



Periprosthetic joint infection in patients with rheumatoid arthritis: case series

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Abstract

Introduction The differential diagnosis of periprosthetic joint infection (PJI) is challenging in patients with systemic diseases due to identical clinical and laboratory patterns and activity of the inflammatory process.

The **objective** was to evaluate the diagnostic data and results of debridement of PJI in patients with rheumatoid arthritis using a case series.

Material and methods A retrospective analysis of surgical treatment of PJI was produced in patients with rheumatoid arthritis between 2014 and 2022. PJI was verified based on ICM criteria. A poor outcome included the presence of clinical and laboratory signs of infection on admission to the second stage of treatment and recurrence after successful debridement.

Results Among the 524 cases of PJI, 35 (6.7 %) were patients with rheumatoid arthritis with 48.6 % receiving antibiotics prior to admission. Culture-negative infection was recorded in 38.4 %. PJI was not confirmed in five cases (14.3 %). High average values of inflammatory markers were registered in the blood (ESR, CRP and D-dimer) before and after debridement; decreased ESR and leukocyte count in the synovial fluid was statistically significant. Favorable outcomes were obtained in 82.9 % of cases at mid term with every fifth patient treated with a spacer or arthrodesis.

Discussion The incidence of culture-negative infection in patients with systemic diseases was reported as much as 27–37 %. A systematic review of the literature showed that the percentage of band neutrophils in synovial fluid has a sensitivity of 95.2 % and a specificity of 85.0 %, with an optimal threshold of 78 % sufficient to verify infection. The poor outcomes we identified resulted from two- or three-stage surgical treatment. Other authors reported better outcomes with two-stage debridement.

Conclusion Culture-negative infection was common in cases of PJI observed in patients with rheumatoid arthritis. Favorable outcomes were seen mostly with two-stage surgical treatment. Inflammatory markers ESR, CRP and D-dimer did not reach normal values during diagnosis and treatment of infection indicating the inapplicability of standard diagnostic criteria for PJI in patients with rheumatoid arthritis.

Keywords: periprosthetic joint infection, culture-negative infection, revision joint replacement, rheumatoid arthritis

For citation: Lyubimova LV, Pchelova NN, Nikolaev NS, Preobrazhenskaya EV, Lyubimov EA. Periprosthetic joint infection in patients with rheumatoid arthritis: case series. *Genij Ortopedii*. 2024;30(4):552-560. doi: 10.18019/1028-4427-2024-30-4-552-560

INTRODUCTION

Joint replacement surgery is a medical technique used to treat severe joint disorders of various localizations allowing patients to return to active lifestyle. About 24 % of the patients with rheumatoid arthritis (RA) undergo primary joint replacement within 16–20 years after verification of the diagnosis [1]. The incidence of RA among patients who undergo arthroplasty is 2–7 % [2–4]. Patients with RA are at higher risk of infectious complications, which may have atypical symptoms complicating the diagnosis and treatment of periprosthetic joint infection (PJI) [5]. Studies have shown that RA is an independent risk factor for postoperative prosthetic joint infection [6–8]. The incidence of PJI among patients with RA (3.1–4.2 %) is 1.8–4 times higher than that in patients with conditions of other etiologies [6, 8]. Immunosuppressants, often used in the treatment of RA, may increase the risk of PJI due to a decrease in the immune response [9].

The differential diagnosis of exacerbated RA and an infectious process in the prosthetic joint is another important problem for patients with systemic diseases. Standard diagnostic tests and biomarkers (ESR, CRP, synovial fluid leukocytes, leukocyte esterase or alpha-defensin) may show high values in both cases and may be misleading. In 2019, a systematic review of studies of inflammatory biomarkers in the diagnosis of PJI in patients with arthritis was performed and the authors reported low specificity despite the high sensitivity of many serum and synovial tests [10]. Some patients with systemic arthritis may experience an exacerbation of the underlying process after joint replacement procedure with no PJI. The differential diagnostic signs of PJI can be less informative in patients with RA. The cases of PJI reported in patients with inflammatory arthritis are limited to a small sample. A systematic review of the literature produced by Mirza et al. included a total of 90 cases of arthritis after arthroplasty, including PJI confirmed in 26 cases [10]. The paucity of studies on the diagnosis of PJI in patients with systemic diseases and the lack of clear differential diagnostic criteria for distinguishing between the exacerbation phase of RA and infection in the prosthetic joint aroused interest in analyzing PJI in this group of patients in a federal trauma and orthopaedic centre.

