Atypical erosive osteoarthritis and Sjögren’s syndrome

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SUMMARY An unusual, destructive form of erosive hand arthropathy is described in five postmenopausal women. Although early clinical and radiological findings were most in keeping with a diagnosis of erosive osteoarthritis (EOA), hand involvement progressed to a distribution intermediate between EOA and rheumatoid arthritis (RA). Although asymptomatic, all patients had features of Sjögren’s syndrome (SS), including keratoconjunctivitis sicca (KCS) and lymphocytic foci in labial biopsy specimens. These cases, which are clinically unlike either RA or EOA, may represent a unique arthropathy associated with sicca features.

Key words: inflammatory osteoarthritis, rheumatoid arthritis.

Erosive inflammatory variants of generalised osteoarthritis have been described by several authors, who emphasise differences between these conditions and rheumatoid arthritis (RA). Sjögren’s syndrome (SS), although well known to be an extra-articular feature of RA, has not been thought to occur in increased frequency in association with osteoarthritis (OA).

We have encountered five women, all with sicca features and two with definite SS, who presented with a destructive arthropathy most consistent with erosive osteoarthritis (EOA). After an interval of several years wrist involvement in three cases and severe proximal interphalangeal joint (PIP) destruction in all raised the possibility of progression to RA. Such atypical cases provoke important questions about the pathogenesis and clinical spectrum of EOA and its relationship to other rheumatic disorders.

Patients and methods

CLINICAL FEATURES
All five patients were seen over an eight year interval in a hospital based rheumatology practice. All were females with a mean age at initial assessment of 68 years. Follow up ranged from one to 10 years, with a mean of six years.

All patients had a history of asymptomatic Heberden’s nodes for several years before presentation and then developed new symptoms in the distal interphalangeal (DIP) joints characterised by marked redness, swelling, pain, and stiffness, followed by similar PIP joint involvement. No other joints were symptomatic initially, and none of the five had constitutional symptoms.

On initial examination all patients showed inflammatory changes of DIPs and PIPs characterised by tenderness and swelling with synovial thickening or effusions, or both (Fig. 1). Bilateral first carpometacarpal (CMC) joint tenderness and squaring developed in all cases. There was a striking lack of metacarpophalangeal (MCP), wrist, and foot involvement. Decreased range of motion, flexion deformities, and horizontal subluxations of interphalangeal joints were universally present, and one case developed ankylosis of multiple PIP joints as well.

After a mean interval of 3.5 years three patients developed extensor carpi ulnaris (ECU) tenosynovitis, and in two of these patients wrist joint involvement with swelling and joint line tenderness occurred. Wrist disease was bilateral in one case and has remained unilateral in the other. One patient developed bilateral hip disease with radiological evidence of superolateral joint space narrowing and went on to total hip replacement. Two patients developed knee disease, one necessitating surgical intervention. The lower limb arthritis in these patients was clinically characteristic of degenerative
rather than inflammatory disease, with minimal postrest stiffness and significant weight bearing discomfort.

Morning stiffness was less than 30 minutes in all cases. None had nodules or other extra-articular manifestations suggestive of RA, with the exception of Sjögren's features. All but one have remained seronegative throughout their course. None of the cases had nail or skin changes compatible with a diagnosis of psoriasis, and there were no acute episodes of joint inflammation suggestive of crystal induced arthritis.

All five patients were treated with non-steroidal anti-inflammatory drugs throughout follow up. In addition, three patients received chloroquine phosphate and one penicillamine.

**Radiographic Features**
The radiographic features of the hands were the most striking and remarkable findings in these patients. Erosions of DIP and PIP joints were characterised by severe central subchondral erosions leading to a 'gull wing' appearance of the joint space. In addition, bony overgrowth and lateral subluxations were dramatic in DIP and PIP joints. On radiological and clinical evaluation the MCP joints were universally spared through follow up.

