Extra-articular rheumatoid arthritis: prevalence and mortality

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Abstract

Objective. The prevalence and distribution of extra-articular manifestations of rheumatoid arthritis (ExRA) and associated mortality were studied retrospectively in a cohort of RA patients admitted to University Hospital, Malmö, Sweden, during the period 1990–94.

Results. Of 489 patients who fulfilled the 1987 ACR criteria for RA, 37 manifested onset of ExRA, predominantly serositis and cutaneous vasculitis, during the period, corresponding to a cumulative incidence of 7.9%. The occurrence of ExRA was independent of disease stage. Among patients with ExRA, 1 death/4.3 person-years at risk (pyr) occurred, as compared with 1 death/11.4 pyr in the non-ExRA subgroup. The age- and sex-adjusted mortality rate ratio was 2.49 (95% confidence interval 1.43–4.03). The major cause of death among ExRA cases was heart disease, which occurred in 9/13 cases (69%) in comparison to the expected 2.4 cases.

Conclusion. In this series, serositis and cutaneous vasculitis were predominant extra-articular manifestations of RA; and mortality was greater in the ExRA than in the non-ExRA subgroup, perhaps due to a high frequency of associated heart disease.

KEY WORDS: Rheumatoid arthritis, Extra-articular manifestations, Mortality, Prevalence, Vasculitis, Pericarditis, Pleuritis, Cardiovascular co-morbidity.

Rheumatoid arthritis (RA) is a chronic, often severely disabling disease, with a prevalence of roughly 1% in most populations [1]. Apart from the potentially destructive joint manifestations of the disease, it is also characterized by systemic features. Severe weight loss [2] and generalized osteoporosis [3] are often present in severe disease. Benign lymphadenopathy, a common finding in active disease [4], is an example of inflammation involving tissue outside the locomotor system. The rheumatoid nodule is another.

Some patients develop signs and symptoms of more severe extra-articular inflammation in distant organs. These include pericarditis, pleuritis, Felty’s syndrome and various manifestations of vasculitis, including the chronic ‘rheumatoid’ leg ulcers, which are thought to be at least partly due to small-vessel vasculitis [5, 6].

Extra-articular manifestations (ExRA) are thought to be particularly frequent in severe, active disease [7]. This subgroup of patients have been said to suffer from ‘malignant rheumatoid vasculitis’ [8]. The frequency of ExRA is difficult to estimate. Most studies have been performed at highly specialized centres, with poorly defined catchment areas. Population studies of ExRA, on the other hand, are difficult to perform since they require uniform and consistent ascertainment of such complications in a defined catchment area population.

RA is associated with an increased mortality, as compared to the general population [9–20]. Although a few patients die of disease-specific complications, such as cervical instability or the side-effects of drugs [21], the major part of the surplus mortality is due to other co-existing disease [17, 22], particularly cardiovascular disease [12, 17, 19, 20, 23]. Available data on the impact of ExRA on mortality in RA are contradictory. Extra-articular mortality has been shown to be increased in some studies [7, 24–27], but not in the most recent one [28]. The problem of referral bias when studying this aspect at major research centres has been emphasized [29].

The aims of the present study were to investigate the period prevalence of the onset of extra-articular manifestations in a well-defined RA series, and their influence on mortality.

Materials and methods

The study was carried out at University Hospital, Malmö, Sweden, the only secondary and tertiary facility serving the city of Malmö (population ~240000 inhabitants). A computerized retrieval system was used to identify all patients with a registered diagnosis of RA and treated at the hospital during a 4.5 yr period (1 January 1990–30 June 1994). (This period was chosen

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as data on diagnosis were available from the period after 1 January 1990, and work on the study was started in the autumn of 1994.) The medical records of these patients were subjected to structured review by either of two of the authors (CT or UB). Of the 510 cases, 21 were excluded as the diagnosis was patently incorrect (i.e. erroneous registration, premature diagnosis by an inexperienced physician, etc.), or the case record did not contain enough data to support the diagnosis. Twenty patients had a known history of previous extra-articular disease, leaving 469 previously non-ExRA patients who fulfilled the 1987 ACR (American College of Rheumatology) criteria for RA [30] to be included in the study.

