Amyloidosis as a cause of death in patients with rheumatoid arthritis

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Abstract

Objective

To study amyloidosis as a cause of death along with associated factors and frequency of pre-mortem diagnosis in patients with rheumatoid arthritis (RA) autopsied between 1952 and 1991.

Methods

We studied causes of death in 369 consecutively autopsied RA and 370 autopsied non-RA patients of the same sex, age at death, and year of autopsy. In those RA patients who died from 1973 onwards, we were also able to analyse clinical data: pre-mortem diagnosis of amyloidosis, clinical features of RA, and treatment.

Results

Based on autopsy, amyloidosis was determined as a cause of death in 9.5% of RA and in none of the non-RA patients ($p<0.001$). In our RA patients, we detected no trend in deaths from amyloidosis between 1952 and 1991. The RA patients dying of amyloidosis died younger than those dying of other causes ($p=0.001$). During the course of the disease, the RA patients with amyloidosis had: higher erythrocyte sedimentation rate ($p=0.002$), lower haemoglobin ($p<0.001$), more frequently proteinuria ($p<0.001$) and renal failure ($p<0.001$) than did the rest of the RA patients. Pre-mortem, amyloidosis was diagnosed by biopsy in 65% of the RA patients with amyloidosis as their cause of death.

Conclusion

Amyloidosis may be undetected during the course of RA. Thus, it should be actively searched for in the patients with long-lasting and active disease, especially, if they have proteinuria or renal failure.

Key words

Rheumatoid arthritis, amyloidosis, cause of death, autopsy.

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Introduction

Secondary amyloidosis is a life-threatening complication of rheumatoid arthritis (RA). Death rates for secondary amyloidosis show a considerable variation in prospective hospital-based studies with follow-up times of 9 to 15 years: from 1.5% in a British to 17.3% in a Spanish study (1-4). In an autopsy-based study from Finland, amyloidosis manifesting as renal failure was the cause of death in 17% of RA patients (5).

Development of secondary amyloidosis is a lengthy process (6), and detection of amyloidosis depends on the intensity and methods of search. Of one series of RA patients with amyloid in their gastroduodenal biopsies, 91% showed amyloid also in their renal biopsies, but amyloid in their abdominal fat aspiration biopsies occurred in only 52% (7). In an autopsy-based study of 76 American RA patients, 7% had amyloidosis (8), but the detection rate was triple to that figure in an autopsy-series of 81 Japanese RA patients (9). In a 5-year follow-up series of 526 Turkish RA patients, only 1% developed amyloidosis (10). In amyloidosis, cardiac involvement (11) and impaired renal function (11, 12) are unfavourable prognostic factors.

We studied amyloidosis as a cause of death in consecutively autopsied 369 RA and 370 non-RA patients between 1952 and 1991. In addition, of the RA patients dying between 1973 and 1991, we were also able to study medical records with information about the frequency of pre-mortem diagnosis of amyloidosis, clinical features of RA, and treatment.

Materials and methods

Patients

All data of the autopsy register including referrals for autopsy, clinicians' statements of cause of death, and autopsy reports with information on death certificates from 1946 to 1991 were screened for a diagnosis of RA at the Department of Pathology of the Kivelä Municipal Hospital in Helsinki. If RA was mentioned on the referral or in the autopsy report, the patient was selected. For each of these 591 RA patients, the next autopsied non-RA patient of the same sex, the same age at death (within a 2-year margin), and same year of autopsy was chosen as reference case. Because very few RA patients fulfilled the inclusion criteria for RA used before the year 1952, the starting point for the study was 1952.

The Kivelä Hospital, besides being an acute-care medical hospital, was responsible for primary as well as tertiary treatment of RA patients in the Capital city area of Finland during the study period.

The mean autopsy frequency at the Kivelä Hospital from 1952 to 1991 was 67% (range of 10-year periods, 57%–72%). The majority of the patients autopsied were also treated at the Kivelä Hospital. Patients referred for autopsy from a surgical or psychiatric hospital were excluded to avoid bias. Complete autopsies, including macroscopic assessment of head and internal organs along with histological examination of organs with suspected abnormality, were performed on all patients. In addition, autopsies included inspection and dissection of joints.

Diagnosis

Because of lack of international diagnostic criteria for RA before 1958 and unavailable medical records before 1973, diagnosis of RA was set by the criteria applied by Aho and colleagues in a review article on epidemiology of RA in Finland (13). They considered the presence of clinical arthritis or of deformities as a sequel to previous arthritis – associated with rheumatoid factor (RF) positivity or radiological changes typical for RA or both – to be a more reliable measure of RA than was RA defined by the American Rheumatism Association criteria from 1958. We therefore modified the Aho group criteria as follows: (i) For RA patients with unavailable medical records, diagnosis was based on information on RA on referrals for autopsy or in autopsy reports completed with the following findings at autopsy: erosions or macroscopic synovitis of a dissected joint or deformities typical for chronic RA at inspection or two or all of these; (ii) If medical records were available, we included patients with clinical polyarthritis and

joint erosions or rheumatic involvement of the cervical spine on radiographs or positive RF or two or all of these. Numbers of the RA patients fulfilling these inclusion criteria have been presented previously (14).

