Research Article
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Prevalence and mortality of gastric and duodenal ulcers in rheumatoid arthritis-a retrospective clinicopathologic study of 234 autopsy patients

Summary

Aim: The aim of this study was to determine the prevalence and mortality of gastric (gU) and duodenal (dU) peptic ulcers in rheumatoid arthritis (RA). Also, to evaluate the possible relationship between gU and dU and autoimmune vasculitis (A-SV), AA amyloidosis (AAa) or lethal septic infection (SI) with or without purulent arthritis (PA).

Patients and methods: A randomized autopsy population of 234 in-patients with RA was studied. RA was confirmed clinically according to the criteria of the ACR. The presence of gU and dU, A-SV, AAa, SI, or PA was determined at autopsy and supported by histological examination. The relationships between prevalence and mortality of gU or dU and A-SV, AAa, SI or PA were analyzed by Pearson's chi-squared ($\chi 2$) test.

Results and conclusions: gU was found in 11 (4.70%), dU in 9 (3.85%), A-SV in 47 (20.08%), AAa in 48 (20.51%), and SI in 31 (13.24%), accompanied with PA in 15 (6.41%) of 234 patients. The negative correlation between A-SV, AAa, or PA and prevalence of gU or dU suggests that-in our autopsy population-A-SV, AAa or PA had no pathogenic role in development of gastric or duodenal ulcers. A-SV, AAa or PA not influenced the mortality of gU or dU. Gastric or duodenal ulcers can be regarded as associated diseases of RA and not as complications of it. The significant connection between SI and prevalence and mortality of gU or dU indicates a causal relationship between them: the development of gU or dUs increase the risk of lethal SI.

Keywords: rheumatoid arthritis, gastric and duodenal peptic ulcers, autoimmune vasculitis, AA amyloidosis, lethal septic infection; purulent arthritis

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Miklós Bély,[1] Ágnes Apáthy[2]
[1]Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary
[2]Department of Rheumatology, St. Margaret Clinic Budapest, Hungary

Correspondence: Miklós Bély, Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary, Email dr.bely.miklos@gmail.com

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Introduction

Gastric and duodenal peptic ulcers (gU or dU) are of different etiologies and are common in rheumatoid arthritis (RA). The prevalence of gU or dU is higher in RA than in the general population.[1] Numerous early and recent studies discuss the relationship between gU or dU and non-steroidal anti-inflammatory drugs,[2-5] corticosteroids,[4-8] anticoagulants,[6] with or without other contributing common factors (sex, age, smoking, alcohol consumption, etc.).The therapy induced peptic ulcers (with complications like perforations, peritonitis, septic infections or bleeding) play an important role in the mortality of RA.[9,10] Gastrointestinal involvement by complications of RA, such as systemic vasculitis or amyloidosis - with or without peptic ulcers-is also well known.[9-11] The aim of this study was to determine the prevalence and mortality of gU and dU in RA. Also, to identify the possible role of systemic autoimmune vasculitis (A-SV) or AA amyloidosis (AAa) in the prevalence and mortality of gU and dU, furthermore to evaluate the possible relationship between gU and dU and lethal septic infection (SI) with or without purulent arthritis (PA).

Patients and methods

At the National Institute of Rheumatology 11558 patients died between 1969 and 1998; among them 234 with RA (females 170, average age: 66.31 years, range 88-16, onset of RA: 50.46, average disease duration: 12.96 years; males 64, average age: 66.08 years, range 88-19, onset of RA: 52.55, average disease duration: 12.96 years at death), and all of them were autopsied.

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR).[12] The basic disease, its complication(s), and the lethal outcome caused by gU and dU were determined and analyzed retrospectively, reviewing the clinical and pathological reports. The presence of gU or dU and A-SV, AAa furthermore SI (with or without PA) was determined at autopsy and confirmed by a detailed review of extensive histological material. From each patient 50-100 tissue blocks of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) were studied microscopically.[13] Amyloid A deposits were diagnosed histologically according to Romhányi[14] by a modified (more sensitive) Congo red staining,[15] and were confirmed histochemically.[16] The relationships between prevalence and mortality of gU or dU and A-SV, AAa furthermore SI (with or without PA) were analyzed by Pearson's chi-squared (χ^2) test.[17]

