ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Diagnostic Pitfalls of Rheumatoid Arthritis - A Postmortem Clinicopathologic Study of 161 Autopsy Patients

Ágnes Apáthy[1] and Miklós Bély[2]*

[1]*Department of Rheumatology, St. Margaret Clinic, Budapest, Hungary*

[2]*Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary*

***Corresponding Author:** Miklós Bély, Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary.

Received: April 16, 2026; **Published:** April 29, 2026

Abstract

Over the last decades the number of autopsies has drastically been reduced. Due to lack of verification, the true number of clinical errors, misdiagnosed and unrecognized cases may remain hidden.

This study focuses on those complications or comorbidities of rheumatoid arthritis (RA), where there was a significant difference between the incidence of the most important complications or comorbidities and the number of clinically recognized cases.

AA amyloidosis (AAa) was the most common complication of RA, while autoimmune vasculitis (AV) was the second most common, and acute bacterial septic infection (AbSI) the third one.

The most dangerous (and most commonly overlooked) complication of RA was AV, including fatal undiagnosed cases.

Detection of dormant tuberculosis (TB) or acute flare ups is really a great challenge for the rheumatologist, based on the clinically recognized and missed cases.

Keywords: *Rheumatoid Arthritis; Autoimmune Vasculitis; AA Amyloidosis; Acute Bacterial Septic Infection; Purulent Arthritis; Tuberculosis; Missed Diagnosis*

Introduction

Clinical symptoms can be misleading. Complications of the underlying disease or associated diseases can affect each other, classic clinical symptoms can change, and fatal complications or important associated diseases can go unrecognized.

The processing of surgical and biopsy material is essential; histological examination often yields unexpected results.

Pathologists must process tissue samples with utmost circumspection, consider possible complications, and use appropriate methods to detect them. On the other hand, the microscopic finding or diagnosis must be evaluated by clinicians on its own merits.

Objective of the Study

- This study focuses on those complications or comorbidities of rheumatoid arthritis (RA), which showed a significant difference between the incidence of the most important complications or comorbidities and the number of clinically recognized cases.
- The claims are based on previous clinicopathological studies [1-5].
- Similar analytical work was not encountered in the literature.

Methodology

Autopsy population

Different patient groups of autoimmune diseases were analyzed; all died at the National Institute of Rheumatology and Physiotherapy (ORFI).

One hundred sixty-one (161) patients with rheumatoid arthritis (RA) were autopsied to determine the incidence and mortality of systemic autoimmune vasculitis (AV), AA amyloidosis (AAa), fatal acute bacterial septic infection (AbSI), or purulent arthritis (PA). Attention was paid to one of the most important comorbidities, post-primary tuberculosis (TB).

The patients died between 1970 and 1990.

The patients with clinically diagnosed RA fulfilled the criteria of the American College of Rheumatology (ACR) [6].

The patient's history and protocols were clinically controlled by the co-author, Ágnes Apáthy, rheumatologist, neurologist; the autopsies and histopathologic reports were reviewed by Miklós Bély.

Methods

Existence and mortality of AV, AAa, AbSI, PA, or TB was specified histologically, based on a detailed evaluation of twelve organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) in 161 RA patients.

Mortality of AV and AAa were determined on the basis of autopsy and clinical protocols. In the case of AbSI (with or without PA), only the fatal acute bacterial septic infections were considered.

AA amyloid deposition in different tissue structures of various organs was diagnosed histologically according to Romhányi [7] by a modified, more sensitive Congo red staining [8]. The types of amyloid deposits were identified by immunohistochemical [9] and histochemical methods [10-12].

Results

Demographics of patients with RA and PSS

RA was complicated with AV in 33 (20.49%), with AAa in 34 (21.12%), with AbSI in 24 (14.98%), with PA in 15 (9.32%) patients, and was associated with TB in 21 (13,03%) cases.

Table 1 summarizes the demographics and mean age of the entire population of RA patients, along with the main complications (AV, AAa, AbSI, PA) and with the most important comorbidity (TB).

Demographics of RA and PSS patients	Number of autopsies	Mean age in years at death ± SD
RA patients (total)	161	65,32 ± 12,99
Female	116	64,95 ± 11,84
Male	45	66,27 ± 15,67
With AV	33 of 161	67,18 ± 10,80
Female	20	66,95 ± 11,40
Male	13	67,46 ± 10,24

With AAa	34 of 161	62,41 ± 15,82
Female	29	64,34 ± 11,27
Male	5	52,20 ± 31,51
With AbSI*	24 of 161	61,25 ± 8,73
Female	17	60,41 ± 9,50
Male	7	63,29 ± 6,70
With PA**	12 of 161	59,08 ± 5,90
Female	8	58,75 ± 5,80
Male	4	59,75 ± 6,95
With TB	21 of 161	69,00 ± 9,94
Female	15	70,20 ± 10,54
Male	6	66,00 ± 8,32

Table 1: *Demographics and mean age of RA and PSS patients with the main complications and coexistent tuberculosis.*

*Legends to table 1: *: In the case of AbSI (with or without PA), only the fatal septic infection was considered. **: PA did not exist without AbSI.*

Abbreviations to table 1: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AAa: Systemic AA Amyloidosis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; PA: Purulent Septic Arthritis; TB-post: Primary Tuberculosis; SD: Standard Deviation.

Comparing the mean age of RA patients at the time of death, there was no significant difference in survival time between the total population (n = 161) and patients with AV (n = 33) ($p < 0.389$), neither in women ($p < 0.477$), nor in men ($p < 0.748$) patients with AAa (n = 24) ($p < 0.321$), neither in women ($p < 0.800$), nor in men ($p < 0.348$ patients with AbSI (n = 24) ($p < 0.054$), neither in women ($p < 0.088$), nor in men ($p < 0.398$) or patients with TB (n = 21) ($p < 0.136$), neither in women ($p < 0.090$), nor in men ($p < 0.950$).

The life expectancy of patients with PA (n = 12) was significantly worse, and the patients with PA died earlier compared to the overall population (59.08 years versus 65.32 years, $p < 0.005$), either in women (58.75 years versus 64.95 years, $p < 0.021$) or in men (59.75 years versus 66.27 years, $p < 0.00013$).

AV, AAa, AbSI and TB involved both genders and developed at any time in the course of RA (Table 1 and 2).

Table 2 summarizes the relationship in mean age of female and male RA patients ("p" correlation values) between the overall population (n = 161) and AV, AAa or AbSI (with and without PA).