Due to insufficient data or referral for autopsy from a psychiatric or a surgical hospital, two RA patients and one non-RA patient were excluded from our study. The final subject pool comprised 369 RA patients, with 370 non-RA patients serving as reference cases. Because of incomplete information on the cause of death, analysis in one RA patient could only be conducted partially.

Variables evaluated

1. Autopsy reports with information from death certificates

For cause-of-death analysis, we collected immediate, underlying, and contributory causes of death from death certificates filled in by the pathologists performing the autopsies. Whatever clinical manifestation associated with amyloidosis, it was coded as amyloidosis. Presence of renal or heart failure were recorded from referrals for autopsy.

2. Medical records

Because 95% of the medical records between 1952 and 1972 had been destroyed in accordance with archiving legislation (1989), a systematic survey of clinical data of RA patients had to be conducted from 1973 onwards. In that subgroup, the following information was recorded: RF as latex ≥32 (a reciprocal of titre) or + (if qualitative) or Waaler Rose ≥64 (a reciprocal of titre) regarded as positive, duration of RA, presence of extra-articular manifestations (rheumatic nodules, pericarditis, pleuritis, pulmonary fibrosis, pneumonitis, rheumatic eye involvement – also including secondary Sjögren's syndrome, vasculitis and neuropathy which were estimated to associate to RA, and Felty's syndrome), radiographic changes (presence of erosions in joints or rheumatic involvement of the cervical spine), medication: use and duration of disease modifying anti-rheumatic drugs (DMARDs) or glucocorticoids (GC), laboratory features reflecting inflammatory status: erythrocyte sedimentation rate (ESR) and haemoglobin (HB) as mean of the values recorded on the medical records, and orthopaedic operations. Further, we collected information concerning the presence of proteinuria (+ or –) and histological findings in biopsies taken for discovering amyloid.

The Ethics Committee of Helsinki University Central Hospital and the Ministry of Social Affairs and Health approved the study protocol.

Statistical analysis

Statistical analysis was performed with NCSS software. The chi-square or Fisher exact probability test served to compare frequencies. Comparisons of continuous variables were executed by Student's *t*-test or Welch's test for independent samples. Analysis of variance with linear trend was used for calculation of age at death and duration of treatment. Calculations of trend in frequencies were conducted by Armitage test for trend in proportions. A *p*-value of less than 0.05 was considered significant.

Table I. Characteristics of patients dying at the Kivelä Hospital.

10-year periods	1952-1961	1962-1971	1972-1981	1982-1991	All
Rheumatoid arthritis (RA) patients					
Number of patients	50	124	122	73	369
- female (%)	38 (76)	99 (80)	84 (69)	59 (81)	280 (76)
Age at death (years); mean ± SD	65 ± 9	70 ± 9	70 ± 8	75 ± 6	70 ± 9
non-RA patients					
Number of patients	50	126	122	72	370
- female (%)	38 (76)	101 (80)	86 (71)	57 (79)	282 (76)
Age at death (years), mean ± SD	65 ± 9	70 ± 9	70 ± 8	75 ± 6	70 ± 9

Results

Time-period between 1952 and 1991

Demographics

Our study group consisted of 280 female and 89 male RA patients (Table I). Mean age at death of the RA patients was 70±9 years. Over the whole study-period, mean age at death increased from 66 to 77 years in females and from 58 to 73 years in males (*p*-value for linear trend <0.001 for both sexes).

Amyloidosis as a cause of death

Amyloidosis was a cause of death in 35 (9.5%) of the 368 autopsied RA patients – in 22 female (8%) and in 13 male (15%) (p=0.060) – but in none of the non-RA patients (p<0.001). Renal failure appeared in 28 (80%) RA patients dying of amyloidosis and in 45 (14%) dying of other causes (p<0.001). No such difference was detectable in respect to heart failure (34% *vs.* 40%, p=0.481, respectively). In the RA patients dying between 1952 and 1991, we detected no trend with time in cause of death from amyloidosis. All the RA patients

Table II. Causes of death in patients with rheumatoid arthritis.