The included patients were referred because of planned orthopaedic surgery (42.5% of referrals according to the register of all in-patient surgery), flares in disease activity, rehabilitation and also because of other, concomitant disease. They make up a significant part of controls. Dates of ExRA diagnosis and death were ascertained using previously established criteria (see Table 1). These criteria limit the ExRA studied to manifestations that are possible to evaluate retrospectively in a uniform manner from consultations recorded as free text. Interstitial lung disease, for example, a diagnosis heavily dependent on the method of investigation [40], was not included in the ExRA studied.

All cases of verified or suspected ExRA were reviewed by all three authors. When the presence of ExRA was suspected, but there were insufficient data, additional records were obtained from primary care facilities, private practitioners, etc. The database of the department of dermatology was used to identify any cases of cutaneous vasculitis in the group with known RA. Potential cases were validated in a similar manner as mentioned above.

Patients with a known history of extra-articular manifestations before the study period were not included in the ExRA group. Thus, the ExRA subgroup (n = 37) consisted exclusively of patients with onset of ExRA during the studied period, the remaining 432 serving as controls. Dates of ExRA diagnosis and death were obtained from the case records, and causes of death from the national register of death certificates (death certificates being available in all cases). For each participant, the duration of observation was estimated from the date of first admittance to University Hospital, Malmö, as in-patients, calculated from the starting date of the study (1 January 1990) until death or the end of the study period (30 June 1994). The duration of observation was registered separately as that without previous ExRA during the study period and that after the onset of ExRA. Thus, patients who developed ExRA contributed to observation time in both subgroups.

To enable age- and sex-specific death rates, and overall age–sex-adjusted mortality in the series as a whole to be computed, the male and female subgroups were stratified separately by age into seven age groups [i.e. six 10 yr periods (16–24 yr olds, 25–34 yr olds, etc.) and a ≥75-yr-old group].

Age–sex-specific death rates were calculated as the quotient of the number of deaths in a given age group divided by the person-years at risk (pyr) for all patients in that age group. Each patient contributed pyr to the total for a given age–sex–specific stratum, according to the time spent in that stratum. For example, a woman who was 32 yr old at admission in 1990, developed ExRA in 1991 and died in 1993, would contribute 1 pyr to the 25–34-yr-old non-ExRA female stratum, 1 pyr to the 25–34-yr-old ExRA female stratum and 1 pyr to the 35–44-yr-old ExRA female stratum, where her death was counted as an event. Mortality rates were compared for those with and those without ExRA. Age- and sex-adjusted mortality rate ratios with 95% confidence intervals (CI) were computed for mortality as a whole, using stratified incidence density data as previously described [31, 32].

Using these data and data from the 1992 Swedish population census, standardized mortality ratios (SMRs; i.e. 100 × observed deaths/expected deaths) were calculated for the ExRA and control groups. The number of expected deaths in each stratum was calculated from corresponding age–sex–specific mortality rates for the

### Table 1. Criteria for inclusion in the ExRA subgroup

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria for Inclusion</th>
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<tbody>
<tr>
<td>Pericarditis and/or pleuritis</td>
<td>Clinical suspicion of and Exudation (objectively verified by ultrasound or X-ray)</td>
</tr>
<tr>
<td>Felty’s syndrome</td>
<td>Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (neutrophils &lt; 1.8 × 10^9/L) on two occasions</td>
</tr>
<tr>
<td>Major cutaneous vasculitis</td>
<td>Diagnostic biopsy or clinical judgement by dermatologist (excluding isolated nailfold vasculitis)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Clinical judgement by physician and signs of polyneuropathy or monoclonal protein at electroneurography/ectroclinical examination</td>
</tr>
<tr>
<td>Scleritis or retinal vasculitis</td>
<td>Clinical judgement by ophthalmologist</td>
</tr>
<tr>
<td>Glomerulonephritis and vasculitis involving other organs</td>
<td>Clinical judgement by organ specialist and biopsy compatible with vasculitis</td>
</tr>
</tbody>
</table>
Table 2. Demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-ExRA</th>
<th>ExRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female ratio</td>
<td>1.2.8</td>
<td>1.2.7</td>
</tr>
<tr>
<td>Age at beginning of study (yr) (median; IQ range)</td>
<td>68.4 (57.8–78.6)</td>
<td>70.3 (60.6–76.4)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Disease duration at beginning of study (yr) (median; IQ range)</td>
<td>14.2 (5.9–23.2)</td>
<td>17.7 (4.7–29.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of previous admissions (median, IQ range)</td>
<td>2 (0–5)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion taking steroids at the beginning of the study</td>
<td>19%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion on DMARD treatment at the beginning of the study</td>
<td>35%</td>
<td>30%</td>
</tr>
</tbody>
</table>