Hand films of the two most severe cases illustrate the progressive and destructive nature of this arthropathy. In case 1 (Fig. 2a) initial x rays showed changes confined to DIP and PIP joints, with central erosions and crush deformities. Four years later (Fig. 2b) the disease had advanced markedly, with dramatic increase in severity of erosions of interphalangeal joints. This was accompanied by evidence of new cysts and joint space narrowing of radiocarpal and intercarpal joints. Fullness was present clinically and radiographically in the ECU tendons, though the ulnar styloid processes were radiologically spared. Erosive dissolution of the first CMC joints was striking.

Initial radiographs of case 3 again showed striking central IP joint erosions with crush deformity (Fig. 3a), asymmetric radiocarpal and intercarpal joint space narrowing and cysts, advanced first CMC disease, and a 'rheumatoid like' erosion at the tip of the ulnar styloid. Progression of these changes with ultimate fusion of some PIPs is shown in Fig. 3b.

Similar IP erosions were present in the hand radiographs of the other cases, though progression was not as severe. Moreover, wrist joints were hot affected, though one additional case had clinical evidence of ECU tenosynovitis. All patients had joint space narrowing and osteophytosis of the first MTP joints, without accompanying cysts or erosions. There was no evidence of chondrocalcinosis or diffuse idiopathic skeletal hyperostosis.

**Features of Sjögren's Syndrome**
Results of evaluation for SS are shown in Table 1. None of the five patients had sicca symptoms. In case 1 direct questioning elicited complaints of mild dryness of eyes and, once an association was suggested, investigation was carried out in the other cases. All had keratoconjunctivitis sicca on the basis of positive Schirmer's test or rose bengal test, or both. The salivary pool appeared adequate on inspection in all cases, but four of the five had abnormal parotid scans with delayed uptake and excretion patterns compatible with SS. Four patients underwent lip biopsy, which was performed and graded according to the method of Chisholm et al.8 This grading score is based on the degree of lymphocytic infiltration or the number of lymphocytic foci/4 mm² of gland tissue, or both. A focus is defined as an aggregate of >50 lymphocytes, with
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Fig. 2  (a) Radiological appearance of case 1 on initial evaluation. (b) Radiological appearance of case 1 four years later. Note further DIP and PIP destruction and CMC and wrist erosions, with sparing of MCP joints.

the grading system as follows: grade 1 = lymphocytes absent; grade 2 = moderate infiltrate; grade 3 = one focus/4 mm$^2$ tissue; grade 4 = more than one focus/4 mm$^2$ tissue. In all cases neoplasm, labial gland infection, local mucosal trauma, and cytotoxic drug therapy were ruled out. When biopsies were interpreted duct dilatation, extravascular polymorphonuclear leucocytic infiltration, and areas of atrophy adjacent to lymphocytic foci were excluded. When biopsies were interpreted duct dilatation, extravascular polymorphonuclear leucocytic infiltration, and areas of atrophy adjacent to lymphocytic foci were excluded. With this scoring system all four biopsy specimens had at least one lymphocytic focus/4 mm$^2$ tissue, in keeping with the presence of focal lymphocytic sialadenitis (FLS). Two patients had a score of 4, indicating more than one focus/4 mm$^2$. These two cases fulfilled criteria for the diagnosis of definite SS as defined by the presence of two of the following: (a) KCS signified by a positive Schirmer's test or rose bengal test, or both; (b) labial salivary gland biopsy specimen with more than one lymphocytic focus/4 mm$^2$ gland tissue (i.e., focus score > 3); (c)
connective tissue disease. The lip biopsy score of 3 seen in case 5, although indicating the presence of FLS, is considered to be a transitional value, suggesting possible SS. However, this patient and the case who did not undergo lip biopsy had KCS, and the latter had an abnormal parotid scan characteristic of SS, strengthening the likelihood of this diagnosis. The labial biopsy specimen of one patient, case 4, showed one focus/4 mm², but considerable fibrosis and fatty infiltration of
surrounding gland tissue rendered a diagnosis of FLS in this patient uncertain. Thus all four biopsied patients fulfilled criteria for definite (or possible) SS on the basis of clinical or pathological glandular disease, or both. If their arthritis manifestations were considered to fulfill the third criterion—that of an associated connective tissue disease—all would meet requirements for a diagnosis of definite SS.