Cause of death*	Amyloidosis + ** n (%)	Amyloidosis - n (%)	*p*-value
Rheumatoid arthritis	35 (100)	220 (66)	< 0.001
Cardiovascular disease ***	11 (31)	194 (58)	0.002
Coronary heart disease	5 (14)	86 (26)	0.132
Infection	12 (34)	119 (36)	0.865
Renal	4 (11)	18 (5)	0.145
Malignancy	0 (0)	43 (13)	0.022
Respiratory	0 (0)	36 (11)	0.035
Gastrointestinal	0 (0)	38 (11)	0.036
Endocrinological	0 (0)	14 (4)	0.379
Total number of patients	35	333	

*Including immediate, underlying, and contributory causes of death; **Amyloidosis as a cause of death (including immediate, underlying, and contributory causes of death); ***Including cardiac, vascular, and cerebrovascular diseases.

Table III. Organs involved with amyloid deposits in RA patients with and without amyloidosis as a cause of death.

Organ	Amyloidosis+* n (%)**	Amyloidosis – n (%)
Kidney	25 (93)	31 (56)
Spleen	23 (92)	17 (55)
Liver	14 (70)	13 (52)
Heart	10 (42)	10 (33)
Other	18 (78)	17 (53)
- Adrenal gland	10	8
- Thyroid gland	7	5
- Intestine	6	3
- Pancreas	2	2
- Parathyroid gland	0	2
- Lungs	2	2
- Joint	1	0
Total number of patients	27***	38

*Cause of death, including immediate, underlying, and contributory causes of death; **Number of patients with amyloid positive findings (percentage of patients screened); ***At autopsy, amyloid deposits were detectable in 27 out of 35 RA patients with amyloidosis as a cause of death. In the rest of the patients, the pathologist estimated that screening for amyloid is not necessary because diagnosis of amyloidosis had been made before death.

Table IV. Factors associated with amyloidosis in rheumatoid arthritis.

	Amyloidosis as a cause of death	Other causes of death	*p*-value
Mean ESR + SD (mm/h)	74 ± 25	55 ± 23	0.002
Mean HB + SD (g/l)	103 ± 13	118 ± 15	<0.001
Proteinuria; n (%)	15 (75)	33 (23)	< 0.001
Use of DMARDs; n (%)	17 (81)	121 (82)	1.000
Duration of DMARDs + SD (years)	6.6 ± 4.9	4.2 ± 4.9	0.058
Use of GC; n (%)	13 (62)	73 (52)	0.403
Duration of GC + SD (years)	4.6 ± 7.1	2.2 ± 4.5	0.176
Patients with radiographic changes typical for RA; n (%)	20 (100)	131 (94)	0.377
- Severe joint destruction; n (%)	14 (64)	73 (42)	0.060
Rheumatoid factor positivity; n (%)	20 (100)	132 (91)	0.229
Mean duration of RA + SD (years)	21 ± 12	17 ± 11	0.196
Patients with extra-articular manifestations; n (%)	12 (57)	60 (43)	0.209
Patients with orthopaedic operations; n (%)	10 (48)	46 (33)	0.178

Cause-of-death analysis included immediate, underlying, and contributory causes of death between 1973 and 1991; Severe joint destruction included radiographic changes of hip, shoulder, or the cervical spine or two or all of these; ESR: erythrocyte sedimentation rate; HB: haemoglobin; DMARDs: disease modifying anti-rheumatic drugs; GC: glucocorticoids; RA: rheumatoid arthritis.

dying of amyloidosis had also RA as a cause of death (Table II). Almost all the RA patients dying of amyloidosis had renal amyloidosis (Table III). Mean age at death was lower in the RA patients dying of amyloidosis (66±10 years) than in those RA patients dying of other causes (71±8; p=0.001).

Time-period between 1973 and 1991
Duration of RA and medication

In the patients dying between 1973 and 1991, mean duration of RA was 17±11 years. For various time periods, of 169 patients, 138 (82%) and of 161, 86 (53%) had been treated respectively with DMARDs (mean 4.5±4.9 years) and GC (mean 2.5±4.9 years). The proportion of patients receiving these drug therapies and duration of these drug therapies remained unchanged with time (data not shown).

Pre-mortem diagnosis of amyloidosis

Based on post-mortem examination, 20 RA patients had amyloidosis as their cause of death but, diagnosis of amyloidosis had been made pre-mortem in only 13 (65%) of them (12 rectal biopsies, one renal biopsy). Proteinuria had occurred in an additional 6 (30%), but no biopsies had been taken.

Factors associated with amyloidosis as a cause of death

Of the RA patients dying of amyloidosis, 75% had a recording of proteinuria in the medical records. In the RA patients dying of amyloidosis compared to those dying of other causes, mean ESR was significantly higher (p=0.002) and mean HB significantly lower (p<0.001). Although not reaching statistical significance, mean duration of DMARD treatments was longer and severe joint destruction – including radiographic changes of hip, shoulder or the cervical spine or two or all of these – was more frequent in the RA patients dying of amyloidosis. (Table IV).