The number of previous admissions and proportion on steroid and DMARD treatment were calculated in the group of 37 cases of ExRA and in a group of 37 controls, matched for disease duration but otherwise blindly selected.

Fig. 1. Disease duration (after RA diagnosis) at onset of extra-articular manifestations.

city of Malmö. Similarly, age–sex-adjusted cause-specific mortality was compared with that for the general population. When classifying deaths according to the underlying cause, the ICD-9 system was used.

Comparison between ExRA and non-ExRA patients concerning demographic data was performed using the \( \chi^2 \) test and the Mann-Whitney U-test, respectively, when appropriate.

Results

There were 37 cases of onset of ExRA, an overall period prevalence of 7.9% (37/469). In 46% (17/37) of cases, the extra-articular manifestation was diagnosed at an out-patient facility. There was a small but non-significant over-representation of men (Table 3). The median age of the future ExRA cases at the beginning of the observation period was 70.3 yr [interquartile (IQ) range 60.6–76.4], and at the time of first presentation of ExRA the median age was 72.0 yr (IQ range 63.4–76.4). Age and disease duration were similar in the ExRA and non-ExRA subgroups (Table 2). Serositis and cutaneous vasculitis were the predominant first manifestations of extra-articular RA (Table 3). The onset of ExRA was unrelated to disease duration (since the diagnosis of RA), which ranged from 1 to 53 yr (Fig. 1).

Mortality rates were greater among the men than among the women. In all, 13 deaths occurred/56.2 pyr in the ExRA subgroup and 106/1211.6 pyr in the non-ExRA subgroup. This corresponds to 1 death/4.3 pyr in the ExRA subgroup and 1 death/11.4 pyr in the non-ExRA subgroup. The excess mortality associated with ExRA tended to be greater among the men than among the women (Table 4). Mortality rates were compared for each age group, and the age–sex-adjusted mortality rate ratio was found to be 2.49 (95% CI 1.44–4.31).

The expected survival rates for the two subgroups were calculated using age-specific mortality statistics for Malmö. The SMR was greater in the ExRA than in the non-ExRA subgroup [2.50 (95% CI 1.02–3.98) vs 1.82, (95% CI 1.48–2.16)].

There was a marked predominance of heart disease as the cause of death in both subgroups, although the observed:expected ratio was higher in the ExRA subgroup (Fig. 3).

Patients with ExRA had not been admitted as in-patients more frequently before the beginning of the study than non-ExRA controls, matched for disease duration. They were treated to an equal extent with disease-modifying anti-rheumatic drugs (DMARDs) at the beginning of the study, but more frequently with steroids than the controls (Table 2).
Table 4. Mortality in ExRA and non-ExRA subgroups

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>ExRA Incidence (deaths/1000 pyr)</th>
<th>ExRA No. of deaths</th>
<th>ExRA Pyr</th>
<th>Non-ExRA Incidence (deaths/1000 pyr)</th>
<th>Non-ExRA No. of deaths</th>
<th>Non-ExRA Pyr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–34</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35–44</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45–54</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>55–64</td>
<td>1</td>
<td>0.4</td>
<td>2627.70</td>
<td>4</td>
<td>89.5</td>
<td>44.71</td>
</tr>
<tr>
<td>65–74</td>
<td>1</td>
<td>2.3</td>
<td>430.21</td>
<td>12</td>
<td>94.0</td>
<td>126.35</td>
</tr>
<tr>
<td>≥75</td>
<td>3</td>
<td>1.0</td>
<td>2891.16</td>
<td>21</td>
<td>101.1</td>
<td>207.81</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25–34</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>34–45</td>
<td>0</td>
<td>4.7</td>
<td>0</td>
<td>0</td>
<td>58.5</td>
<td>0</td>
</tr>
<tr>
<td>45–54</td>
<td>0</td>
<td>3.2</td>
<td>0</td>
<td>2</td>
<td>113.4</td>
<td>17.64</td>
</tr>
<tr>
<td>55–64</td>
<td>1</td>
<td>9.7</td>
<td>103.06</td>
<td>3</td>
<td>138.3</td>
<td>21.69</td>
</tr>
<tr>
<td>65–74</td>
<td>2</td>
<td>13.7</td>
<td>146.16</td>
<td>16</td>
<td>291.4</td>
<td>54.91</td>
</tr>
<tr>
<td>≥75</td>
<td>5</td>
<td>21.3</td>
<td>235.19</td>
<td>48</td>
<td>265.2</td>
<td>180.98</td>
</tr>
</tbody>
</table>