Serological investigations

Haemoglobin, white blood cell count, and platelet counts were normal in all except case 1, in whom a normocytic anaemia characteristic of chronic disease developed. The erythrocyte sedimentation rate was intermittently raised in two patients in relation to flares of inflammatory disease. Serum calcium, phosphorus, and uric acid were within normal limits in all cases. The relevant serological findings are shown in Table 2, which shows that the patients were remarkable for their lack of the serological reactivity usually associated with RA or SS, or both. Only one patient was rheumatoid factor positive at a titre of 1/640, while the others were persistently seronegative. A fluorescent antinuclear antibody test carried out on HEp₂ cells was negative in all cases. Anti-Ro and La antibody tests performed by Ouchterlony diffusion (courtesy of Dr Morris Reichlin, Oklahoma City) showed that anti-La was absent in all cases and anti-Ro was present only in case 1, the case with rheumatoid factor activity also. Antisalivary gland antibody tested for by indirect immunofluorescence with goat antihuman IgG, IgM, and IgA polyclonal antiserum was negative in all patients. Case 1 developed biochemical hypothyroidism without thyroid antibodies, and case 2 had both antithyroglobulin and antimicrosomal antibodies in the absence of clinical thyroid disease. Complete HLA typing showed that case 1, with the most widespread inflammatory disease and the most active labial biopsy, was HLA-A1, B8, DR2. Two cases, which were the least rheumatoid like since they lacked both wrist and MCP disease, were HLA-DR4. None was HLA-DR3.

Synovial fluid was aspirated on two occasions each from the knee and wrist in case 1 and from the knee in case 5. Only small amounts of fluid were obtained, allowing limited examination. The knee fluid from case 1 was turbid, with increased neutrophils on smear and no crystals. The wrist aspirates and that of the knee in case 5 were clear, non-inflammatory fluids with few cells and no crystals.

Synovial tissue was obtained at surgery in three instances: bilateral hip replacement in case 1, fusion of the IP joint of the thumb in case 2, and at total knee replacement in case 3. Pathology in all cases showed modest synovial cell hyperplasia, with mild subsynovial increase in vascularity and a scattered lymphocytic infiltrate. No lymphoid follicles were seen.

Discussion

Awareness of a polyarticular form of OA of the hands was reflected in the 19th century writings of Haygarth, Garrod, and Adams. More detailed clinical descriptions have since followed, and with these, various terms for this condition have emerged in the literature. These include 'generalised OA' 'inflammatory OA', and 'erosive OA' (EOA). Generalised osteoarthritis was initially described in the classic monograph of Kellgren and Moore, in which a characteristic distribution of OA with

Table 1  Sicca features of cases with erosive OA and Sjögren’s syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sicca</th>
<th>Scan</th>
<th>Lip Bx</th>
<th>Schirmer</th>
<th>R-B</th>
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<tr>
<td>1</td>
<td>69</td>
<td>±</td>
<td>&gt;4</td>
<td>++</td>
<td>++</td>
<td>±</td>
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<tr>
<td>2</td>
<td>66</td>
<td>±</td>
<td>4</td>
<td>++</td>
<td>±</td>
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</tr>
<tr>
<td>3</td>
<td>68</td>
<td>—</td>
<td>ND</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>74</td>
<td>—</td>
<td>2-5</td>
<td>++</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>—</td>
<td>N</td>
<td>++</td>
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</table>

*Sicca= symptoms of dry eyes or mouth, or both; Scan= parotid scan; Lip Bx= focus score; Schirmer= Schirmer’s test; R-B= rose-bengal test.