The **objective** was to evaluate the diagnostic data and results of debridement of PJI in patients with rheumatoid arthritis using a case series.

MATERIAL AND METHODS

The study is based on a continuous retrospective analysis of patients treated surgically for PJI between 2014 and 2022 using medical information system (MIS) of the Federal Center for Trauma, Orthopaedics and Joint Replacement (Center, Cheboksary). Inclusion criteria included a history of RA, surgical treatment of PJI using one-, two-, or three-stage revision arthroplasty. Informed consent for the use of anonymized electronic medical record data was obtained from all individuals included in the study. The patients were treated with intravenous antibiotics for two weeks post op, followed by oral antibiotics for 10 weeks with one-stage revision arthroplasty and for four weeks at each phase of two-stage or three-stage treatment. Primary clinical evaluation criteria included medical history, gender and age characteristics, information on the use of antibacterial drugs at the prehospital stage, location of the infected joint, clinical forms and time from verification of the diagnosis of RA to the date of primary joint replacement. Laboratory criteria included microbiological examination of synovial fluid punctate for leukocyte count, tissue samples and swabs from metal constructs after ultrasonic treatment. Monomicrobial PJI included one pathogen in the test samples, polymicrobial

PJI included two or more pathogens isolated. Culture-negative PJI was considered with the absence of pathogen growth in all biomaterial samples. Hematologic examination included blood erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) and plasma D-dimer levels. The tests were produced at the stage of diagnosis of PJI and prior to the second stage of debridement. All cases of PJI were assessed in terms of PJI diagnosis criteria, adopted at the International Consensus Meeting on Prosthetic Joint Infection in 2018 including major and minor criteria [11] (Table 1).

Table 1

Diagnostic criteria of periprosthetic joint infection according to the Second International Consensus Meeting (ICM) on PJI (Philadelphia, USA)

Major criteria (at least one of the following)				Decision
Two positive growths of the same organism on standard cultures				Infected
Sinus tract communicating with joint or visible prosthesis				
Minor Criteria	Threshold		Score	Decision
	Acute	Chronic		
Serum CRP, mg/L or D-Dimer, mkg/L	100	10	2	≥ 6 Infected; 4 to 5: inconclusive; 3 and less: Not infected
	Unknown	860		
Serum ESR, mm/h	None	30	1	
Elevated synovial WBC, cells/mkl	10000	3000	3	
Elevated synovial PMN, %	90	70	2	
Single positive culture			2	
Positive histology: inflammation of periprosthetic tissue (> 5 neutrophils in each of 5 fields of view at 400× magnification)			3	
Intraoperative visualization of purulent contents			3	

Classification of periprosthetic infection graded by Zimmerli and modified by Li et al. was used in the study [13]. A poor outcome of treatment was rated with clinical and laboratory signs of infection at the time of admission to the second stage of treatment and with signs of infection after successful debridement. The same pathogen isolated as during the first episode of PJI was classified as relapse of PJI, and a different pathogen was classified as reinfection.

Statistical data processing The findings were recorded in the form of spreadsheets and MS Office Excel, 2007 (Microsoft, USA) and the Graf Pad program were used to review the data and visualize the structure. A test for normality of distribution was performed to describe quantitative parameters using the Kolmogorov – Smirnov test. The mean and standard deviation were used for a normal distribution; for a distribution other than normal, the median and upper and lower quartiles Me (Q1–Q3); 95 % CI was used in both cases. The significance of differences was identified with the Student t-test in the case of a normal distribution, and the nonparametric Mann – Whitney test (m–u) was employed in the absence of a normal distribution. Categorical data (sex, type of PJI, outcome) were described by conditional codes of unmeasured categories that were not subject to ordering.

RESULTS

According to the ICM, the primary sample size was detected in 524 cases of PJI with 35 cases (6.7 %) diagnosed with RA. Female patients aged 60 years predominated in the group with an equal ratio

of patients of working age and elderly. By the time of primary arthroplasty, the patients had a late stage of RA (radiologically confirmed stage III–IV arthritis) with a predominance of the seropositive type of the disease (Table 2).