Results

gU was found in 11 (4.70%), and dU in 9 (3.85%) of 234 RA patients (Figure 1.1). Seven gU of 11, and 6 dU of 9 led to death in 13 (65.0 %) of 20 patients (Figure 1.2). In 4 patients (in 2 with gU and in 2 with dU) the direct cause of death was massive internal bleeding, and in 3 (in 2 with gU and in 1 with dU) it was perforation of an ulcer accompanied by peritonitis. Perforated gU (n=3 of 11) and dU (n=3 of 9) existed in further 6 patients with peritonitis and generalized lethal SI (the outcome of 3 gU and 3 dU in all of these 6 cases were lethal). In 7 (35.0 %) of 20 patients 4 gU and 3 dU existed without

lethal complications (Figure 1.2). gU and dU (with or without lethal outcome) were recognized clinically in 14 (in 8 with gU and in 6 with dU; 70.0 %) of 20 cases, and missed in 6 (in 3 with gU and in 3 with dU; 30.0 %) of 20 (Figure 1.3). A-SV (Figure 2a-d) was observed in in 47 (20.08%), AAa (Figure 3 & 4) in 48 (20.51%), and SI in 31 (13.24%), accompanied with PA in 15 (6.41%) of 234 patients.

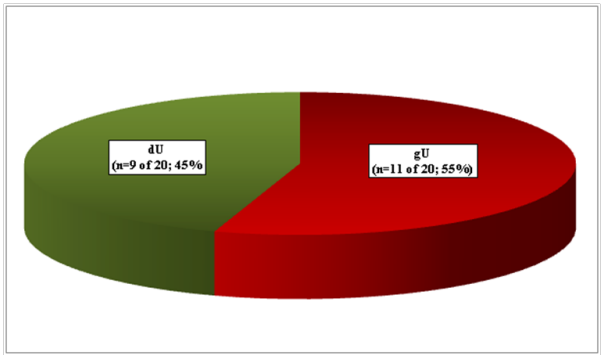

Figure 1.1 Prevalence of gastric n=11 (55.0%) and duodenal n=9 (45.0%) peptic ulcers in 234 RA patients.

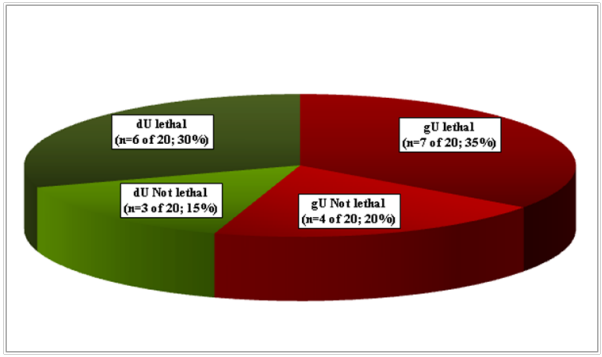

Figure 1.2 Prevalence: n=20 (8.55%), and mortality n=13 (5.56%) of gastric or duodenal peptic ulcers-by bleeding, peritonitis or SI- in 234 RA patients.

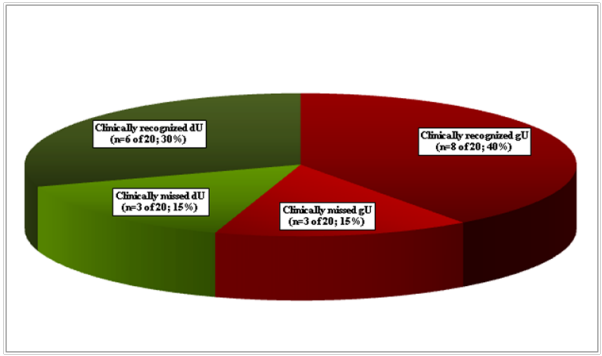

Figure 1.3 Clinically recognized n=14 (70.0%) or missed n=6 (30.0%) of gastric or duodenal peptic ulcers in 234 RA patients.

Sex, average age (range) and disease duration, and onset of RA in patients with or without gU or dU, and with or without A-SV, AAa, SI, or PA are summarized in Table 1. The basic disease, complication(s) and associated diseases of 20 RA patients with gU or dU are summarized in Table 2. gU or dU were associated with A-SV in 3, with AAa in 3, with lethal SI in 6 of 20 patients. gU or dU with lethal outcome were associated with systemic A-SV in 3, with AAa in 3, with lethal SI in 6 of 13 patients. In this autopsy population gU or dU was never associated with PA.