RA patients n = 161 (total)	**Age**
RA patients n = 161 versus pts. with AV n = 33	0,389
Female n = 116 of 161 versus n = 20 of 33	0,477
Male n = 45 of 161 versus n = 13 of 33	0,748
RA patients n = 161 versus pts. with AAa n = 34	0,321
Female n = 116 of 161 versus n = 29 of 34	0,8
Male n = 45 of 161 versus n = 5 of 34	0,348
RA patients n = 161 versus pts. with AbSI n = 24	0,054
Female n = 116 of 161 versus n = 17 of 24	0,088
Male n = 45 of 161 versus n = 7 of 24	0,398

RA patients n = 161 versus pts. with PA n = 12	0,005
Female n = 116 of 161 versus n = 8 of 12	0,021
Male n = 45 of 161 versus n = 4 of 12	0,000129
RA patients n = 161 versus pts. with TB n = 21 of 234	0,136
Female n = 116 of 161 versus n = 15 of 21	0,09
Male n = 45 of 161 versus n = 6 of 21	0,95

Table 2: *Statistical correlations ("p" values of significance) between female and male RA patients, with AV, AAa, AbSI or PA.*

Legend to table 2: There was no significant difference in the mean age of RA patients comparing the total autopsy population (n = 161) and the patient cohorts with AV, AAa, AbSI or TB; "p" values were higher than 0.05. The survival of RA patients complicated with PA was worse than the life expectancy of the total RA population.

Abbreviations to table 2: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AAa: Systemic AA Amyloidosis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; PA: Purulent Septic Arthritis; TB-post: Primary Tuberculosis; SD: Standard Deviation.

Incidence and mortality of autoimmune vasculitis (AV), AA amyloidosis (AAa), and fatal acute bacterial septic infection (AbSI), purulent arthritis (PA) and post-primary tuberculosis (TB) in rheumatoid arthritis (RA)

In 161 patients with RA systemic vasculitis occurred in 36 patients (22.36%/161). Vasculitis of autoimmune origin was identified in 33 patients (20.50%/161) and vasculitis of septic origin (as part of the generalized fatal septic infection) in 3 patients (1.86%/161) (Table 3 and 5).

Incidence and mortality of autoimmune vasculitis (AV)

Autoimmune vasculitis (AV) caused directly the death of 19 (57.58%/33) patients, while 14 (42.42%/33) patients died from other causes (myocardial necrosis, heart or circulatory failure, purulent bronchiolitis, uremia caused by AV with renal AAa or cachexia).

Autoimmune vasculitis was clinically recognized in 6 patients (18.18%/33), while in 27 patients' vasculitis remained undiagnosed (81.82%/33).

Of the 6 clinically recognized cases, vasculitis was fatal in 4 patients (21.05%/19) and not fatal in 2 patients; the 15 (78.95%/19) additional fatal cases of AV remained clinically unrecognized.

Table 3 summarizes the incidence and mortality of AV with the most important complications and concomitant diseases in RA.

	Basic disease		Complication (1)	Complication (2)	Cause of death	Associated disease(s)	Cl+ Cl-	Pr. n^0/ Year
1	RA	AV	Coronary thrombovasculitis	Coronary arteriolitis	Myocardial necrosis	fcTB-Ca- Ath	Cl	65/90
2	RA	AV	Coronary arteritis-arteriolitis		Myocardial microinfarctions, multiple		Cl-	20/70
3	RA	AV	Coronary arteritis-arteriolitis		Myocardial microinfarctions, multiple		Cl+	110/80
4	RA	AV	Coronary arteritis-arteriolitis	Myocarditis	Myocardial microinfarctions, multiple		Cl+	275/87

5	RA	AV	Coronary arteritis-arteriolitis		Myocardial microinfarctions, multiple		Cl	312/87
6	RA	AV	Coronary arteritis-arteriolitis	Pancarditis	Myocardial microinfarctions, multiple	Ath	Cl	295/88
7	RA	AV	Coronary arteritis-arteriolitis		Myocardial microinfarctions, multiple		Cl	285/89
8	RA	AV	Coronary arteritis-arteriolitis	AA amyloidosis	Myocardial microinfarctions, multiple	fcTB-mTB	Cl+	395/76
9	RA	AV	Coronary arteriolitis	AA amyloidosis	Myocardial microinfarctions, multiple	fTB-mTB	Cl	240/88
10	RA	AV	Coronary arteriolitis	Myocarditis	Myocardial microinfarctions, multiple	fcTB-mTB	Cl	227/89
11	RA	AV	Coronary arteriolitis		Myocardial microinfarctions, multiple		Cl	221/91
12	RA	AV	Coronary arteriolitis		Myocardial microinfarctions, multiple	Ath	Cl	81/70
13	RA	AV	Pulmonary arteriolitis		Rheumatoid pneumonia		Cl	V/A
14	RA	AV	Pulmonary arteriolitis		Rheumatoid pneumonia		Cl	25/85
15	RA	AV	Pulmonary arteriolitis		Rheumatoid pneumonia	Ath	Cl	119/85
16	RA	AV	Cerebral vasculitis	Pulmonary embolism	Infarct pneumonia		Cl	123/86
17	RA	AV	Cerebral vasculitis, multiple	Bronchopneumonia	Brain necrosis, multiple	DM-TB- CAA	Cl	279/87
18	RA	AV	Thrombovasculitis renal artery	Coronary arteriolitis	Renal necrosis		Cl+	194/88
19	RA	AV	Thrombovasculitis mesenteric a.		Hemorrhagic intestinal necrosis	DM	Cl	144/92
20	RA	AV	AA amyloidosis		Myocardial necrosis	DM- Ath	Cl	90/85
21	RA	AV	Nodular pancarditis		Circulatory failure	fcTB-mTB-Ath	Cl	87/90
22	RA	AV	Pancarditis	Coronary arteriolitis	Circulatory failure		Cl+	146/91
23	RA	AV	Coronary arteritis-arteriolitis		Circulatory failure	fTB- Ath	Cl	36/86
24	RA	AV	Coronary arteritis-arteriolitis	AA amyloidosis	Circulatory failure		Cl	243/87
25	RA	AV	Coronary arteriolitis	Microinfarction	Circulatory failure	Ath	Cl+	20/80
26	RA	AV	Coronary arteriolitis	Pancarditis	Circulatory failure	DM-fcTB- Ath	Cl	41/90
27	RA	AV	Vasculogenic pancreatitis		Circulatory failure	fTB	Cl	174/72

28	RA	AV	Coronary arteritis-arteriolitis	Myocarditis	Circulatory failure	DM-Ath	Cl	114/71
29	RA	AV	Valvular endocarditis		Heart failure	DM	Cl	40/89
30	RA	AV	Nodular pancarditis	Coronary arteritis	Heart failure-Broncho-pneumonia	Ath	Cl	14/92
31	RA	AV			Purulent bronchiolitis		Cl	175/82
32	RA	AV	AA amyloidosis		Uremia	DM-HT	Cl	43/85
33	RA	AV			Cachexia	Ath	Cl	288/73

Table 3: *Incidence and mortality of systemic autoimmune vasculitis (AV) with major complications and comorbidities in RA (by the fatal outcome of AV).*

Glossary to table 3 (33 AV of 161): Basic disease: Underlying disease related to death.

Complication: Consequence of basic disease leading directly to death (bold).

Cause of death: Fatal outcome of AV (bold) (19 of 33).

Clinically recognized 4 of 19 fatal cases, and missed in 15 of 19.

Not fatal outcome of AV (14 of 33). In these cases, the AV was so moderate and did not explain in itself the fatal outcome.

Clinically recognized 2 of 14 not fatal cases, and missed 12 of 14.