Chronic PIS was hematogenous in most cases with involved knee. About 50 % of patients received antibiotics during preadmission stage. Patients received basic therapy for RA: a combination of cytostatics with hormonal drugs ($n = 10$; 28.6 %), hormonal drugs ($n = 5$; 14.3 %), cytostatics ($n = 9$; 25.7 %), genetically engineered drugs and sulfasalazine ($n = 2$; 5.7 % each), non-steroidal anti-inflammatory drugs only ($n = 7$; 20 %). The average follow-up period after revision arthroplasty was 41/2 years. With use of the ICM diagnostic criteria (2018) PJI was diagnosed in 85.7 % of cases ($n = 30$) including fistulous tract communicating with the cavity of the implants ($n = 13$; 37.2 %), positive cultural growth in at least two biological samples ($n = 6$ cases; 17.1 %), the presence of 6 or > scores (infected cases) according to minor criteria for PJI detected in 11 cases (31.4 %). In the remaining 5 cases (14.3 %), evidence for the diagnosis of PJI was inconclusive or did not meet the criteria for diagnosing an infectious process. Culture-negative infection was most common for the etiology of PJI, coagulase-negative staphylococci (CoNs) was second common for monomicrobial infection and *Staphylococcus aureus* was third common (Fig. 1).

Table 2

General characteristics of the study group

Description			Values	
Mean age, years			60.2 ± 10.3	
Average time from verification of RA diagnosed to the time of primary arthroplasty, years			21.6 ± 9.9	
Average follow-up period after debridement, months			53.2 ± 31.7	
			abs.	%
Gender	Female		30	86
	Male		5	14
Age, years	Young age (18–44)		3	8.5
	Middle adulthood (45–59)		15	42.9
	Late adulthood (60–74)		15	42.9
	Old age (75–89)		2	5.7
Clinical types of RA	Sero-positive		24	68.6
	Sero-negative		7	20.0
	Juvenile		4	11.4
Localization of PJI	Knee joint		26	74.3
	Hip joint		8	22.8
	Proximal metacarpophalangeal joint		1	2.9
Individuals who received antibiotic therapy at the preadmission stage			17	48.6
Classification of periprosthetic infection graded by Zimmerli [12] and modified by Li et al. [13]	Post-op (< 90 days of surgery)	acute	5	14.3
		chronic	0	0
	Hematogenous (> 90 days of surgery)	acute	0	0
		chronic	30	85.7

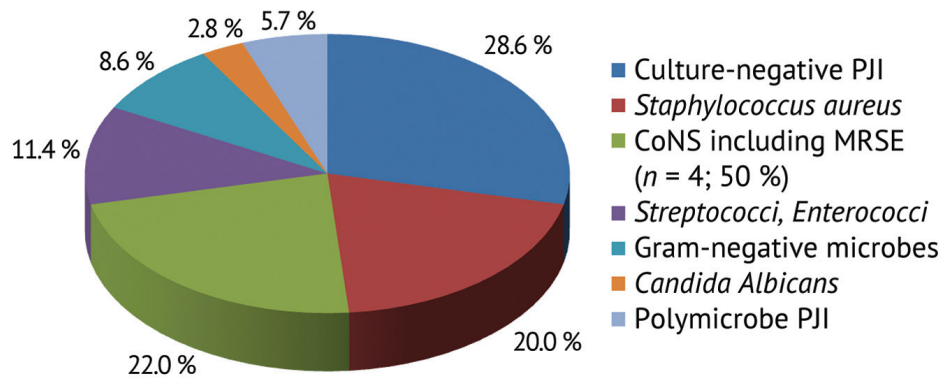


Fig. 1 Microbiological structure of PJI examined with joint fluid punctate in patients with RA

Gram-negative pathogens included *Proteus mirabilis*, *Escherichia coli*, *Burkholderia cepacia*. Microbial associations were represented by MRSE combined with *Enterococcus faecalis* and *Enterococcus faecalis* with *Corynebacterium spp.* The maximum number of positive cultures ($n = 25$, 71.4 %) was seen in the joint fluid punctate taken preoperatively. Intraoperative tissue biopsies showed a positive culture in 20 cases (57.1 %) and in 17 (48.6 %) aspirates from removed implants. MRSE was increased in one case prior to the second stage of treatment. All cases of PJI were treated with surgical debridement and antibiotics. One-stage debridement with replacement of the liner and head component was performed in 4 patients (11.4 %); two- and three-stage debridement was performed ($n = 31$, 88.6 %) in other cases: an articulating spacer was placed in 26 (83.9 %) cases and a static spacer installed in 5 patients (16.1 %). ESR, CRP and D-dimer showed high average values before and after debridement in all patients with two-stage procedure (Table 3).

