

EXTENDED REPORT

Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years

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Objective: To investigate the trends in incidence of extra-articular rheumatoid arthritis (ExRA) in a well defined community based cohort of patients with rheumatoid arthritis (RA), and to examine possible predictors of ExRA occurrence.

Methods: Using the resources of the Rochester Epidemiology Project, a retrospective medical record review was conducted of a cohort of 609 cases of RA in Olmsted County, MN, diagnosed during 1955-94. These cases had been previously classified using the ACR 1987 criteria for RA. Patients were followed up from 1955 to 2000 (median follow up 11.8 years; range 0.1-42.8), and incident ExRA manifestations were recorded according to predefined criteria. Time to first presentation of ExRA was compared in patients with RA by decade of diagnosis. Possible ExRA risk factors were identified in case record reviews.

Results: ExRA occurred in 247 patients (40.6%). A subgroup of 78 patients (12.8%) had ExRA manifestations considered to be severe in a previous study from Malmö, Sweden. The incidence of severe ExRA did not change significantly over the decades ($p=0.165$). In a multivariate analysis the main predictors of severe ExRA were smoking at RA diagnosis (risk ratio (RR)=2.94; 95% confidence interval (95% CI) 1.68 to 5.13) and early disability (Steinbrocker class III-IV at diagnosis) (RR=2.45; 95% CI 1.51 to 4.00). The effect of smoking overwhelmed the weaker effect of rheumatoid factor seropositivity.

Conclusion: There was no decrease in the incidence of extra-articular manifestations in patients with RA diagnosed up to 1995. Smoking and early disability are independent risk factors for extra-articular RA.

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Rheumatoid arthritis (RA) is a systemic inflammatory disease, which is associated with a number of extra-articular organ manifestations. Studies of extra-articular RA (ExRA) include cross sectional hospital based¹ and multi-centre clinical² surveys, series of consecutive patients seen in clinical practice,³ and retrospective surveys of clinic based RA cohorts.⁴⁻⁷ The population based study of RA in Norfolk, UK, has been used to investigate the occurrence of systemic rheumatoid vasculitis.⁸

Case definitions of extra-articular manifestations vary in different studies, and the problem of selection bias in studies from major research centres has been underlined.⁹ In a retrospective study of a hospital based RA series from a single rheumatology centre in Malmö, Sweden,¹⁰ clinically evident ExRA manifestations (pericarditis, pleuritis, major cutaneous vasculitis, Felty's syndrome, neuropathy, ophthalmological manifestations, glomerulonephritis, and other types of vasculitis) were identified according to predefined criteria.

Using the resources of the Rochester Epidemiology Project, we have previously conducted a preliminary survey of ExRA manifestations in a community based cohort of incident patients with RA resident in Rochester, Minnesota.¹¹ All case records from every adult patient with onset of RA between 1955 and 1984 were reviewed, and ExRA manifestations were identified. In these two studies,^{10, 11} as well as in others,^{3, 4, 9, 12} mortality was increased in patients with ExRA compared with patients with RA in general. RA has been associated with a shortened life expectancy in many studies,¹³⁻²⁰ and the ExRA criteria may define a subgroup of patients with RA with a particularly poor prognosis.

There is evidence for secular trends in the occurrence of RA,²¹⁻²³ and some data indicate that the incidence of RA is decreasing.^{22, 24-26} It has been suggested that RA is becoming on average a less severe disease,²⁷ and a historical comparison of RA patient series in the 1970s and 1990s showed a lower inci-

dence of severe disability in the latter decade.²⁸ Such changes over time may be due to differences in patient selection, improved treatment, or other environmental changes that may induce cohort or period effects. Owing to the variation in case definition and methods of investigation, which limits comparability between studies, it is unknown whether there are any temporal trends in the occurrence or severity of ExRA.

Suggested predictors of ExRA manifestations include constitutional factors such as male sex and disease associated HLA genes (in particular homozygosity for certain DRB1*04 subtypes),²⁹ autoantibodies such as rheumatoid factor³⁰ and antinuclear antibodies (ANA),³¹ and environmental factors such as smoking.³² The strength of these associations is probably variable depending on the exact definition of ExRA used and on the method of patient selection.

The purpose of this study was to investigate the trends in incidence of ExRA over time in a community based cohort of patients with RA, by including all incident RA cases of adults > 18 years of age during the period 1955-94 in the analysis. We also studied possible predictors of ExRA in these patients.