Pyr, person-years at risk.

Discussion

Mortality in the ExRA subgroup was not only greater than that in the age-matched general population, but also greater than that in the non-ExRA subgroup, who, it should be borne in mind, were also treated at the hospital. If RA mortality is related to disease severity, as suggested by findings in some studies [16, 34–36], the difference in mortality between the present ExRA subgroup and a completely unselected RA cohort attending out-patient facilities would probably be even greater than that between the ExRA and non-ExRA subgroups in this study.

The increased mortality associated with extra-articular disease was demonstrated in a well-defined group of hospitalized patients, making up about one-third of the total number of subjects with RA in the city of Malmö (see Materials and methods), and consisting of patients with moderate to severe disease.

From the Kaplan–Meier survival curve (Fig. 2), it is apparent that the major part of excess mortality in the ExRA subgroup occurred soon after the onset of extra-articular manifestations. An analogous pattern was found in a study of survival among hospitalized patients with rheumatoid pericarditis [25]. At first glance, the close conjunction between the onset of ExRA and death might be interpreted as suggesting a very direct link.

Table 5. Causes of death in ExRA and non-ExRA subgroups (classified according to ICD-9) (observed vs expected)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>ExRA Observed</th>
<th>ExRA Expected</th>
<th>Non-ExRA Observed</th>
<th>Non-ExRA Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease (ICD 410–14, 420–29)</td>
<td>9</td>
<td>2.4</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>Cerebrovascular disease (ICD 430–38)</td>
<td>1</td>
<td>0.9</td>
<td>13</td>
<td>8.8</td>
</tr>
<tr>
<td>Malignancy (ICD 140–239)</td>
<td>0</td>
<td>1.4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1.9</td>
<td>44</td>
<td>18</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases.
patients with a clinical suspicion verified by a histopathological interpretation which highlights the drawbacks of studying mortality in hospitalized cohorts. However, the present study was not solely based on ExRA diagnosed at hospital, but was a retrospective study of the occurrence of ExRA during a limited period in a series of patients, one of whose common denominators was having been hospitalized for RA at sometime during the period. In fact, in a substantial part of the cases (46%), the extra-articular manifestation was diagnosed at an out-patient facility.

The excess mortality associated with extra-articular manifestations tended to be greater in men than in women, as has been reported by others [43]. Taken together with a slight over-representation of ExRA in men, it suggests an importance of sex hormones or other gender-specific risk factors in the development and course of extra-articular disease.

The definition of extra-articular manifestations merits consideration. In autopsy series, a large proportion of RA patients have been found to manifest signs of inflammation in the pleura and pericardium that are compatible with rheumatoid serositis [37]. Thus, extra-articular manifestations may be the rule rather than the exception in RA.

Owing to the retrospective nature of the study, we found it convenient to include in the ExRA subgroup only patients with signs and symptoms that had given rise to a suspicion of extra-articular manifestations, and where this had been objectively verified (see Table 1). Hence, only patients with manifest disease were included in the ExRA subgroup, and thus some patients with less obvious ExRA may have been classified as non-ExRA. If anything, however, such misclassification would tend to reduce differences between the subgroups.

On the other hand, some authors have included only patients with a clinical suspicion verified by a histopathological finding of vasculitis in biopsy material [28]. Although that approach is useful in the sense that it reduces the risk of including patients with non-RA-related manifestations, it may also bias the findings in the series as a whole in a different way. Inclusion of only patients with such a well-established diagnosis may result in a selection of long-term survivors, by excluding some severely ill or rapidly deteriorating patients.