Table 3

Results of laboratory tests in patients with RA

Description	Prior to debridement, $n = 35$	Prior to the second stage of debridement, $n = 28^*$	$P < 0,05$
Serum			
ESR, mm/hour	45.5 (34.4–56.6)	26.0 (16.0–36.0)	0.0047**
CRP, mg/mL	34.6 (22.3–46.9)	8.2 (4.0–10.4)**	0.4422
D-Dimer, ng/mL	1670 (1067.9–2272.1)	1749.5 (1161.7–2337.3)	0.9325
Synovium			
<i>First sample</i>			
Leukocytes, cells/ μ L	9000.0 (1905.0–18495.0)**	320.0 (82.0–825.0)**	0.0017*
Neutrophils, %	88.0 (81.4–94.6)	63.0 (1.5–94.5)	0.0705
<i>Second sample</i>			
Leukocytes, cells/ μ L	4687.0 (1450.0–9100.0)**	180.0 (45.0–450.0)**	0.0038***
Neutrophils, %	87.0 (75.0–93.0)**	45.0 (22.0–80.0)**	0.1760
<i>Third sample</i>			
Leukocytes, cells/ μ L	1355.0 (85.0–8150.0)**	130.0 (35.0–225.0)**	0.2637
Neutrophils, %	76.0 (62.0–90.0)**	–	–

Note: * — patients treated with a one-stage procedure ($n = 4$) and patients with a spacer replacement ($n = 3$) without subsequent debridement were excluded; ** — Me (Q1–Q3); *** — m-u.

A decrease in all inflammatory markers was noted after debridement with changes in serum ESR and the joint leukocyte count being statistically significant. Favorable results were obtained in the majority of cases with RA (82.9 %) treated for PJI at an average follow-up period of 53.2 ± 31.7 months after debridement (Table 4).

Table 4

Outcomes of treatment of PJI

Poor outcomes, $n = 6$ (17.1 %)	Good outcomes, $n = 29$ (82.9 %)
Recurrent PJI*, $n = 2$ (33.3 %)	Repeated joint replacement**, $n = 23$ (79.4 %)
Three-stage treatment*, $n = 4$ (66.7 %)	Arthrodesis**, $n = 3$ (10.3 %)
	Life with a spacer**, $n = 3$ (10.3 %)

Note: * — among poor outcomes; ** — among good outcomes.

A reinfection caused by a microbial association (*Acinetobacter baumannii*, *Enterococcus faecalis*, *Streptococcus mitis*) developed after a primary staphylococcal PJI in one case that resulted in a poor outcome. A recurrent PJI was caused by the same streptococcal infection in the second case. Four patients were treated with a three-stage debridement due to the persistent high levels of inflammatory markers after the second stage of debridement and poor condition of the bone tissue recorded by the operating surgeon, including one patient with isolated MRSE. The three-stage debridement in the patients resulted in arthrodesis ($n = 1$) and repeated joint replacement ($n = 2$) as the fourth stage; one patient lives with a spacer. Every fifth patient with a favorable outcomes is forced to live with a spacer or with fused joint. Static spacers were used in 16.1 % of cases at the first stage of debridement which limited joint mobility.

DISCUSSION

The characteristics of the course of PJI in patients with rheumatoid arthritis indicated the signs and symptoms of systemic diseases as imitating PJI with pain in the joints, swelling of the periarticular tissues, fever, increased serum ESR and CRP, joint leukocytes. The proportion of patients with rheumatoid arthritis among all cases of PJI ranges from 4.5 to 13.3 % [14–16], which is consistent with our data (6.7 %). Hsieh et al. [14] and Berbari et al. [17] identified *Staphylococcus aureus* as the leading pathogen in the development of PJI in patients with rheumatoid arthritis, but we were unable to confirm the data. Culture-negative infection was common in our series. *Coagulase-negative staphylococci* was more common among culture-positive infection being opportunistic pathogens and causing infection and forming biofilms in immunocompromised rheumatoid arthritis patients. Some foreign authors report changes in the leading role of *Staphylococcus aureus* to coagulase-negative strains in the etiology of PJI. Fröschen et al. reported coagulase-negative staphylococci found in 44.61 % and *Staphylococcus aureus* in 14.31 % of cases [18] and Tai et al. reported bacteria found in 37 and 24 %, respectively [19]. *Candida albicans* was isolated in one case of our series as a rare and difficult to treat pathogen (DTT). Chronic PJI in our series was mostly hematogenous and could be resulted from chronic infection and immunocompromised patients with RA. *Candida albicans* as a saprophyte that colonizes the skin and mucous membranes provoked the development of PJI in a patient with rheumatoid arthritis who received immunosuppressants and antibiotics [20]. Therefore, culturing is practical for patients with rheumatoid arthritis if a PJI is suspected to expand the spectrum of pathogens including fungi and acid-fast bacilli and if other traditional pathogens are not identified by routine culturing.

