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Periprosthetic Joint Infection with Negative Culture Results: Clinical Characteristics and Treatment Outcome

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ABSTRACT

Negative culture result is frequently encountered in periprosthetic joint infection, but its clinical feature has not been well studied. In this study, clinical characteristics and treatment outcome were compared in two patient groups: (1) 40 periprosthetic joint infections with negative culture results (culture-negative group) and (2) 135 patients with positive culture results (culture-positive group). In comparison of two groups, the culture-negative group showed significantly higher incidence of prior antibiotic use ($p = 0.005$), higher incidence of prior resection surgery ($p < 0.001$) and lower ESR ($p = 0.02$) than the culture-positive group. The success rate of infection control was higher in the culture-negative group ($p = 0.006$), which suggests that culture negativity may not necessarily be a negative prognostic factor for periprosthetic joint infection.

Periprosthetic joint infection (PJI) is one of the most challenging complications after total hip arthroplasty (THA) and total knee arthroplasty (TKA). In order to optimize treatment outcomes, a timely and accurate diagnosis of infection is important. The workgroup of the musculoskeletal infection society recently presented a new definition for periprosthetic joint infection [1,2] providing standardization of diagnosis of PJI. In practice, however, preoperative or intraoperative cultures do not always lead to identification of microorganisms [3,4] even in patients with strong evidence of infection by other parameters, thus making diagnosis of infection more challenging.

Negative culture result in PJI has been reported in most infection series with an incidence ranging from 0 to 25% [5–9]. Meermans and Haddad [10] reported a 17% incidence of negative cultures by preoperative aspiration, 21% by preoperative biopsy, and 8.3% intraoperatively. Culture negativity is an important clinical issue. The lack of positive cultures raises the uncertainty of the diagnosis of infection, and the absence of cultures makes choosing the appropriate antibiotics challenging. However, there are few studies reporting this issue and information regarding clinical characteristics and treatment results of infected arthroplasties with negative cultures are very limited.

The purpose of this study was to compare infected arthroplasties that did not yield positive cultures at the time of our treatment with those that had positive cultures to determine the clinical characteristics and treatment outcome of infection with negative culture result. We hypothesized that infections with negative cultures would have less favorable outcome.

Materials and Methods

This study has been approved by institutional review board (2008P002146). Using an institution-based registry database which was entered prospectively, we identified 211 PJIs surgically treated at our hospital from January, 2000 to January, 2009. Of these 211 PJIs, 36 patients were excluded because 11 patients died of unrelated disease within 2 years and 25 were lost to follow-up. The remaining 175 PJIs were then included in this study and retrospectively analyzed. Among 36 excluded patients, 30 patients had positive cultures (8 died, 22 lost to follow-up) and 6 had negative cultures (3 died, 3 lost) at the time of our treatment.

There were 97 THAs and 78 TKAs in 89 males and 86 females. The mean age at the time of initial surgery for infection at our hospital was 65 years (range, 38–88 years). Primary arthroplasty was performed at our institution in 71 patients and an outside hospital in 104. The underlying diagnoses leading to the primary arthroplasty were osteoarthritis ($n = 108$), posttraumatic arthritis ($n = 15$), rheumatoid arthritis ($n = 11$), sequelae of developmental hip dysplasia ($n = 9$), acute femoral neck fracture ($n = 8$), osteonecrosis ($n = 6$), congenital

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dislocation of the knee ($n = 1$), and unknown ($n = 17$). The mean follow-up period after initial surgical treatment was 58 months (range, 24–126 months).

As per the new definition for periprosthetic joint infection by the workgroup of the musculoskeletal infection society [1,2], diagnosis of infection was made by presence of sinus tract communicating with the prosthesis; or growth of the microorganism from at least two separate tissue or joint fluid specimens from the affected prosthetic joint; or when four of the following six criteria existed: elevated erythrocyte sedimentation rate (ESR, ≥30 mm/h) and C-reactive protein (CRP, ≥10 mg/L), elevated synovial white blood cell (WBC) count (≥2000/μL), elevated synovial neutrophil percentage (PMN%, ≥65%), presence of purulence in the affected joint, isolation of a microorganism in one culture of tissue or fluid, more than 5 neutrophils per high-power field on histopathologic examination [11–15]. Infection was classified as early postoperative, acute hematogenous, and chronic infection according to Tsukayama et al.[16]. Clinical host condition was classified as uncompromised, compromised, and significant compromise based on the classification of McPherson et al. [17].

Study patients were divided into two groups based on culture results from both preoperative joint aspirate and intraoperative periprosthetic tissues from the affected joint at the time of initial surgical treatment at our institution; (1) 40 patients with negative culture results (culture-negative group), and (2) 135 patients with positive culture results (culture-positive group). Patients' demographics, clinical characteristics, and treatment results were compared between the two study groups. History of previous antibiotic treatment for infected arthroplasty of the same joints and follow-up cultures of the same joints after failure of our initial surgical treatment were also documented to outline the pattern of 40 patients with negative culture results.

Treatment was defined as successful if a patient did not receive any additional surgical procedure for persistent or recurrent infection after our initial surgical treatment. Treatment was defined as a failure if a patient necessitated any additional surgical procedure for infection control. The planned second-stage reimplantation was not considered additional surgical procedure for infection control.