Cl+ or Cl- -Clinically recognition refers in table 3 only to the AV.

Associated (Accompanying) disease: Important disorder without direct causal role in death.

Abbreviations to table 3: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AAa: Systemic AA Amyloidosis; fTB: Post Primary Fibrous Tuberculosis; fcTB: Post Primary Fibro Caseous Tuberculosis; mTB: Miliary Dissemination of Post Primary Tuberculosis; Ath: Atherosclerosis; HT: Hypertension; DM: Adult Type 2 Diabetes Mellitus; Ca: Bronchoalveolar Carcinoma; CAA: Cerebral Amyloid Angiopathy (Cerebral Aβ Protein-Related Amyloidosis); Pr. n⁰/ Year: Protocol Number/Year.

Figure 1 and 2 demonstrate the ratio of clinically diagnosed fatal and not fatal outcome of AV, furthermore the cause of death due to AV.

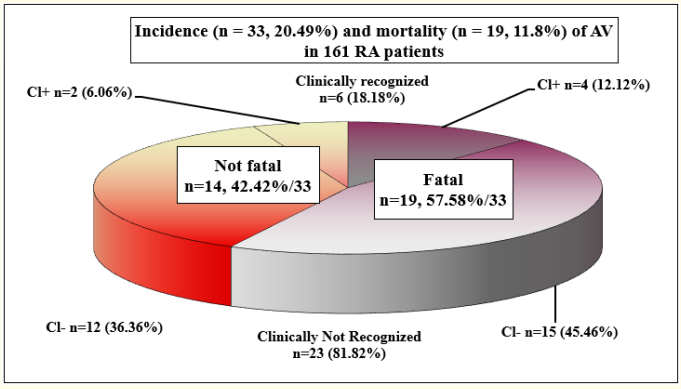

Figure 1: *Clinical diagnosis of fatal or non-fatal AV.*

Legends to figure 1: AV was fatal in 19 (57.58%) and not fatal in 14 (42.42%) of 33 patients. AV was detected clinically in 6 (18.18%), and not detected in 27 of (81.82%) of 33 patients.

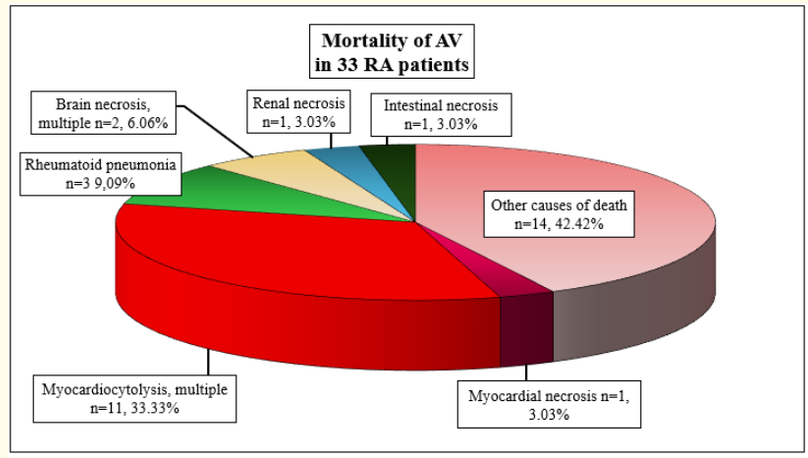

Figure 2: *Mortality of AV.*

Legends to figure 2: AV led directly to death in 19 (57.58%) of 33 patients, due to myocardial infarction in 1, multiple myocardiocytolysis in 11, rheumatoid pneumonia in 3, multiple brain necrosis in 2, renal necrosis in 1, and hemorrhagic intestinal necrosis in 1 patient.

AV had no direct causal role of death in 14 (42.42%) of 33 patients.

Incidence and mortality of AA amyloidosis (AAa)

Systemic AA amyloidosis (AAa) occurred in 34 patients (21.12%/161).

Seventeen (50.0%/34) patients died of uremia due to renal failure, and 17 (50.0%/34) patients died of other causes (myocardial necrosis, myocardiocytolysis, heart or circulatory failure, bronchopneumonia, pulmonary embolism, peritonitis, AbSI).

Amyloidosis was clinically recognized in 9 (26.47%/34) patients, while in 25 (73.53%/34) patients it was not.

Known AAa caused fatal renal failure and uremia in 9 (52.94%/17) patients. In further 8 (47.06%/17) patients who died of uremia, the possibility of AAa was not considered clinically; other causes were considered for the origin of uremia (atherosclerosis, diabetes etc.).

Table 4 summarizes the incidence and mortality of AAa with the most important complications and concomitant (associated) diseases in RA.

	Basic disease	Complication (1)	Complication (2)	Cause of death	Associated disease(s)	Cl+ Cl-	Pr. n^0 / Year
1	RA	AAa		Uremia	Ath	Cl-	237/70
2	RA	AAa		Uremia		Cl+	232/74
3	RA	AAa		Uremia	Ath	Cl-	39/76
4	RA	AAa		Uremia		Cl+	137/76
5	RA	AAa		Uremia	Ath	Cl+	80/80
6	RA	AAa		Uremia	Neurinoma	Cl+	181/80
7	RA	AAa		Uremia	Ca*	Cl+	265/80
8	RA	AAa		Uremia	DM	Cl+	255/83
9	RA	AAa	AV	Uremia	DM, HT	Cl-	43/85
10	RA	AAa		Uremia		Cl-	V/T
11	RA	AAa		Uremia	Ath, Neurinoma	Cl-	342/86
12	RA	AAa		Uremia		Cl+	53/87
13	RA	AAa		Uremia		Cl+	73/87

14	RA	AAa		Uremia		Cl-	174/88
15	RA	AAa		Uremia		Cl-	203/88
16	RA	AAa		Uremia		Cl-	101/90
17	RA	AAa		Uremia		Cl+	306/90
18	RA	AAa		Myocardial necrosis	Ath, DM	Cl-	367/75
19	RA	AAa	Nodular epicarditis	Myocardial necrosis	(Ca)	Cl-	287/91
20	RA	AAa	AV	Myocardial necrosis	Ath, DM	Cl-	90/85
21	RA	AV	AAa	Myocardiocy-tolysis	fTB-mTB	Cl-	240/88
22	RA	AV	AAa	Myocardiocy-tolysis	fTB-mTB	Cl-	395/76
23	RA	AAa		Heart failure		Cl-	45/74
24	RA	AAa		Circulatory failure	Ca	Cl-	430/80
25	RA	AAa		Circulatory failure		Cl-	322/81
26	RA	AV	AAa	Circulatory failure		Cl-	243/87
27	RA	AAa	Obliterative bron-chiolitis	Multifocal pneu-monia	DM	Cl-	245/88
28	RA	AAa		Bronchopneu-monia	Ath, HT	Cl-	52/92
29	RA, Ca**	AAa	Sporadic Tu associ-ated vasculitis*	Perifocal pneu-monia	Ath	Cl-	226/85
30	RA, Ependy-moma	AAa -	Fracture of vertebra	Pulmonary embolism	Ath	Cl-	155/87
31	RA	AAa	Duodenal ulcer, Perforation	Peritonitis		Cl-	76/79
32	RA	AAa	Gastric ulcer, Perfo-ration	Peritonitis, AbSI		Cl-	162/78
33	RA	AAa	Colitis-	Peritonitis, AbSI		Cl-	183/92
34	RA	AAa	Ascending urinary tract infection, bedsores	AbSI	Ath	Cl-	266/78

Table 4: *Incidence and mortality of AA amyloidosis (AAa) with major complications and comorbidities in RA (by the fatal outcome of AAa).*

Glossary to table 4 (34 AAa of 161): Basic disease: Underlying disease related to death (RA).