With the frequency of culture-negative PJI of 28.6 % reported we obtained results similar to those reported by Sculco et al. amounting to 27 % [15], while Schrama et al. reported the incidence as high as 37 % [21]. The authors reported the lack of growth of pathogens in the biological materials with the use of antibiotics at the preadmission stage, which was confirmed in our series with almost half of the patients receiving antibiotics prior to verified PJI. We have shown the effect of antibiotics on the results of bacteriological examination in other series [22].

This cohort of patients can be problematic for verifying the diagnosis of PJI. There is a risk of a false diagnosis of infection in the absence of a fistula tract communicating with the joint cavity relying on inflammation markers, which may have high values due to systemic inflammation. In our series, 14.3 % of patients with rheumatoid arthritis surgically treated for PJI did not meet the ICM criteria (2018). A review of 36 cases of PJI in patients with inflammatory arthritis conducted by Sculco et al. showed the absence of microbiological culture growth in 10 patients and 50 % ($n = 5$) did not meet MSIS criteria for infection [15, 23]. Foreign researchers suggested test strips for leukocyte esterase to be used in doubtful cases including those with rheumatoid arthritis, with a sensitivity of 80.6 % and a specificity of 100 % for PJI [24–26].

The method has not been used at the Center, and differential cell count in synovial fluid is considered to be more informative. A systematic review of the literature on synovial fluid biomarkers for the diagnosis of PJI in patients with inflammatory arthritis showed that the percentage of band neutrophils has the highest sensitivity (95.2 %) and specificity (85.0 %) with an optimal threshold of 78 % sufficient to verify infection [10]. We believe that leukocyte count (no more than 2000 cells / μ l) and band neutrophils (no more than 70 %) in the synovial fluid can be a prognostic sign of the effectiveness of debridement prior to the second stage of revision arthroplasty.

Our study showed that a favorable outcome of treatment of PJI with eradication of infection in patients with rheumatoid arthritis could be achieved in most cases. However, a fifth of patients in the cohort who had static spacers or arthrodesis had limited motion in the operated joints and significantly reduced quality of life. The treatment methods were practical for large bone defects and fragile bone due to osteoporosis associated with long-term use of corticosteroids. Poor outcomes resulted from two- or three-stage surgical treatment. On the contrary, Berbari et al. reported better outcomes of two-stage debridement with a five-year disease-free period achieved in 79 % of cases (95 % CI, 66–93 %) [17]. Two-stage debridement was performed in 19 % of PJI, but in our series this figure amounted to 88.6 %. A limitation of our study included the lack of differentiation between patients with acute and chronic PJI in the assessment of laboratory findings in the small sample. It was a retrospective study and did not allow for histological examination to diagnose infection. An expanded prospective study using a larger sample can be more practical to evaluate findings of patients with rheumatoid arthritis and suspected PJI if international diagnostic criteria cannot be applied.

CONCLUSION

Diagnosis of PJI in patients with rheumatoid arthritis and other systemic diseases remains challenging. Favorable surgical outcomes have been achieved in 82.9 % of cases due to two-stage procedure in most cases. Culture-negative infection was most common (38.4 %) among the PJI cases identified. Laboratory serum markers of inflammation (ESR, CRP and D-dimer) could not reach normal values

at stages of diagnosis and treatment of PJI indicating the inapplicability of standard diagnostic criteria in patients with rheumatoid arthritis. A prospective study using histological examination of intraoperative tissues can be considered for a larger cohort of patients with rheumatoid arthritis featuring a primary inflammation history due to reduced reactivity of the body, and inconsistency of diagnostic parameters and international criteria for PJI.

Conflict of interest Not declared.

Funding Not declared.

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The article was submitted 01.03.2024; approved after reviewing 21.03.2024; accepted for publication 18.06.2024.

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