PATIENTS AND METHODS

Patients

The population of Rochester, Minnesota, is well suited for an investigation of the epidemiology of RA and associated extra-articular features because comprehensive medical records for all residents seeking medical care are available. A record linkage system allows ready access to the medical records from all

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibodies; CI, confidence interval; ExRA, extra-articular rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk

Table 1 Criteria for inclusion as extra-articular manifestations of RA

1. Pericarditis	(A) Clinical judgment and exudation verified by echocardiography If ultrasound not available: criteria according to Hara <i>et al</i> ⁴ (B) Clinical criteria: (1 required) Typical pericardial pain, peripheral oedema, dyspnoea/orthopnoea, ascites, dysrhythmia (heart rate >140/min, atrial flutter/fibrillation, 2–3 degree atrioventricular block, ventricular tachycardia) Objective criteria compatible with pericarditis: (1 required) Physical examination Cardiac catheterisation findings Histological examination Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma
2. Pleuritis	Clinical judgment and exudation verified by x ray examination Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma
3. Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (<1.8×10 ⁹ /l) on two occasions Other causes improbable, such as drug side effect or infection
4. Major cutaneous vasculitis	Diagnostic biopsy or clinical judgment by dermatologist
5. Neuropathy	Clinical judgment by doctor and signs of polyneuropathy/mononeuropathy at electromyography/electroneurography Other causes, such as diabetes or alcohol abuse, improbable
6. Scleritis, episcleritis or retinal vasculitis	Clinical judgment by ophthalmologist
7. Glomerulonephritis	Clinical judgment by nephrologist and positive biopsy
8. Vasculitis affecting other organs	Clinical judgment by organ specialist and biopsy compatible with vasculitis
9. Amyloidosis	Clinical judgment and positive biopsy from affected organ
10. Keratoconjunctivitis sicca	Clinical judgment Positive rose-bengal staining or result of Schirmer's test <5 mm/min
11. Xerostomia	Clinical judgment Abnormal sialometry, sialography, salivary scintigraphy or salivary gland biopsy with lymphocytic infiltrate
12. Secondary Sjögren's syndrome	Two of three criteria: Keratoconjunctivitis sicca (see above) Xerostomia (see above) Serological evidence: rheumatoid factor, ANA, anti-Ro (SSA), anti-La (SSB) positive, or hypergammaglobulinaemia
13. Pulmonary fibrosis	Clinical judgment and Decreased vital capacity or carbon dioxide transfer factor by 15% from normal
14. Bronchiolitis obliterans organising pneumonia	Clinical judgment by pulmonologist
15. Cervical myelopathy	Clinical judgment Increased atlantoaxial movement—verified by x ray examination
16. Subcutaneous rheumatoid nodules	Clinical judgment
17. Rheumatoid nodules in other locations	Positive biopsy

healthcare providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Group, the Olmsted Community Hospital, local nursing homes, and the few private practitioners. The potential of this data system for use in population based studies has been described previously.^{33,34} This system ensures virtually complete ascertainment of all clinically recognised cases of RA among the residents of Rochester, Minnesota.

In previous surveys^{21,22} all diagnosed cases of RA aged ≥ 18 years between 1 January 1955 and 31 December 1994, (n=609) were identified using the computerised diagnostic index and a review of the complete medical record in each potential case, as previously described.²² The incidence date was defined as the earliest date at which the patient fulfilled four or more of the 1987 American College of Rheumatology (ACR) classification criteria for RA.³⁵ This study was undertaken as part of further characterisation of the RA cohort.

Incidence estimates

One of the authors (CT) used a structured protocol to review the complete medical records of all patients in the cohort. Extra-articular manifestations were identified according to predefined criteria (table 1) as previously described.¹¹ To ensure completeness and accuracy of the diagnosis of ExRA manifestations, a subsample was reviewed by another author (ELM), with concordant results.¹¹ The criteria for severe disease manifestations (table 1; criteria 1–8) were based on those used in a previous study of the occurrence of ExRA performed in Malmö, Sweden,¹⁰ where they were found, as a group, to identify patients with poor survival. To assess the

occurrence of rheumatoid pericarditis during the time before echocardiography was available, the criteria for pericarditis were modified as previously described.^{4,11} In the present study further ExRA manifestations (table 1; criteria 9–17) were also investigated. The criteria for Sjögren's syndrome (SS) have been used previously to identify cases of primary and secondary SS in epidemiological surveys.^{36,37}

The patients were followed up from 1 January 1955 until 31 December 2000, or until death or loss to follow up (median follow up 11.8 years; interquartile range 6.8–18.9). For patients who moved away from the area, the date of the last physical examination noted in the case record was used as the date of loss to follow up. The date of fulfilment of the criteria for ExRA was noted, as well as the date of death according to the death certificate. The cumulative incidence of ExRA was calculated and adjusted to the follow up time, which was calculated using the actuarial method. The cumulative incidence at 30 years' follow up time was estimated.