Complication: Consequence of basic disease leading directly to death (AAa - bold).

Cause of death: Fatal outcome of AAa (Uremia - bold) (17 of 34).

Clinically recognized 9 of 17 fatal cases, and missed 8 of 17.

Not fatal outcome of AAa (17 of 34) were in all patients clinically missed.

Cl+ or Cl- -Clinically recognition in table 4 refers only to the AAa.

AAa was clinically diagnosed (recognized) in 9 (26.5%) of 34 cases.

AAa was clinically missed in 25 (73.52%) of 34 cases.

Associated (Accompanying) disease: important disorder without direct causal role in death.

Abbreviations to table 4: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AAa: Systemic AA Amyloidosis; fTB: Fibrous Post Primary Tuberculosis; mTB: Miliary Dissemination of Post Primary Tuberculosis; Ath: Atherosclerosis; HT: Hypertension; DM: Adult Type 2 Diabetes Mellitus; Ca: Pancreatic Carcinoma; Ca**: Bronchoalveolar Carcinoma; (Ca): Breast cancer, surgically removed (no tumor at autopsy); Pr. n^{0}/ Year: Protocol Number/Year.*

Figure 3 and 4 demonstrate the ratio of clinically diagnosed fatal and not fatal outcome of AAa, furthermore the cause of death due to AAa.

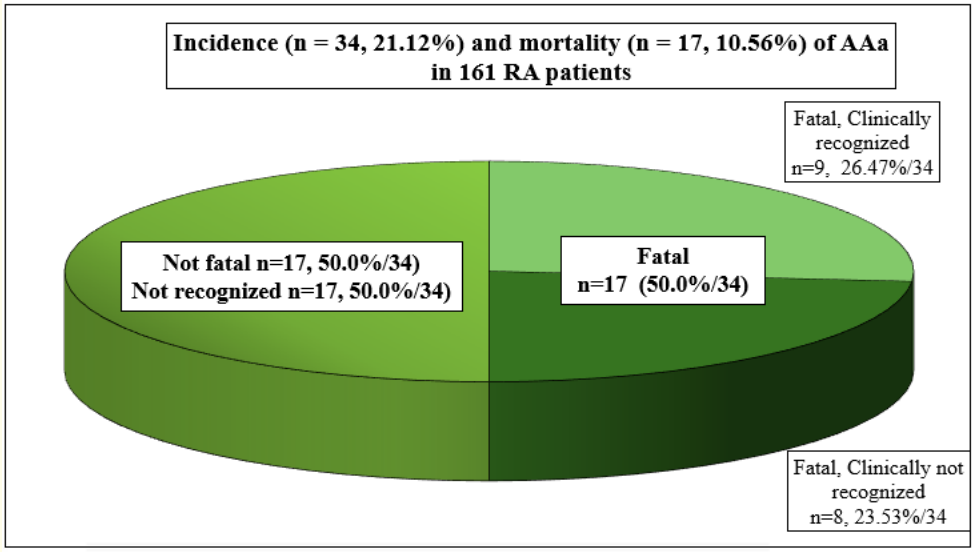

Figure 3: *Clinical diagnosis of fatal or non-fatal AAa.*

Legends to figure 3: AAa was fatal in 17 (50.0%) and not fatal in 17 (50.0%) of 34 patients. AAa was detected clinically in 9 (26.47%), and not detected in 8 of (23.53%) of 34 patients.

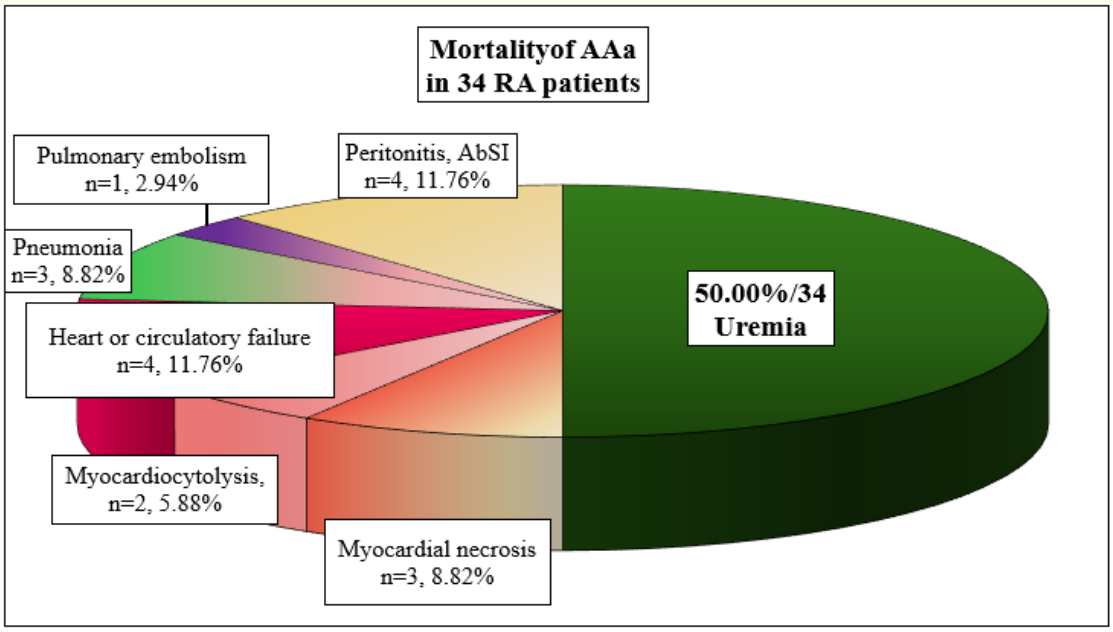

Figure 4: *Mortality of AAa.*

Mortality of acute bacterial septic infection (AbSI) and purulent arthritis (PA)

Fatal acute bacterial septic infection (AbSI) occurred in 24 patients (14.9%/161), in 12 patients (7.45%/161) as a result of purulent arthritis, and in 12 (7.45%/161) patients due to other causes such as gastrointestinal inflammation, ulcer, gastrointestinal perforation, peritonitis, decubital ulcer and ascending urinary tract infection or gangrene. In one patient the origin of AbSI was not identified because of the drastic antibiotic treatment; the case was registered as "Sepsis sine Sepsi", only the toxic signs of sepsis were detected.