Table 2  Serological features of cases with erosive osteoarthritis and Sjögren’s syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>RF*</th>
<th>ANF*</th>
<th>Ro*</th>
<th>La*</th>
<th>Sal*</th>
<th>G*</th>
<th>HLA-A</th>
<th>HLA-B</th>
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<td>0</td>
<td>N</td>
<td>2.11</td>
<td>13.14</td>
<td>7.6</td>
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*RF=rheumatoid factor; ANF= antinuclear factor; Ro= anti-Ro antibody; La= anti-La antibody; Sal= antisybarivary gland antibody; G= gammaglobulin.
prominent hand involvement and predilection for middle aged females was reported.\(^1\) In 1961 Crain initiated the concept of OA of the finger joints with striking inflammatory features and frequent progression to ankylosis.\(^2\) Shortly after, Kidd and Peter\(^3\) and Peter et al\(^4\) coined the term ‘erosive OA’ to denote characteristic erosive lesions of the interphalangeal joints. Clearly, the abundant nomenclature for interphalangeal OA can lead to considerable confusion. These terms, however, should probably be regarded as descriptions of variants of the same disease category.

Several others have added to the list of reports on inflammatory, erosive variants of OA, emphasising features which help to distinguish this condition from RA.\(^4\)\(^-\)\(^7\) In contrast with RA, inflammatory erosive OA is characterised by lack of juxta-articular osteoporosis, the presence of prominent DIP joint involvement, and radiological subchondral sclerosis and hypertrophic new bone formation at both the DIP and PIP joint. Wrist involvement occurs in EOA but is generally confined to the radial side of the carpus, with frequent involvement of the trapezium and adjacent metacarpal and carpal bones.\(^8\)

It is noteworthy that Peter et al found that synovial pathology in cases of EOA was not qualitatively different from that of RA, with synovial lining cell hyperplasia, round cell infiltration, subsynovial fibrosis, and pannus being common findings.\(^2\) However, others have felt that despite many similarities, significant differences in the synovial pathology do exist.\(^16\) Moreover, the radiological findings of central subchondral erosions and hypertrophic bone reaction in EOA, in contrast with the peripheral ‘pocket’ erosions due to pannus in RA, imply critical differences in synovial-cartilage interaction in the two conditions.

Although several reports suggest that judicious x-ray interpretation facilitates differentiation between EOA and RA, potential for confusion still exists. Moreover, Ehrlich has described progression to features of classical or definite RA in 15% of patients with typical inflammatory OA.\(^17\)\(^-\)\(^18\) ‘Conversion’ to RA was signalled by clinical and radiological involvement of joints typical of RA such as MCPs, wrists, and elbows. Three of our cases with wrist or ECU tendon involvement, or both, are highly reminiscent of Ehrlich’s experience, though none of our small group developed nodules or MCP synovitis and only one case was seropositive.

The development of disease similar to RA in his cases led Ehrlich to speculate on the relationship between EOA and RA and to suggest that the former condition may represent a disease ‘interface’ between RA and benign OA.\(^18\)\(^-\)\(^19\) As Ehrlich pointed out cases that begin with inflammatory or erosive OA are distinct from the ‘engrafted RA’ described in the German literature, which refers to the concurrence of non-inflammatory Heberden’s and Bouchard’s nodes with RA.\(^20\) In view of the known high prevalence of benign Heberden’s nodes in middle aged females, and the not infrequent occurrence of RA in this population, coexistence of the two conditions would not be surprising. However, inflammatory, erosive variants of hand OA are far less prevalent than Heberden’s nodes and are estimated to affect approximately 1% of females in the age range at risk.\(^6\) Concurrency of EOA and RA would therefore not be expected to be frequent.

