, it cannot be statistically excluded that its overlap with CP (8% of our cases) is coincidental.

The review of the English-language literature provided 20 cases—mostly case reports—showing an association between CP and arthritis. Fourteen of these patients had spondyloarthritis, whereas other forms such as RA were extremely rare. Our findings thus challenge the view that spondyloarthritis is the most common arthritis occurring in CP patients; conversely, they show that RA or other entities such as palindromic rheumatism (often considered a smouldering form of RA) are more frequent. Compared with previous reports, our study has the advantage of having screened quite a large population of CP patients for associations with other immune-mediated diseases; in addition, our patients had a long follow-up that allowed detection of overlapping conditions such as arthritis.

Of the 14 reported cases of CP-associated spondyloarthritis, five were HLA-B27-positive [14, 16, 18, 22, 23, 25], which led to the hypothesis that HLA-B27 may be a genetic risk factor for CP [8, 14]. However, in a recent study, we found that HLA-DRB1*03 but not HLA-B27 is associated with an increased susceptibility to CP [6].

The overlap between CP and RA suggests that these two diseases may follow common immune-mediated pathways. RA is an archetypal example of autoimmune disease hallmarkcd by the production of autoantibodies (e.g. RF, ANA and anti-CCP) [28]. Similarly, circulating autoantibodies (e.g. ANA, anti-smooth muscle antibodies) have also been found in CP patients [5–7, 24]. The presence of autoantibodies, the association with HLA-DRB1*03 and the abundance of B cells in the retroperitoneal lesions also indicates that, like in RA, B cells play a major role in CP.

Similarities between CP and RA are also found by examining the composition and architectural organization of the inflammatory infiltrate in the diseased sites. As in RA, the key players of the inflammatory infiltrate in CP lesions are B- and T-cells, plasma cells and macrophages [1, 4, 28]. The topographic distribution of the inflammatory elements shows similar patterns in RA and CP: mononuclear cells may be diffusely distributed within the CP lesions (as in the ‘diffuse’ synovitis) or arranged in aggregates and sometimes show germinal centre reactions, as observed in a subset of RA patients [28–30].

Finally, both RA and CP have a restricted HLA repertoire, although the disease-associated alleles are different (HLA-DRB1*04 and HLA-DRB1*03, respectively) [6, 28].

In conclusion, different forms of peripheral inflammatory arthritis, particularly RA, may occur in CP patients; this reinforces the hypothesis of an autoimmune origin of CP and suggests that the two diseases share common pathophysiological mechanisms.
Rheumatology key messages

- Inflammatory arthritis, particularly RA or RA-like forms, may be part of the spectrum of CP.
- The association with RA supports the hypothesis that CP may have an autoimmune origin.

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References