Septic infection was clinically diagnosed in 11 (45.83%/24) patients, while in 13 (54.17%/24) patients it was not (the diagnosis of "sepsis" was not included in the final report).

Purulent arthritis (PA) was clinically known in 6 (50.0%/12) patients and not in 6 (50.0%/12) patients. PA did not exist without fatal AbSI.

AbSI was complicated with systemic vasculitis of septic origin (acute bacterial septic vasculitis - AbSV) in 3 patients. AbSV was clinically recognized in one (33.33%) of these three patients.

Table 5 summarizes the mortality of AbSI with or without PA, and the most important complications and concomitant (associated) diseases in RA.

	Basic disease	Complication (1)	Complication (2)	Cause of death	Associated disease	Cl+ Cl-	Pr. n^0/Year
1	RA	PA (Cl+)		AbSI	Ath	Cl+	267/75
2	RA	PA (Cl+)		AbSI	fcTB	Cl+	287/75
3	RA	PA (Cl-)		AbSI	Ath	Cl-	301/75
4	RA	PA (Cl-)		AbSI	DM	Cl-	234/79
5	RA	PA (Cl+)		AbSI		Cl+	269/81
6	RA	PA (Cl-)		AbSI		Cl-	267/83
7	RA	PA (Cl+)	Septic vasculitis (Cl-)	AbSI		Cl+	332/84
8	RA	PA (Cl+)		AbSI	DM	Cl+	V11/85
9	RA	PA (Cl+)		AbSI		Cl+	199/88
10	RA	PA (Cl-)		AbSI	DM	Cl-	221/88
11	RA	PA (Cl-)		AbSI	fcTB, Ath	Cl-	169/89
12	RA	PA (Cl-)		AbSI	CAA	Cl-	178/90
13	RA	Gangrene		AbSI		Cl+	162/71
14	RA	Decubital ulcer		AbSI	Ath, HT	Cl+	14/72
15	RA	Septic vasculitis (Cl+)	Hemorrhagic pancreatitis	AbSI		Cl+	166/86
16	RA	Septic vasculitis (Cl-)	Duodenal ulcer	AbSI	Ath	Cl+	318/89
17	RA	Colitis	Duodenal ulcer,	AbSI		Cl-	243/78
18	RA	Colitis	Gastric ulcer,	AbSI	DM, Ath	Cl-	228/72
19	RA	AAa	Gastric ulcer	AbSI		Cl-	162/78

20	RA	AAa	Colitis, Colonic ulcers	AbSI		Cl+	183/92
21	RA		Colitis, Colonic ulcers	AbSI	DM	Cl-	27/73
22	RA	AAa	Not identified	AbSI	Ath	Cl-	266/78
23	RA	Diverticulitis, Colitis	Diverticulum perforation	AbSI	Ath, HT	Cl-	380/78
24	RA	Diverticulitis, Colitis, Ulcerative gastritis	Diverticulum perforation	AbSI		Cl-	55/82

Table 5: *Mortality of AbSI and PA, with the major complications and comorbidities (only the fatal AbSI were considered exclusively; PA did not exist without fatal AbSI).*

Glossary to table 5 (24 AbSI with or without PA or SV of 161): Basic disease: Underlying disease related to death (RA).

Complication: Consequence of basic disease leading directly to death (bold).

Cause of death: Fatal outcome of AbSI (bold) (24 of 24) with (12 of 24) or without PA (12 of 24).

AbSI was clinically recognized in 11 of 24 fatal cases, and missed in 13 of 24.

Cl+ or Cl- - Clinically recognition refers in table 5 to the AbSI.

In parenthesis (Cl+ or Cl-) clinical diagnosis refers to the PA, and to the systemic vasculitis of septic origin.

Associated (Accompanying) disease: important disorder without direct causal role in death.

Abbreviations to table 5: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AAa: Systemic AA Amyloidosis; fTB: Post Primary Fibrous Tuberculosis; fcTB: Fibro Caseous Post Primary Tuberculosis; mTB: Miliary Dissemination of Post Primary Tuberculosis; Ath: Atherosclerosis; HT: Hypertension; DM: Adult Type 2 Diabetes Mellitus; Pr. n^0/ Year: Protocol Number/Year.

Figure 5 and 6 demonstrate the clinically recognized fatal AbSI with or without PA, and the suspected origin of AbSI.

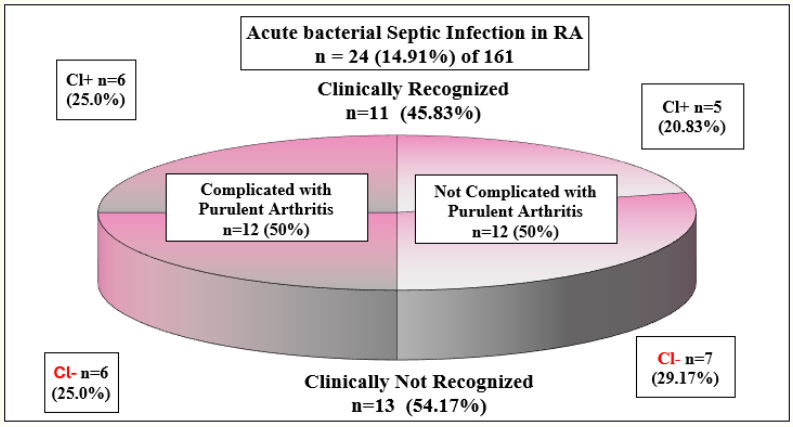

Figure 5: *Clinical diagnosis of fatal AbSI with or without PA.*

Legends to figure 5: Fatal AbSI was accompanied by purulent (suppurative) arthritis in 12 (50.0%) of 24 patients, and were not in 12 (50.0%) patients. AbSI was detected clinically in 11 (45.8% of 24), and not detected in 13 of 24 fatal cases (54.2% of 24).

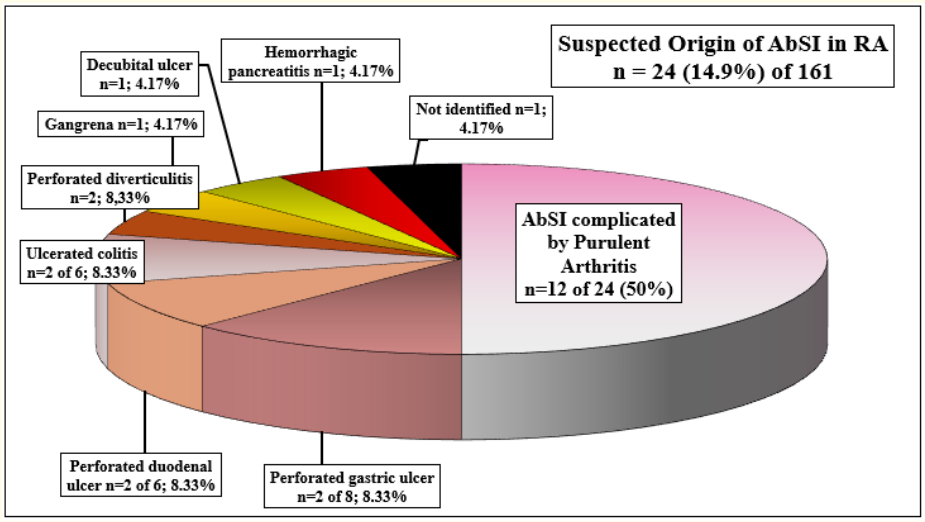

Figure 6: *Suspected origin of fatal AbSI with or without PA.*

Legends to figure 6: AbSI was caused by PA in 12 patients, and were caused by others such as gastrointestinal inflammation, ulcer, perforation, peritonitis, decubital ulcer and ascending urinary tract infection or gangrene in further 12 patients.