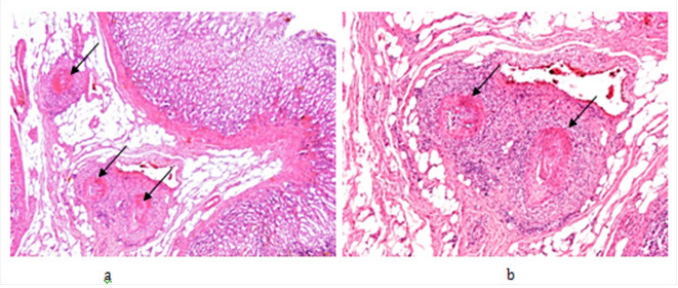

Figure 2 Rheumatoid arthritis, gastrointestinal tract (stomach), systemic vasculitis of autoimmune origin (A-SV).

Small arteries, non-specific vasculitis with sectorial fibrinoid necrosis (arrows) in subacute-subchronic stage of inflammation.

(**a**) HE, x 20, (**b**) same as (a) x40, (**c**) and (**d**) same as (a) x100

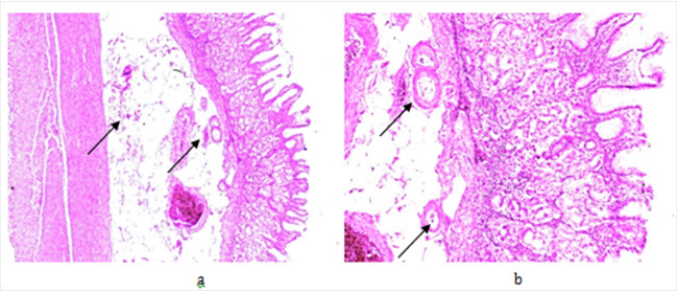

Figure 3 Rheumatoid arthritis, gastrointestinal tract (stomach), systemic secondary AA amyloidosis (AAa).

Amyloid A deposits in the wall of arterioles, small arteries and within interstitial reticulin and collagen fibers (arrows).

(a) PAS, x 50, (b) same as (a) x125

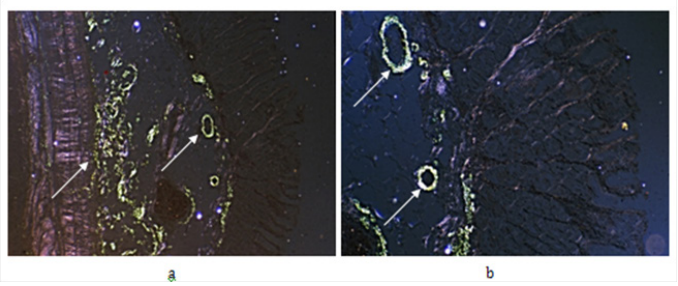

Figure 4 Rheumatoid arthritis, gastrointestinal tract (stomach), systemic secondary AA amyloidosis (AAa).

Same as Figure 3ab, Congo red staining, without alcoholic differentiation, covered with gum arabic. Viewed under polarized light (a) x50 (b) same as (a) x125

The relationship between gU or dU and coexistent SV, AAa, furthermore lethal SI (with or without PA) in 234 RA patients is summarized in Table 3. There was no significant correlation between A-SV, AAa, PA and prevalence or mortality of gU or dU. There was a significant correlation between SI and prevalence and mortality of gU or dU. A-SV coexisted with AAa in 9 of 47 patients. The relationship between A-SV and AAa was not significant (x^2=0.0032, $p<0.95$); the A-SV did not influence the prevalence of AAa, and AAa did lead to A-SV in our autopsy population.

Discussion

Numerous publications discuss the prevalence of peptic ulcers (Table 4), vasculitis (Table 5), amyloidosis (Table 6) or lethal septic

infection (Table 7) in RA with or without its role in mortality.[17-55] Unfortunately these studies do not specify the relationship between gU or dU and A-SV, AAa or SI. In most of these early studies the prevalence or mortality of gU or dU seems to be underestimated, presumably due to the limited microscopic examination of the gastrointestinal tract.