Rheumatoid nodules, secondary Sjögren’s syndrome and Raynaud’s phenomenon are, by definition, extra-articular manifestations. In a previous study by others [24], no increase in mortality was found in patients with isolated nodules, Sjögren’s syndrome or Raynaud’s phenomenon, whereas mortality was increased among patients with other manifestations.

Interstitial lung disease (ILD) is another extra-articular manifestation of RA [38]. Some available evidence suggests that the presence of ILD may have an important impact on prognosis [39]. Figures for the prevalence of ILD among RA patients have been shown to vary markedly, depending on the method of investigation used [40]. As the presence or absence of ILD is extremely difficult to evaluate retrospectively when no standardized diagnostic criteria have been used, we chose not to include ILD in the extra-articular manifestations studied.

The extra-articular manifestations found in this series of RA patients were characterized by a predominance of serositis and cutaneous vasculitis. Pleuritis was more common than pericarditis, as also found by others in studies of Scandinavian RA patients [41, 42]. Although present in a few cases, manifestations associated with ‘malignant rheumatoid arthritis’ [8] (e.g. mononeuritis multiplex, scleritis and internal organ vasculitis) were infrequent findings.

The overall period prevalence of onset of extra-articular manifestations in the series was 7.9%. In all likelihood, the extra-articular manifestations detected represent the major part of such manifestations in the population of Malmö as a whole (i.e. 240 000, adult population 188 000), as it is reasonable to suppose most patients with severe ExRA to have required hospital care and thus to have been included in the study. Thus, the 37 cases of ExRA detected during this 4.5 yr period would correspond to an annual incidence of 44/million adults (95% CI 32–62). The annual incidence of systemic rheumatoid vasculitis (SRV), according to Scott and Bacon criteria [27], was 7.1/million adults (95% CI 2.7–16.1). In reality, these incidence rates are probably somewhat higher, as a few patients with ExRA may never have been admitted to the hospital during the study period. The annual incidence of SRV found in this study should be compared to the recent observations in Norfolk, UK, where an annual incidence of 12.5/million adults was found [43].

As has been reported by others [7], ExRA was not correlated with disease duration or disease stage. Patients with ExRA were on steroid treatment to a greater extent at the beginning of the study than non-ExRA controls. The cause and importance of this difference are not clear, but our own data seem to indicate that patients who later develop ExRA have a tendency to a more rapid disease progression in the first years after diagnosis, which may lead to a more frequent use of glucocorticosteroids (L. Turesson, unpublished results). However, patients who later developed ExRA were not admitted more frequently before the beginning of the study.

What is the nature of the excess mortality observed? Although the absolute number of deaths in the patients with ExRA was limited, there was a marked predominance of heart disease as the cause of death. A similar, but less marked, trend was observed in the non-ExRA subgroup. Several studies have shown cardiovascular disease to account for the major part of excess mortality in RA [12, 17, 19, 20, 23]. In a study of patients with severe rheumatoid vasculitis [8], cardiovascular co-morbidity was found to be more frequent than in RA controls without vasculitis.

Laboratory investigations have yielded support for the hypothesis that inflammation may be an important
feature of the pathogenesis of atherosclerosis [44], and in the subsequent development of myocardial infarction [45]. This might have implications for patients without a history of RA. In a large study by Helio¨vaara et al. [14], the presence of rheumatoid factor was found to be a risk factor for mortality not only in RA, but also in the absence of diagnosed arthritis. The serum CRP level has been found to be an independent correlate of the risk of myocardial infarction [46], a finding recently verified in a study of apparently healthy men, which showed the variable to be similarly applicable in smokers and non-smokers [47]. This finding is important, as it suggests inflammation to be important per se, and not as a marker of the presence of other risk factors.

To sum up, in this series we found serositis and cutaneous vasculitis to be the predominant extra-articular manifestations in RA and to be associated with increased mortality, especially due to heart disease. The latter finding may be another example of the relationship between inflammation and coronary heart disease. Future prospective studies of patients with vs without ExRA should be designed to elucidate the mechanisms underlying these relationships.

Acknowledgements

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