Incidence and mortality of tuberculosis (TB)

Post-primary tuberculotic foci of the lungs (TB) were found in 21 (13.04%/161), patients with RA at autopsy; chronic pigmented fibrous scars (fTB) in the lungs were identified in 12 (57.14%/21) patients and fibro-caseous tuberculotic foci (fcTB) in 9 (42.86%/21) patients.

TB was active (with miliary epithelioid granulomatous dissemination - mTB) in 6 (28.57%/21) patients, and inactive (without mTB) in 15 (71.43%/21).

Miliary epithelioid granulomas were not seen without fTB or fcTB.

TB with miliary dissemination (mTB) was fatal in 2 (33.33%/6) patients; they died of circulatory failure. The miliary dissemination and the fatal role of mTB was not recognized clinically.

TB was clinically known in 2 (9.52%/21) patients, in final reports chronic inactive fTB was mentioned. The clinical diagnosis of TB based in both cases on the patient history (anamnesis) and was confirmed by X-ray examination.

In 19 (90.48%/21) patients TB remained hidden (not recognized).

Table 6 summarizes the incidence and mortality of TB with the most important complications and comorbidities in RA.

Figure 7 and 8 demonstrate the incidence of post-primary TB, furthermore the mortality of TB in 161 RA patients.

	Basic disease	Complication (1)	Cause of death	Associated disease	Cl+/ Cl-	Pr. n^0 / Year
1	fcTB	mTB	Circulatory failure	RA DM	Cl-	61/70
2	fcTB	mTB	Circulatory failure	RA	Cl-	140/70
3	RA	AV-AAa	Myocardiocytolysis	fcTB-mTB	Cl-	395/76
4	RA	AV-AAa	Myocardiocytolysis	fTB-mTB	Cl-	240/88
5	RA	AV	Myocardiocytolysis	fcTB-mTB, HT	Cl-	227/89
6	RA	AV	Circulatory failure	fcTB-mTB, Ath	Cl-	87/90
7	RA	AV	Circulatory failure	fTB	Cl+	174/72
8	RA	Fibrinous pericarditis	Circulatory failure	fTB, Ath	Cl-	30/75
9	RA	PA	AbSI	fcTB	Cl-	287/75
10	RA	Interstitial pneumonitis, ILH	Multifocal pneumonia	fTB, -DM, Ath, HT	Cl-	115/84
11	RA	AV	Circulatory failure	fTB, Ath	Cl-	36/86
12	RA	AV	Multifocal brain necrosis	fTB, CAA, DM	Cl-	279/87
13	RA	PA	AbSI	fcTB, Ath	Cl-	169/89
14	RA	AV	Circulatory failure	fcTB, DM, Ath	Cl-	41/90
15	RA	AV	Myocardial necrosis	fcTB, Ca*, Ath	Cl-	65/90
						318/76
16	Ath	Myocardial fibrosis	Bronchopneumonia	RA-fTB	Cl-	208/77
17	Ath	Myocardial fibrosis	Circulatory failure	RA- fTB	Cl+	257/80
18	Ath	Myocardial fibrosis	Circulatory failure	RA- fTB	Cl-	283/80
19	Ath	Coronary thrombosis	Myocardial necrosis	RA- fTB -DM-G	Cl-	62/83
20	Ath	Cerebral artery sclerosis	Multifocal brain necrosis	RA- fTB -DM-G	Cl-	121/87
21	Ath	Coronary thrombosis	Myocardial necrosis	RA- fTB -DM	Cl-	61/70

Table 6: *Incidence and mortality of TB with the major complications and comorbidities in RA (by the basic diseases of mTB, RA or Ath, related to death).*

Glossary to table 6 (21 TB of 161): Basic disease: Underlying disease related to death (RA, Ath or TB).

Complication: Consequence of basic disease leading directly to death.

Cause of death: Fatal outcome of TB (2 of 21); clinically recognized 0 of 2 fatal cases (bold).

Not fatal outcome of TB (19 of 21); clinically recognized 2 of 19 not fatal cases.

Cl+ or Cl- -Clinical recognition in table 6 refers only to TB.

Associated (Accompanying) disease: important disorder without direct causal role in death.

Abbreviations to table 6: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AAa: Systemic AA Amyloidosis; TB-Post: Primary Tuberculosis; fcTB: Fibro-Caseous Post-Primary Tuberculosis; mTB: Miliary Dissemination of Post Primary Tuberculosis; Ath: Atherosclerosis; HT: Hypertension; DM: Adult Type 2 Diabetes Mellitus; ILH: Interstitial Lymphoid Hyperplasia; CAA: Cerebral Amyloid Angiopathy (Cerebral Aβ Protein-Related Amyloidosis); Ca: Bronchoalveolar Carcinoma; G: Gout; Pr. n^0/ Year: Protocol Number/Year.*

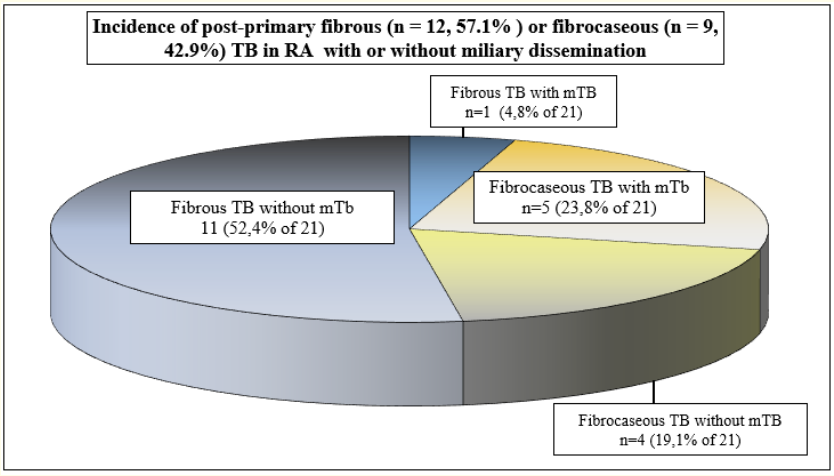

Figure 7: *Incidence of post-primary fibrous or fibro-caseous TB in 161 RA patients.*