It is difficult to estimate the true prevalence of A-SV, AAa or SI. Most studies do not specify the type of vasculitis (autoimmune, septic-bacterial, viral, fungal-hypertonic, endocrine disease associated, etc.). Amyloidosis in most studies is diagnosed with different methods of diverse specificities and sensitivities (with or without identification of the types of amyloid deposits).

According to our best knowledge a detailed analysis of A-SV or AAa and its role in the prevalence and mortality of gU or dU has not been available in the literature. The negative correlation between A-SV (c^2=0.09107, p<0.76), AAa (c^2=0.1217, p<0.72) or PA (c^2=0.5573, p<0.45), and prevalence of gU or dU suggests that-in our autopsy population - A-SV, AAa or PA had no pathogenic role in the development of gastric or duodenal ulcers.

A-SV (x^2=0.0062, p<0.93), AAa a (x^2=0.0138, p<0.91) or PA (c^2=0.1508, p<0.69) did not influence the mortality of gU or dU. Gastric or duodenal ulcers may be regarded as associated diseases of RA and not as complications. The significant correlation between gU or dU and lethal SI indicates a causal relationship: the development of gU or dUs increases the risk of lethal SI; in case of a perforated ulcer there is a direct relationship. The positive and significant correlation between SI and PA-as it was found in our previous study[13] -indicates also a similar causal relationship. At the same time the negative association's coefficient (-1) and lack of a significant correlation between gU or dU and PA suggests that these are individual phenomena which may exist simultaneously in RA leading to lethal SI independently from each other.

Table 1 Sex, average age (range), onset of disease and disease duration (in years) of RA patients with or without gU or dU and SV, AAa, SI or PA

Sex	Number of Autopsies	Average age in years at Death	Range (in Years)	Age at Onset of Disease	Disease Duration (in Years)
RA patients	234	66.25	88 - 16	51.02	14.76
Female	170	66.31	88 - 16	50.46	15.42
Male	64	66.08	88 - 19	52.55	12.96
With gU or dU	20	65.1	88 - 45	51.15	13.31
Female	14	66	88 - 45	51.44	12.33
Male	6	63	70 - 48	50.5	15.5
Without gU or dU	214	66.36	88 - 16	51.01	14.87
Female	156	66.34	88 - 16	50.39	15.65
Male	58	66.4	88 - 19	52.73	12.73
A-SV	47	68.09	88- 32	55.89	12.8
Female	29	68.83	88- 32	55.69	14.23
Male	18	66.89	83- 53	56.17	10.72
Without A-SV	187	65.78	88 - 16	49.46	15.38
Female	141	65.79	88 - 16	48.92	15.8
Male	46	65.76	88 - 19	51.25	14
With AAa	48	63.75	88 - 19	46.66	17.18
Female	38	65.13	88 - 32	46.54	17.91
Male	10	58.5	88 - 19	47.11	14.33
Without AAa	186	66.9	88 - 16	52.41	13.99
Female	132	66.66	88 - 16	51.65	14.56
Male	54	67.5	87 - 20	54.22	12.63
With SI	31	62.45	83 - 41	49.59	13
Female	22	61.5	83- 41	49.53	12.32
Male	9	64.78	71 - 52	49.75	14.63
SI with PA	15	59.47	71 - 46	44.08	16.38
Female	10	58.2	68 - 46	42.88	16.63
Male	5	62	57 - 20	46	16
SI without PA	16	65.25	83 - 41	54.71	9.86

Table continued...

Sex	Number of Autopsies	Average age in years at Death	Range (in Years)	Age at Onset of Disease	Disease Duration (in Years)
Female	12	64.25	83 - 41	54.36	9.18
Male	4	68,3	70 - 66	56	12.33
Without SI	203	66,1	88 - 16	51,1	14,9
Female	148	66,1	88 - 16	49,9	15,9
Male	55	66,3	87 - 19	54,1	12,5
Without Complications	121	68.01	88 - 16	51.77	15.1
Female	92	67.59	88 - 16	50.44	15.56
Male	29	70,3	87 - 20	56.28	13.56

Table 2 Prevalence and mortality of gastric or duodenal peptic ulcers in 20 of 234 RA patients