In the culture-negative group, there were 24 males and 16 females with a mean age of 64 years (range, 40–82 years). Twenty-seven patients had primary arthroplasty, five had revision arthroplasty, and eight patients were referred from outside after treatment with resection arthroplasty with ($n = 7$) or without ($n = 1$) cement spacer insertion. In the culture-positive group, there were 65 males and 70 females with a mean age of 66 years (range, 38–88 years). There were 85 primary, 47 revision arthroplasties, and 3 resection arthroplasties (Table 1).

When patients visited our outpatient clinic or were referred to the emergency department from outside, preoperative joint aspiration was performed to confirm the diagnosis by orthopedic surgeons or musculoskeletal radiologists. For total hip aspiration, fluoroscopic guidance was used. At the time of surgery, periprosthetic tissues were taken for culture study from at least three different areas, and antibiotics were held until periprosthetic tissue sampled. Irrigation and debridement (I/D) with implant retention was performed when patients presented within 4 weeks of symptom duration and without radiographic evidence of implant loosening or chronic draining sinus ($n = 56$). Two-stage revision arthroplasty was performed when patients presented after 4 weeks of symptoms ($n = 110$). Reimplantation ($n = 7$) or arthrodesis ($n = 2$) was chosen as primary treatment for nine patients. Parenteral antibiotic therapy was determined with consultation with an infectious disease specialist. Broad-spectrum antibiotic was given empirically, and then therapy was adjusted subsequently based on the sensitivities. When the culture study showed negative results, empirical antibiotic treatment was maintained. If infection was not controlled by initial surgical treatment or recurred after reimplantation by two-stage revision, additional surgical procedures were performed with follow-up culture studies. All patients underwent operative treatment when they had a persistent or recurrent infection, and there were no patients who did not receive surgical procedure just because an organism was not isolated or patient condition was not suitable for operative procedure.

Statistical analysis was performed using SPSS Ver. 17.0 (SPSS Inc/IBM, Chicago, IL). Chi-square and Fisher's exact tests were used to determine the differences in proportions for each variable. The independent-samples t-test was used to compare the means of continuous variables between groups. Two-tailed p values <0.05 were considered statistically significant. Multivariable logistic regression analysis was performed to identify risk factors for treatment failure.

Table 1
Comparison of Variables Between Culture-Positive and Culture-Negative Groups.

Variable	Culture Negative ($n = 40$)	Culture Positive ($n = 135$)	p Value
Age, years	63.9 ± 10.5	65.9 ± 11.7	0.33
Gender			0.19
Male	24 (60%)	65 (48%)	
Female	16 (40%)	70 (52%)	
Joint			0.43
THA	20 (50%)	77 (57%)	
TKA	20 (50%)	58 (43%)	
Host condition			0.67
Uncompromised	16 (40%)	49 (36%)	
Compromised	24 (60%)	86 (64%)	
Implant			<0.001*
Primary	27 (68%)	85 (63%)	
Revision	5 (12%)	47 (35%)	
Others[a]	8 (20%)	3 (2%)	
Type of infection			0.61
Early postoperative	6 (15%)	15 (11%)	
Acute hematogenous	9 (23%)	40 (30%)	
Chronic	25 (62%)	80 (59%)	
Draining sinus			0.14
Yes	6 (15%)	10 (7%)	
No	34 (85%)	125 (93%)	
Preoperative antibiotic treatment			0.005*
Yes	27 (68%)	57 (42%)	
No	13 (32%)	78 (58%)	
IV antibiotics			0.37
Vancomycin	28 (70%)	84 (62%)	
Others	12 (30%)	51 (38%)	
Oral antibiotics			0.29
Yes	16 (40%)	42 (31%)	
No	24 (60%)	93 (69%)	
Laboratory data			
WBC (/cmm)	9197 ± 2901	9396 ± 4125	0.78
ESR (mm/h)	61.5 ± 35.1	78.8 ± 38.4	0.02*
CRP (mg/L)	30.6 (5.7–102.0)	42.4 (12.2–102.0)	0.27
Aspirate WBC (/cmm)	28,500 (9011–56,375)	44,500 (23,000–97,250)	0.05
Aspirate neutrophil (%)	92 (82–95)	93 (89–97)	0.34
Treatment			0.03*
Retention	11 (28%)	43 (32%)	
Removal	23 (58%)	87 (64%)	
Others[b]	6 (15%)	5 (4%)	
Follow-up (months)	52 ± 27	60 ± 26	0.13
Treatment results[c]			0.006*
Success	34 (85%)	83 (61%)	
Failure	6 (15%)	52 (39%)	

WBC = white blood cell; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
Continuous data are mean ± SD, except CRP and aspirate, which are presented as median (interquartile range).
[a] Cement spacer ($n = 8$) or resection arthroplasty ($n = 3$) state.
[b] Reimplantation ($n = 9$) or arthrodesis ($n = 2$).
[c] Any type of additional surgery for recurrent infection was considered treatment failure.
* Statistically significant, Pearson chi-square test.