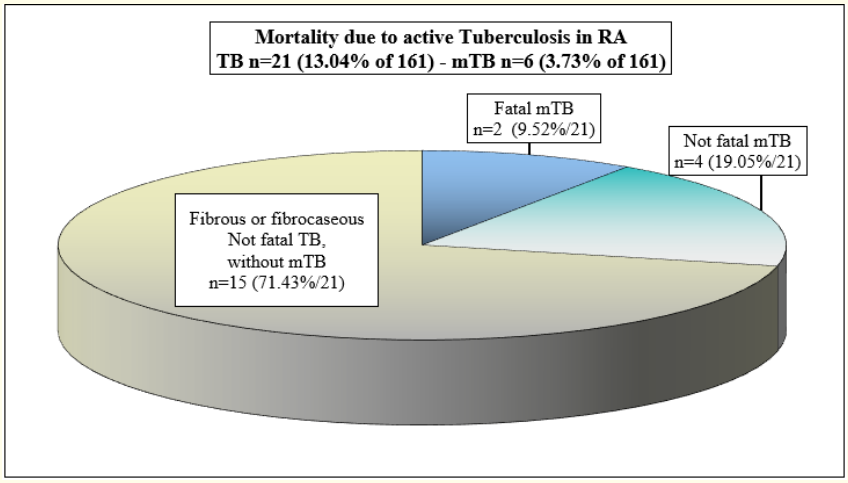

Figure 8: *Mortality of post-primary fibrous or fibro-caseous TB.*

Discussion

Recognition of the underlying disease (RA) itself, can also be delayed by overlapping symptoms. Clinical symptoms may mimic other diseases, especially in the early stages of RA.

Gomez., *et al.* (2015) evaluated 4780 patients with clinical diagnosis of RA in primary level of Colombian medical centers; in 2905 patients (60.7%) diagnosis of RA was correct, in the remaining 1875 patients (39.3%) it was incorrect and misleading [13].

In a group of patients (n = 2543) who met fewer than four of the ACR 1987 criteria, RA had to be reassessed in 45 patients (1.769% of 2543 patients) [14].

To an RA center were referred 4424 patients with presumptive RA diagnosis. RA was ruled out in 70% of patients; of them patients 50% had a final osteoarthritis diagnosis or other arthropathies 20% [15].

Even in known RA the complications of basic disease or comorbidities may remain hidden. Early complications are usually asymptomatic and difficult to recognize.

Coexisting complications and associated diseases accompanying RA may modify the clinical course and symptoms of RA and may influence the prevalence and mortality of complications related to the basic diseases and vice versa. The lack of classic clinical symptoms may result in unrecognized cases.

The demographic data of our patient groups did not help in the clinical diagnosis of serious complications of RA or associated diseases such as tuberculosis.

There was no significant difference in survival time (mean age) between the total population and patients with AV, AAa, AbSI, and TB neither in women, nor in men.

AV, AAa, AbSI, and TB involved both genders and developed at any time in the course of RA.

There were no significant differences in classical laboratory parameters between groups of patients with and without AV, AAa, AbSI or PA; no specific diagnostic parameter was found for complications [1].

The classic clinical-laboratory parameters (Latex, Waaler-Roose values, BSR, CRP, albumin/globulin ratio, serum electrophoresis (albumin, alpha-1-globulin, alpha-2-globulin, beta-globulin, gamma-globulin), RBC, hemoglobin, WBC, systolic and diastolic blood pressure, blood urea nitrogen (BUN), serum creatinine, serum potassium and sodium values, urine specific gravity, proteinuria, urine sediment (RBC, WBC content), serum bilirubin, LDH, GPT, gamma GT, and diastase values) with or without significant differences, were not sufficient to predict AV, AAa, AbSI or PA.

They were related to the basic activity of RA (to the actual intensity of inflammatory processes of the disease) or indicated involvement of different organs, cardiomyopathy, renal insufficiency etc. [1].

Cohen's statement (1968) that "there are no laboratory abnormalities specific to or unique for amyloid" still holds true," there is no one feature in the blood, urine, electrocardiogram or x-ray that is specific for amyloidosis", "the diagnosis should be based upon a biopsy using an „appropriate staining procedure" [16].

Congophilia and birefringence is the gold standard" for the microscopic diagnosis of amyloid deposits [17, p.: 209].

RA itself or its treatment modify the clinical symptoms of associated diseases and present atypical clinical manifestations leading to late recognition or missed diagnosis. The limited immune reactivity of elderly patients, the autoimmune character of RA, steroid and/or immunosuppressive drugs, and nowadays biological therapy may also play a role in missing the diagnosis of inactive or active TB, including lethal cases.

Detection of dormant TB or acute flare-ups is challenging for the rheumatologist mainly due to the limited response in elderly autoimmune patients. Despite the presence of TB, patients may have no clinical complaints or radiological abnormalities, and the value of a tuberculin skin test may be also limited due to poor response of the patients [18], as well the QuantiFERON blood test [19,20]. A positive Interferon-Gamma (γ) Release Assays (IGRA) result may not necessarily indicate TB infection with tuberculous mycobacteria [19]. A negative IGRA does not rule out active TB disease [20].

The value of inflammatory clinical-laboratory parameters is limited; none of them is specific for tuberculosis, and indicates only actual inflammatory activity [21,22].

Microbiological culture may be necessary, but it is time-consuming, the results may be false-negative and it may not be clinically indicated in latent tuberculosis.

Even the detection of acid-fast bacilli may be inconclusive (Ziehl-Neelsen staining is often negative and "acid-fast bacilli" do not necessarily indicate pathogenic bacteria).

Clinical diagnosis and adequate treatment are important in early stage of complications or comorbidities, inclusive tuberculosis.

The heart, muscles, nerves, kidneys and lungs are most commonly affected by AV in RA [3].

The optimal site for the early diagnosis of AV is the biopsy of the sural nerve and surrounding skeletal muscle, where granulomatous vasculitis has been found in nearly two-thirds of RA patients with autoimmune vasculitis [3].

AAa is a progressive and cumulative process. Deposition of amyloid A most commonly starts in the kidney and heart with massive deposits [23].

In agreement with Kobayashi., *et al*. (1996) the gastroduodenal biopsies - especially from a practical point of view - is useful for diagnosing secondary AAa [1,4,24,25].

Identification of amyloid protein is required (essential), and should "not solely by reliance on clinical or DNA studies" [26]. "Identification of a point mutation in its own right is no proof of amyloid" [27].

The clinical diagnosis of AbSI and PA may be complicated, especially in cases ineffectively treated with antibiotics ("Sepsis sine Sepsi").

Due to the reduced reactivity of elderly autoimmune patients and medication that dulls or masks symptoms, even fatal AbSI and PA may remain clinically hidden [1].

The lack of a significant association between TB and clinical diagnosis or even between TB mortality and clinical diagnosis, suggests that the detection of TB in our patients was incidental [5].

A detailed medical history and targeted X-ray examination, as well as the tuberculin skin test (despite its limitations) are key factors in diagnosing clinically latent TB with or without subclinical atypical miliary exacerbation [28]. "Histopathology remains one of the most important methods for diagnosing tuberculosis" [29,30].

Conclusion

According to our data, the most common complication of RA was AAa (21.12%/161), while AV was the second most common (20.50%/161) and AbSI was only the third most common (14.9%/161) complication.