Discussion

The present study suggests that if biopsies are not taken intensively, amyloidosis as a cause of death is underdiagnosed. Beyond the number of patients diagnosed pre-mortem with amyloidosis, proteinuria had been observed in an additional 30%, but with no biopsies for diagnosing amyloid taken. Rectal or renal biopsies have been previously as diagnostic tools for detection of amyloidosis. Abdominal subcutaneous fat aspiration biopsy – a convenient and safe technique to diagnose amyloidosis – has been considered to be less sensitive than rectal (15) or gastroduodenal biopsy (7).

Variation occurs in interpretation of death certificates. RA mortality studies have used underlying causes of death (2), both underlying and contributory causes of death (1, 3), and immediate, intervening antecedent, underlying, and contributory causes of death (6). A population-based mortality study on RA (16) found amyloidosis in all classes of death – as immediate (2.6%), as contributory (1.8%), as underlying cause of death (3.1%). However, according to the World Health Organization, amyloidosis should not be recorded as the underlying cause of death. Thus, if only

underlying causes of death are analyzed, information about amyloidosis may be lost. Another reason for low recognition of secondary amyloidosis as a cause of mortality can be the recording bias: amyloidosis may appear in different disease groups according to the organ system affected in the International Classification of Diseases system. As shown also here, secondary amyloidosis frequently manifests as renal failure (4, 5, 9). Mortality from such a manifestation may be recorded as unspecified renal failure if information on amyloidosis is absent from the death certificate.

Finnish studies have reported deaths from amyloidosis in 5.8% to 24% of their RA patients (2, 6, 16, 17). One 10-year follow-up of 500 male and 500 female RA patients (2) showed amyloidosis as a cause of death in 8.7%, parallel to our figure. A higher figure than ours came from another hospital-based study, where 24% of deceased RA patients followed for over 20 years died of amyloidosis manifesting as renal failure (17); the result may be biased, because that setting was a tertiary care hospital. However, the 10-year follow-up of 500 male and 500 female RA patients (2) came from the same hospital and did not report such a high figure of deaths from amyloidosis. A population-based Finnish study observed 5.8% of 1666 deceased RA patients to have died of amyloidosis during 1989 (6), a figure lower than ours. Our hospital-based series of RA patients may have suffered from more severe RA than in the population-based study (6), although, the Kivelä Hospital was responsible for primary as well as tertiary RA treatment. Another explanation may be that autopsies were performed in only 27% of the RA patients in that population-based Finnish series (6). Low autopsy frequency (32%) may also be explanation for lower rate of deaths due to amyloidosis (7%) compared to ours in another population-based study with follow-up of 11 years (16).

Hospital-based series from other countries have reported deaths from amyloidosis to be less frequent in their RA patients than in the hospital-based Finnish series (2, 17). During a 15-year follow-up on Norwegian patients (3), 7% of all deceased RA patients died of amyloidosis, while only 1.5% of British patients died during an 11-year follow-up (1). A Spanish group reported, however, that 17.3% died of amyloidosis during a 9-year follow-up in a hospital-based series with mild forms of RA also included (4). Because no autopsy rates were documented in these series and also variations in follow-up times, comparison of our results with these is difficult. We consider our study population to be representative, as the autopsy frequency was high, and the Kivelä Hospital was responsible for primary to tertiary care of all RA patients in Helsinki.

In our RA patients dying of amyloidosis, mean HB was lower and mean ESR higher than in the RA patients dying of other causes, as reflected also in a 15-year follow-up study of RF-positive RA patients (18). We considered these as indicators of more active inflammation, but proteinuria and renal insufficiency can cause similar changes. Parallel to earlier findings of shortened life-span in RA patients (2, 6) dying of amyloidosis, our RA patients dying of amyloidosis died younger than did the rest of the RA patients. This may contribute – along with the finding that all of them had also RA as a cause of death – to the observation that those patients dying of amyloidosis died less frequently from other diseases (cardiovascular diseases, malignancies, respiratory or gastrointestinal diseases). A finding suggesting that men with rheumatic disease are at higher risk for secondary amyloidosis than are similarly affected women (12) parallels our finding of almost twice as frequent deaths from amyloidosis in men as in women, although the difference did not reach statistical significance. In contrast to earlier Finnish findings showing the incidence of amyloidosis in patients with inflammatory joint disease declining between 1987 and 1997 along with a declining number of biopsies (19), amyloidosis as a cause of death showed no major changes in the present autopsy study.

In conclusion, amyloidosis was undiagnosed pre-mortem in approximately one-third of our RA patients dying of amyloidosis. Amyloidosis, being a life-threatening complication, should be diagnosed as early as possible. An intensive search for amyloid is recommended in RA patients with active and long-lasting disease, especially, if they have proteinuria or renal failure or both. Early diagnosis is even more essential nowadays, when effective medications for RA are available, as they were not during the time covered by this study.

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