Basic Disease		Complication (1-2)		Complication (3)	Cause of Death	Associated Disease(s)	CI+ CI-	Protocol n/Year
1	RA		Gastric ulcer1-Perforation	Gastrectomy	Bronchopneumonia	Ath-DM	CI*	278/71
2	RA		Gastric ulcer2-Colitis	Perforation	Peritonitis- Lethal SI1	Ath-DM	CI-	228/72
3	RA		Felty Syndrome-Splenectomy	Duodenal ulcer1	Massive internal bleeding1	Liver necrosis (red)	CI*	320/72
4	Ath		Thrombosis of femoral vein	Gastric ulcer3	Pulmonary embolism	RA-DM5	CI*	51/74
5	RA		Gastric ulcer4-Bleeding	Gastrectomie	Circulatory failure	Ath	CI*	334/75
6	RA		Nephritis	Gastritis and Duodenal ulc2	Uraemia- Bleeding2		CI*	197/76
7	Ath		Myocardial fibrosis	Duodenal ulcer3	Purulent bronchitis and bronchiolitis	RA-TbF-Meningeoma	CI-	318/76
8	Ath		Myocardial fibrosis	Gastric ulcer5	Circulatory failure	RA	CI*	386/76
9	RA	AA1	Gastric ulcer6-Perforation	Peritonitis	Lethal SI2		CI-	162/78
10	RA		Duodenal ulcer4-Colitis		Lethal SI3		CI-	243/78
11	RA		Erosive gastritis7		Massive internal bleeding3	Ath	CI*	327/78
12	RA		Duodenal ulcer5		Circulatory failure	DM-Hepatic cirrhosis	CI*	385/78
13	RA	AA2	Duodenal ulcer6-Perforation		Peritonitis		CI*	76/79
14	RA		Ulcerative gastritis8-Colitis	Diverticulitis of Colon-Perforation	Lethal SI4		CI-	55/82
15	RA	SV1	Duodenal ulcer7-Perforation	Peritonitis	Lethal SI5	Ath	CI-	318/89
16	RA		Gastric ulcer9	Perforation-	Peritonitis (local) - Circulatory failure	JCA	CI*	25/90
	RA		Gastric ulcer10	Perforation	Peritonitis		CI*	205/91
18	RA		Gastric ulcer11- Perforation	Atlantoaxial subluxation	Peritonitis	HT	CI*	208/93
19	RA	SV2		Duodenal ulcer8-Perforation	Lethal SI5	TbFc	CI*	375/95
20	RA	SV3	AA2	Duodenal ulcer9	Massive internal bleeding4		CI*	33/96

Table 3 Relationship between prevalence and mortality of gU, or dU and coexistent SV, AAa, furthermore SI (with or without PA) in 234 RA patients ($p<0.05$)

Prevalence of Complications in 234 RA pts.	Prevalence of gU or dU n=20	Mortality of gU or dU n=13
A-SV n=47	$\chi^2=0.09107^*$, $p<0.76$	$\chi^2=0.0062$, $p<0.93$
AAa n=48	$\chi^2=0.1217^*$, $p<0.72$	$\chi^2=0.0138$, $p<0.91$
Lethal septic infection n=31	$\chi^2=5.3400$, $p<0.02$	$\chi^2=12.9685$, $p<0.0003$
Purulent arthritis n=15	$\chi^2=0.5573^*$, $p<0.45$	$\chi^2=0.1508^*$, $p<0.69$

Citation: Bély M, Apáthy A. Prevalence and mortality of gastric and duodenal ulcers in rheumatoid arthritis-a retrospective clinicopathologic study of 234 autopsy patients. *Gastroenterol Hepatol Open Access.* 2017;7(1):186–193. DOI: 10.15406/ghoa.2017.07.00221

Table 4 Prevalence and mortality of peptic ulcers in autopsy material of rheumatoid arthritis