The most dangerous (and most commonly overlooked) complication of RA was AV (81.82%/33), including fatal undiagnosed cases (78.95%/19).

The risk of clinically occult AAa was also significant (73.53%/34), and the proportion of fatal undiagnosed cases was also high (47.06% /19).

AbSI with or without PA, was an insidious complication, and the proportion of clinically "asymptomatic" cases is not negligible (54.17%/24), and in half of the cases, purulent arthritis also remained hidden (50.0%/12).

Detection of dormant TB or acute flare-ups is challenging for the rheumatologist mainly due to the limited response in elderly autoimmune patients.

Bibliography

1. Bély M and Apáthy Á. "Clinical pathology of rheumatoid arthritis: Cause of death, lethal complications and associated diseases in rheumatoid arthritis". Akadémiai Kiadó, Budapest, Hungary (2012): 1-440.

2. Bely M and Apathy Á. "Szövodmények és társult megbetegedések rheumatoid arthritisben--234 elhunyt beteg patológiai és klinikai adatainak retrospektív elemzése". [Lethal complications and associated diseases of rheumatoid arthritis--a retrospective clinicopathologic study of 234 autopsy patients]. *Orvosi Hetililap* 147.23 (2006): 1063-1076.

3. Bély M and Apáthy Á. "Complications and mortality in systemic vasculitis - vasculogenic clinicopathologic entities in rheumatoid arthritis and progressive systemic sclerosis autopsy patients". *Journal of Vasculitis* 3.2 (2017): 1-11.

4. Bély M and Apáthy Á. "Systemic and gastrointestinal amyloid A amyloidosis in rheumatoid arthritis: A post-mortem clinicopathologic study of 161 cases". *Global Translational Medicine* 4.1 (2025): 104-125.

5. Bély M and Apáthy Á. "Tuberculosis and associated complications and comorbidities of rheumatoid arthritis - a retrospective clinicopathologic study of 234 autopsy patients". *EC Pulmonology and Respiratory Medicine* 13.10 (2024): 1-25.

6. Aletaha D., *et al*. "2010 rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative". *Annals of the Rheumatic Diseases* 69 (2010): 1580-1588.

7. Romhányi G. "Selective differentiation between AAnd connective tissue structures based on the collagen specific topo-optical staining reaction with Congo red". *Virchows Archive* 354.3 (1971): 209-222.

8. Bély M and Makovitzky J. "Sensitivity and specificity of Congo red staining according to Romhányi - comparison with Puchtler's or Bennhold's methods". *Acta Histochemica* 108.3 (2006): 175-180.

9. Bratthauer GL. "The avidin-biotin complex (ABC) method and other avidin-biotin binding methods". *Methods in Molecular Biology (Clifton N.J.)* 588 (2010): 257-270.

10. Romhányi G. "Selektive Darstellung sowie methodologische Möglichkeiten der Analyse ultrastruktureller Unterschiede von Amyloidablagerungen". *Zentralblatt für Allgemeine Pathologie und Pathologische Anatomie* 123 (1979): 9-16.

11. Bély M. "Histochemical differential diagnosis and polarization optical analysis of amyloid and amyloidosis". *The Scientific World Journal* 6 (2006): 154-168.

12. Bély M and Apáthy, Á. "Differential diagnosis of amyloid deposits by light, polarization and electron microscopy". In: Bély M, Apáthy Á, editors. BP International, UK London, India West Bangalia, Tarakeswar (2021): 1-253.

13. Gomez D., *et al*. "Misdiagnosis of rheumatoid arthritis - the photography". *Annals of the Rheumatic Diseases* 74.2 (2015): 689.

14. Agelii ML., *et al*. "Misdiagnosis of rheumatoid arthritis in a long-term cohort of early arthritis based on the ACR-1987 classification criteria". *Open Access Rheumatology* 14 (2022): 187-194.

15. Santos-Moreno P., *et al*. "A route for the correct diagnosis of rheumatoid arthritis - An opportunity to avoid misdiagnosis and costs associated". *Musculoskeletal Disorders - Clinical Outcomes* 19 (2019): S54.

16. Cohen AS. "Amyloidosis associated with rheumatoid arthritis". *The Medical Clinics of North America* 52.3 (1968): 643-653.

17. Sipe JD., *et al*. "Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines". *Amyloid* 23.4 (2016): 209-213.

18. Silva DGST., *et al*. "Latent tuberculosis in rheumatoid arthritis: evaluating cellular response and high-resolution computed tomography". *Archivos de Bronconeumología* 48.5 (2012): 144-149.

19. Slater M., *et al*. "Investigation of false-positive results given by the QuantiFERON-TB Gold In-Tube assay". *Journal of Clinical Microbiology* 50.9 (2012): 3105-3107.

20. Cho K., *et al*. "Factors associated with indeterminate and false negative results of QuantiFERON-TB Gold In-Tube test in active tuberculosis". *Tuberculosis and Respiratory Diseases (Seoul)* 72.5 (2012): 416-25.

21. Ritchie RF., *et al*. "Reference distributions for the negative acute-phase serum proteins, albumin, transferrin and transthyretin: a practical, simple and clinically relevant approach in a large cohort". *Journal of Clinical Laboratory Analysis* 13.6 (1999): 273-279.

22. Apáthy Á and Bély M. "Prevalence and predictive clinical-laboratory parameters of latent tuberculosis in rheumatoid arthritis - a retrospective clinicopathologic study of 161 autopsy patients". *EC Pulmonology and Respiratory Medicine* 10.5 (2021): 76-89.

23. Bély M and Apathy Á. "A comparative postmortem clinicopathologic study of renal and cardiac AA amyloidosis in rheumatoid arthritis". *Journal of Clinical Trials in Cardiology* 6.1 (2019): 1-20.

24. Kobayashi H., *et al*. "Amyloidosis in patients with rheumatoid arthritis: Diagnostic and prognostic value of gastroduodenal biopsy". *British Journal of Rheumatology* 35.1 (1996): 44-49.

25. Bély M and Apáthy Á. "Comparative study of gastric, small and large intestinal AA amyloidosis in rheumatoid arthritis - a postmortem clinicopathologic study of 161 autopsy patients". *EC Gastroenterology and Digestive System* 12.3 (2025): 01-40.

26. Picken MM. "Amyloidosis-where are we now and where are we heading?" *Archives of Pathology and Laboratory Medicine* 134.4 (2010): 545-551.

27. Röcken C and Sletten K. "Amyloid in surgical pathology". *Virchows Archive* 443.1 (2003): 3-16.

28. Wolfe F., *et al*. "Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy". *Arthritis and Rheumatism* 50.2 (2004): 372-379.

29. Flavin RJ., *et al*. "*Mycobacterium tuberculosis* at autopsy-exposure and protection: an old adversary revisited". *Journal of Clinical Pathology* 60.5 (2007): 487-491.

30. Gupta M., *et al*. "A histomorphological pattern analysis of pulmonary tuberculosis in lung autopsy and surgically resected specimens". *Pathology Research International* (2016): 8132741.

Volume 15 Issue 5 May 2026