The time to first presentation of ExRA was compared in patients with RA by decade of diagnosis (1955–64, 1965–74, 1975–84, and 1985–94). To ensure comparable follow up time in each subgroup in this analysis, patients with RA diagnosis during the period 1955–64 were followed up until 31 December 1970, those diagnosed in 1965–74 were followed up until 31 December 1980, those diagnosed in 1975–84 were followed up until 31 December 1990, and those diagnosed in 1985–94 were followed up until 31 December 2000. ExRA-free survival curves were estimated using the Kaplan-Meier product limit method,³⁸ and the subgroups were compared using the log

Table 2 Data on possible predictors of extra-articular disease in the RA cohort

	No	%
Male sex	164	26.9
RF positive (at diagnosis)	185	30.4
RF positive (at any time)	352	57.8
ANA positive (at any time)	195	52.4*
Ever smokers at RA diagnosis	317†	55.2
Steinbrocker functional class at RA diagnosis‡		
I	54	8.9
II	427	70.5
III	117	19.3
IV	8	1.3

*Of 372 ever tested for ANA; †data available for 574; ‡data available for 606.

rank test. This was done for all ExRA and for ExRA according to the Malmö criteria (table 1; criteria 1–8) separately.

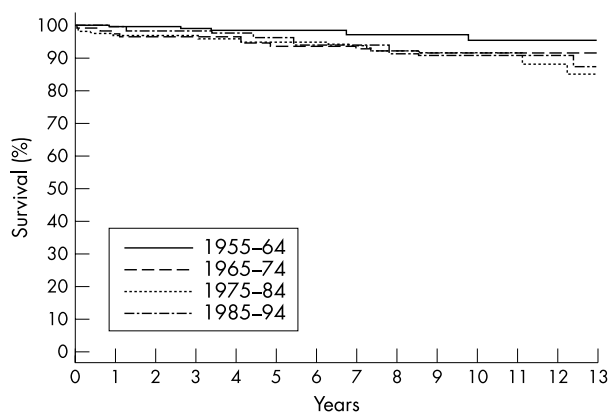
Predictors

Possible ExRA risk factors were identified in case record reviews. The results of all rheumatoid factor (RF) and ANA tests were noted. Disability at diagnosis was measured by estimating the Steinbrocker functional class³⁹ within three months of RA diagnosis (defined as the time of fulfilment of the 1987 ACR criteria for RA³⁵). Data on the smoking history at the time of RA diagnosis were gathered, and the patients were classified as ever versus never smokers (table 2). Investigators collecting smoking and disability data were unaware of the hypothesis that this might influence the risk of ExRA manifestations.

The effects of age, sex, and other possible predictors on the development of ExRA were examined using Cox proportional hazards. Positive RF tests and positive ANA tests were examined in these models as time dependent covariates. As some patients never had an ANA test done, the presence of a completed ANA test was also entered into the models as a time dependent covariate. Variable selection for the multivariate analysis and possible interactions among the significant main effects examined were validated using bootstrap sampling.⁴⁰

Table 3 Cumulative incidence at 30 year follow up of extra-articular disease manifestations

Extra-articular manifestation	Number of patients	30 Year cumulative incidence (SE (%))
Pericarditis	21	5.4 (2.6)
Pleuritis	21	5.2 (2.4)
Felty's syndrome	9	1.6 (0.8)
Major cutaneous vasculitis	19	3.6 (1.5)
Neuropathy	11	2.2 (1.0)
Scleritis	4	0.8 (0.6)
Episcleritis	5	1.0 (0.4)
Retinal vasculitis	0	0.0
Glomerulonephritis	4	1.1 (1.5)
Other vasculitis	1	0.2 (0.2)
Amyloidosis	3	0.7 (0.9)
Keratconjunctivitis sicca	61	11.6 (2.3)
Xerostomia	4	0.7 (0.5)
Sjögren's syndrome	58	11.4 (2.6)
Pulmonary fibrosis	34	6.8 (1.9)
Bronchiolitis obliterans	4	0.5 (0.8)
Cervical myelopathy	12	2.4 (1.2)
Subcutaneous nodules	172	34.0 (3.4)
Other nodules	0	0.0
Any	247	46.0 (3.4)
Malmö	78	16.7 (3.2)

**Figure 1** ExRA-free survival in patients with RA by decade of RA diagnosis. ExRA defined according to the Malmö criteria (table 1; criteria 1–8).