Authors	Reference Year of Publication	Autopsy n=	Prevalence of gU or dU N - %	Mortality of gU or dU N - %
Baggenstoss and Rosenberg	1943 [17]	30	ND	2* - 6.66%
Rosenberg and Baggenstoss	1943 [18]	30	ND	2* - 6.66%
Young and Schwedel	1944 [19]	33	0 - 0%	0 - 0%
Teilum and Lindahl	1954 [20]	28	0 - 0%	0 - 0%
Gedda	1955 [21]	45	ND	0 - 0%
Sinclair and Cruickshank	1956 [22]	16	4** - 25.0%	0 - 0%
Leboowitz	1963 [23]	62	1 - 1.61%	1 - 1.61%
Ozdemir et al.	1971 [24]	47	16 - 34.04%	ND
Püschel	1973 [25]	143	28 - 19.58%	13 - 9.09%
Eulderink	1976 [26]	111	ND	0 - 0%
Suzuki et al.	1994 [27]	81	ND	2 - 2.47%
Bély and Apáthy	2007 [28]	161	14 - 8.69%	9 - 5.59%
Bély and Apáthy	2017 [29]	234	20 - 8.54%	13 - 5.55%

Remarks to Table 4

ND No Data

*mentioned as gastrointestinal diseases

**caused by marked intestinal amyloidosis

Footnote to Table 4

* Negative value of association's coefficient; Significant value is in bold

Table 5 Prevalence and mortality of systemic vasculitis (SV) at autopsy of RA patients (no mention of the origin of SV)

Authors	Year of Publication, References	Autopsy n=	Prevalence of Vasculitis n - %	Mortality of Vasculitis n - %
Cruickshank	1954 [30]	72	18 - 25%	ND
Sinclair and Cruickshank	1956 [22]	16	9 - 56.3%	ND
Cruickshank*	1958 [31]	100	20* - 20%	ND
Lebowitz	1963 [23]	62	6 - 10%	ND
Sokoloff	1964 [32]	19	2 - 10.5%	ND
Karten**	1969 [33]	102	6** - 6%	ND
Gardner	1972 [34]	142	7 - 4.9%	ND
Davis and Engleman	1974 [35]	62	6 - 10%	ND
Eulderink	1976 [26]	111	ND	7 - 6.3%
Albada-Kuipers et al.	1986 [36]	173	17 - 10%	ND
Boers et al.	1987 [37]	132	18 - 13.6%	ND
Suzuki et al.	1994 [27]	81	25 - 30.8%	ND
Bély and Apáthy***	1993 [38]	161	36 - 22.4%	19 - 11.8%
Bély and Apáthy***	2006 [39]	234	51 - 21.8	23 - 9.8%

Remarks to Table 5

ND No Data

*Coronaritis

**102 patients with RA-partially autopsied (Karten)

***The studies discuss 36 SV-33 of autoimmune origin and 3 of septic origin.

****The studies discuss 51 SV- 47 of autoimmune origin and 4 of septic origin; the latter 4 SV of septic origin have been excluded in the present study.

Citation: Bély M, Apáthy A. Prevalence and mortality of gastric and duodenal ulcers in rheumatoid arthritis-a retrospective clinicopathologic study of 234 autopsy patients. *Gastroenterol Hepatol Open Access.* 2017;7(1):186–193. DOI: 10.15406/ghoa.2017.07.00221

Table 6 Prevalence and mortality of AA amyloidosis in autopsy material of rheumatoid arthritis (identified amyloid deposits by different staining methods, such as: Toluidine blue, Crystal violet, Syrius red, Congo-red staining according to Romhányi, Bennhold's, Puchtler's, Bély's Congo red method)