In keeping with Ehrlich’s series our experience indicates a subset of patients with joint disease compatible with a diagnosis of inflammatory, erosive OA but with eventual appearance of rheumatoid like features in the involved joints. This concept is further supported by a recent report by Utsinger.\(^21\)

On the other hand, McCarty’s emphasis on DIP involvement in RA as assessed by joint tenderness raises the issue of rheumatoid disease as the sole diagnosis in such cases.\(^22\) Thus it could be proposed that these women have an unusual localised form of RA with prominent DIP involvement, sparing more classic rheumatoid sites and lacking serological reactivity. This possibility seems unlikely in our cases, though case 1 was seropositive and developed wrist disease. The others, in most respects similar to case 1, look clinically and radiologically distinct from RA.

Apart from RA it is probable that few other arthritides would present like our cases. Despite absence of skin or nail lesions, psoriatic arthritis (PSA) must be considered. PSA is known to occur without psoriasis, and the distribution of joint disease can be similar to that of OA. Erosive OA and PSA are similar in their predilection for DIP joints, lack of juxta-articular osteoporosis, and potential for ankylosis, and even main en lorgnette deformity.\(^23\) However, key radiological differences between the two conditions have been described.\(^24\) The central subchondral IP erosions seen in our cases conform more to the ‘gull wing’ pattern of EOA rather than the peripheral ‘mouse ear’ lesions more typical of PSA. Clearly, a diagnosis of PSA could only be, at best, speculative in the absence of skin or nail lesions.

Calcium pyrophosphate dihydrate (CPPD) deposition disease is known to lead to osteoarthritic involvement of atypical sites, including MCP and radiocarpal joints.\(^25\)\(^-\)\(^27\) This generally, but not invariably, occurs in the context of chondrocalcinosis or documented crystal induced synovitis, or both,
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neither of which were found in our cases. Thus it is unlikely that CPPD arthropathy is present in our cases.

In addition to their unusual arthropathy all of our cases had features of Sjögren’s syndrome. Of the four patients who underwent lip biopsy, two had definite SS pathologically, and the other two had lymphocytic foci of a degree representing a transitional value. The remaining unbiopsied patient had both a positive parotid scan and keratoconjunctivitis sicca.

The incidence of SS is not known to be increased in patients with OA, though this has not been evaluated in a controlled fashion. In one postmortem study of lip biopsy specimens only one of 10 patients with OA had focal lymphocytic saladenitis, and that of non-diagnostic grade. Two other studies report an increased incidence of sicca symptoms in OA, sometimes associated with other autoimmune manifestations. However, lip biopsies were not performed, and a diagnosis of SS is therefore uncertain. Sicca features alone in the absence of glandular infiltrates would be expected to be common among elderly females.

Articular manifestations of primary SS, although ill defined, are not like those seen in our patients. A recent study addressing this issue found a high prevalence of joint involvement, which tended to be polyarticular, symmetrical, and intermittent, with a mild degree of synovitis. Wrist and MCP involvement were common, but the chronic synovitis and erosive disease as encountered in our group were not found.

Our cases, although comprising a small group, are surprisingly inceptive serologically for either primary or secondary SS. Negative rheumatoid factor is particularly unusual in SS occurring with RA, and the presence of anti-Ro in only one case is less than that usually encountered in primary SS and may be related to the presence in the same patient of rheumatoid factor. No case had antisyphilis antibodies, which one would expect in 20–30% of cases of SS with RA.

Our cases provoke several questions about the nature of erosive OA and suggest a greater than expected association with Sjögren’s syndrome. They may represent a subset of patients having EOA with an autoimmune background. The presence of HLA-DR4 in two patients and HLA-A1/B8 in another may be relevant in this regard.

While it remains useful for the sake of consistency in nosology and classification to regard EOA as a separate entity, our experience suggests that at least a subgroup with atypical features exists. Whether this indeed represents a particularly destructive form of EOA, a disease interface with RA, or a distinct arthropathy is at present unclear. Further study of such patients, with close attention to clinical, immunological, and pathological features, should help answer these questions.

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