RESULTS

The RA cohort consisted of 445 women and 164 men. The median age at diagnosis was 58.1 years. The median follow up period was 11.8 years (range 0.1–42.8; interquartile range 6.8–18.9). During the follow up period, 247 (40.6%) patients developed ExRA. The 30 year cumulative incidence of ExRA was 46.0% (standard error (SE) 3.4%). Table 3 shows the incidence of various ExRA manifestations. The most common ExRA manifestations were rheumatoid nodules (n=172; 30 year cumulative incidence 34.0 (3.4)%), secondary Sjögren's syndrome (n=58; 30 year cumulative incidence 11.4 (2.6)%), and pulmonary fibrosis (n=34; 30 year cumulative incidence 6.8 (1.9)%). A subgroup of 78 patients (12.8%) fulfilled the Malmö criteria for severe ExRA (table 1, criteria 1–8)¹⁰ (30 year cumulative incidence 16.7 (3.2)%).

Overall, ExRA-free survival by decade of RA diagnosis decreased significantly during the period (p=0.001), indicating that ExRA occurred more frequently for each new decade. The increasing overall incidence of ExRA manifestations was mainly accounted for by an increase in the number of patients with rheumatoid nodules (data not shown).

For ExRA according to the Malmö criteria (ExRA Malmö) there was no significant trend (p=0.165) over the decades, and although there were fewer ExRA Malmö manifestations among patients with onset of RA in 1955–64, the survival curves of the three other subgroups were virtually identical up to 13 years of follow up (fig 1).

In the multivariate analysis, ExRA manifestations of any type (criteria 1–18) were predicted by the presence of a positive ANA test (relative risk (RR)=1.58; 95% confidence interval (CI) 1.12 to 2.21), RF (RR=1.56; 95% CI 1.19 to 2.04), smoking (RR=1.52; 95% CI 1.15 to 2.01), and Steinbrocker class III-IV at diagnosis (RR=1.42; 95% CI 1.04 to 1.94), but not by age and sex (table 4).

The main predictors of ExRA Malmö manifestations in the multivariate analysis were smoking (RR=2.94; 95% CI 1.68–

Table 4 Multivariate analysis of predictors of all ExRA manifestations

Predictor	Risk ratio	95% Confidence interval
Age	1.00	0.99 to 1.01
Male sex	0.94	0.70 to 1.27
RF positive	1.56	1.19 to 2.04
Ever smoking*	1.52	1.15 to 2.01
Steinbrocker class III-IV*	1.42	1.04 to 1.94
ANA positive	1.58	1.12 to 2.21
ANA status unknown	0.75	0.55 to 1.01

*At RA diagnosis.

Table 5 Multivariate analysis of predictors of ExRA Malmö* manifestations

Predictor	Risk ratio	95% Confidence interval
Age (per year)	1.019	1.00 to 1.038
Male sex	0.98	0.59 to 1.63
Ever smoking†	2.94	1.68 to 5.13
Steinbrocker class III-IV†	2.45	1.51 to 4.00

*According to criteria 1-8 (table 1); †at RA diagnosis.

to 5.13) and early disability (Steinbrocker class III-IV at diagnosis) (RR=2.45; 95% CI 1.51 to 4.00). The occurrence of ExRA Malmö manifestations also increased significantly with age at RA diagnosis (RR=1.019/year; 95% CI 1.00 to 1.038). When these factors were taken into account, male sex did not predict ExRA (table 5). Univariately, RF was weakly associated with ExRA Malmö, and this association did not withstand bootstrap validation (data not shown), indicating that smoking, early disability, and old age are stronger predictors, with a contribution which overwhelmed the contribution of RF.

DISCUSSION

In this community based cohort study of RA, which included patients with incident RA during the period 1955-94, there was no decrease over the decades in the incidence of extra-articular disease manifestations. ExRA was predicted by previous smoking and early disability. Age, RF, and ANA were significant predictors of ExRA manifestations overall, but not specifically of severe ExRA organ manifestations.

As has been discussed previously,¹¹ estimates of the incidence of ExRA manifestations tend to be lower in community and population based studies than in clinic based series, as the latter are selected for disease severity and complications. The occurrence of severe ExRA manifestations can be more reliably estimated, as such manifestations are less likely to go unnoticed. The recognition of mild disease manifestations, such as rheumatoid nodules, depends to a greater degree on the doctor's inclination to record such observations in the case history. When using the criteria for Sjögren's syndrome used in this and other studies,^{36, 37} the frequency of the diagnosis depends heavily on the availability of specific tests for the evaluation of possible xerostomia and keratoconjunctivitis sicca.