Authors	Year of Publication References	Autopsy n=	Prevalence of Amyloidosis n - %	Mortality of Amyloidosis n - %
Bayles	1943 [40]	23	ND*	3 - 13.0%
Baggenstoss and Rosenberg	1943 [17]	30	2 - 6.6%	1 - 3.3%
Young and Schwedel	1944 [19]	33	5 - 15.2%	0 - 0%
Unger et al.	1948 [41]	58	4 - 6.9%	ND
Teilum and Lindahl	1954 [20]	28	17 - 60.7%	7 - 25.0%
Gedda	1955 [21]	45	11 - 24.4%	9 - 20.0%
Sinclair and Cruickshank	1956 [22]	16	4 - 25.0%	0 - 0%
Missen and Tailor	1956 [42]	47	8 - 17.0%	4 - 8.5%
Leboowitz	1963 [23]	62	6 - 10.0%	ND
Sokoloff	1964 [32]	19	0 - 0%	0 - 0%
Cohen	1968 [43]	42	11 - 26%	ND
Karten	1969 [33]	95	1 - 1.05%	ND
Gritsman	1969 [44]	15	6 - 40.0%	ND
Ozdemir et al.	1971 [24]	47	1 - 2.1%	ND
Gardner	1972 [34]	142	17 - 11.97%	ND
Püschel	1973 [25]	143	15 - 10.5%	ND
Vroninks et al.	1973 [45]	62	3 - 4.84%	0 62- 0%
Hajzok et al.	1976 [46]	16	7 - 43.7%	ND
Eulderink	1976 [26]	111	ND	6 111- 5.4%
Rainer et al.	1978 [47]	79	ND	4 79- 5.0%
Boers et al.	1987 [48]	132	14 - 10.6%	ND
Bély	1991 [49]	161	34 - 21.1%	17 - 11%
Suzuki et al.	1994 [27]	81	17 - 21.0%	6 - 7.4%
Bély and Apáthy	2006 [39]	234	48 - 20.5%	20 - 8.5%%

Remarks to Table 6

ND No Data

Table 7 Prevalence of septic infection in autopsy material of rheumatoid arthritis

Authors	Reference, Year of Publication	Autopsy n=	Clinically recognized SI N - %	Mortality of sepsis N - %
Bayles*	1943 [40]	23	ND	2 - 8.7% 4 - 17.4%
Young and Schwedel	1944 [19]	33	ND	1 - 3.03%
Bywaters*	1950 [50]	27	ND	1 - 3.7%
Gedda	1955 [21]	45	ND	8 - 18%
Lebowitz	1963 [23]	62	ND	2 - 3.2%
Bonfiglio and Atwater	1969 [51]	47	ND	4 - 8.5%
Gardner	1972 [34]	142	ND	8 - 5.6%
With septic arthritis				5- 3.5%
Without septic arthritis				3 - 2.1%
Russel and Ansell	1972 [52]	17	ND	2 - 11.7%
Püschel	1972 [25]	143	9 - 6%	8 - 5.6%

Citation: Bély M, Apáthy A. Prevalence and mortality of gastric and duodenal ulcers in rheumatoid arthritis-a retrospective clinicopathologic study of 234 autopsy patients. *Gastroenterol Hepatol Open Access.* 2017;7(1):186–193. DOI: 10.15406/ghoa.2017.07.00221

Table continued...

Authors	Reference, Year of Publication	Autopsy n=	Clinically recognized SI N - %	Mortality of sepsis N - %
Vroninks and mtsi.	1973 [45]	62	2 - 3.2%	3 - 4.8%
Eulderink**	1976 [26]	111	ND	3 - 2.7%
Rainer et al.	1978 [47]	79	ND	21 - 27%
Reilly et al.	1990 [53]	63	ND	3 - 4.8%
Bély et al.**	1992 [54]	100	ND	10 - 10%
Toyoshima et al.****	1993 [55]	1246	ND	52 - 4.2%
Suzuki et al.	1994 [27]	81	ND	5 - 6.2%
Bély***	present work	161	11 - 6.83%	24 - 14.9%
With prulent arthritis			6 - 3.7	12 - 7.45%
Without prulent arthritis			5 - 3.1%	12 - 7.45%

Remarks to Table 7

ND No Data

*Endocarditic bacterial infection (1), or lethal purulent peritonitis (3) leading to death

**Lethal septic infection accompanied with purulent arthritis only

***All lethal septic infections with or without purulent arthritis

****Based on national mortality statistics of Japan without detailed histological analysis of organ involvement.

Conclusion

Vasculitis or amyloidosis may cause gastrointestinal complaints, diarrhea, erosions, and hemorrhages, even peptic ulcers with bleeding, perforation, peritonitis or lethal sepsis. Detailed histological study of a large autopsy population of RA supports and statistically confirms that gU or dU are independent phenomena in RA and their prevalence and mortality is not influenced by the leading complications of RA, e.g by A-SV or AAa. (Peptic ulcers - in agreement with the literature- are probably related to the therapy of RA). gU or dU significantly increases the risk of lethal septic infections, but are independent of purulent arthritis (based on our previous study PA should be regarded a specific source of SI[13]).

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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