The apparently increased incidence of ExRA manifestations as a whole was mainly due to an increased number of patients with rheumatoid nodules in later decades. This may be due to detection bias (that is, increased likelihood of nodules being noticed and reported in case records) or possibly due to changes in other time dependent factors. Methotrexate has been shown to be associated with nodules in patients with RA,⁴¹ and the use of methotrexate in the treatment of RA in the USA expanded greatly during the relevant time period.

There are few data on the incidence of ExRA, and apart from a survey of systemic rheumatoid vasculitis in Norfolk, UK,⁴² no major studies have been published on incidence trends over time. Despite this, there is a widespread belief that severe ExRA manifestations are becoming less common. This study does not support such a concept. Our data are in accordance with those of Watts and coworkers,⁴² who did not find any major decrease in the incidence of rheumatoid vasculitis during the 1990s. However, our study is not large enough to evaluate with certainty every single type of ExRA manifestation, and, possibly, the incidence of some manifestations is decreasing, while that of others is stable or increasing. Also, as the study only includes patients diagnosed up to 1995, we do not know how subsequent changes in antirheumatic treatment in recent years, including the introduction of biological

agents since 1995, may affect the occurrence of ExRA. Treatment with tumour necrosis factor blocking agents seems to have a major impact on disease outcome in many patients,^{43, 44} but their specific effect on ExRA has not yet been evaluated.

Smoking has been shown to be associated with RA and RF.⁴⁵⁻⁴⁸ In a series of patients with early polyarthritis, smokers were more likely to develop rheumatoid nodules and less likely to develop erosions.⁴⁹ In longstanding disease, smoking may predict nodules and joint damage,⁵⁰⁻⁵² but not joint counts, pain, or erythrocyte sedimentation rate.⁵¹ Taken together with our findings on the relation between smoking and ExRA, and similar findings by others,³² this may indicate that smoking in some way drives the rheumatoid process towards extra-articular involvement. Vascular abnormalities may be important not just in rheumatoid vasculitis but also in other ExRA manifestations, such as pericarditis,⁵³ and rheumatoid nodules.⁵⁴ Smoking is a well known predictor of cardiovascular disease⁵⁵⁻⁵⁷ and, possibly, smoking also has specific effects on blood vessels in patients with RA. This is of particular interest, as patients with RA,^{18, 58, 59} in general, and patients with ExRA, in particular,¹⁰ have an increased mortality due to cardiovascular disease, and recent data indicate that patients with RA also have increased cardiovascular morbidity.⁶⁰

The association between smoking and ExRA was independent of RF, indicating that other mechanisms may play a part. Suggested pathogenic factors in ExRA include complement binding and activating circulating immune complexes,^{61, 62} clonally expanded CD4+ CD28(null) T cells⁶³ and generalised endothelial activation.⁶⁴ It is unknown to what extent these mechanisms are directly or indirectly influenced by smoking. Environmental factors such as smoking are likely to interact with the individual genetic background in shaping disease outcome.

Early disability was also associated with the later development of extra-articular disease. Although functional class may be difficult to assess in a retrospective case record review, these findings are in agreement with the generally held view that patients with a delayed diagnosis or a very aggressive disease usually have a complicated disease course. The inclusion of cervical myelopathy, which is a consequence of articular pathology, among ExRA manifestations (but not in the severe ExRA subset) may contribute to the association between disability and overall ExRA, although the impact of this is likely to be limited given the small number of patients with cervical myelopathy. Severe ExRA manifestations also tend to become more common with older age. RF and ANA were also associated with a moderately increased risk of ExRA, and this association seems to be stronger with mild disease manifestations. Male sex is not a strong predictor for ExRA.

The main limitation of this study is the retrospective method, which limits the analysis to the data which are found in the case record. At the same time, this method probably includes the vast majority of clinically important manifestations. Missing and inaccurate data may decrease the likelihood of correctly identifying important associations in such surveys. For example, it is impossible to state that other factors, such as diabetes or alcohol abuse, did not in any single case contribute to neuropathy in the investigated patients with RA. Such misclassification may potentially bias the association between ExRA and smoking, although this is unlikely to be of major importance, as we excluded unclear cases and the number of patients with neuropathy was small. The major strengths are the community based cohort and the data record linkage system, which enable virtually complete ascertainment of all cases in the area. The findings in this study are thus not likely to be explained by selection bias.

In conclusion, we have demonstrated that extra-articular disease manifestations are common and have not become less frequent among patients with RA during a period of 46 years.

The main clinical predictors of extra-articular manifestations are smoking and early disability. As we have no evidence indicating that extra-articular RA is a vanishing phenomenon, it is of major importance to try to elucidate the underlying mechanisms behind these associations.

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