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Intraoperative evaluation of polymorphonuclear leukocyte during second-stage revision surgery promote overdiagnosis of persistent periprosthetic joint infection

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ABSTRACT

Objective: The aim of this study was to evaluate whether intraoperative histopathological examination could predict the risk of relapse of infection in periprosthetic joint infections (PJI).
Methods: The study included 25 patients (14 women and 11 men, with a mean age of 67.0 years (range, 37–83 years)), who had two-staged revision surgery for a PJI. Following prosthetic removal in the first stage, all patient underwent an intraoperative histopathological examination during the second stage. The patients were divided into PMNs-positive group (≥five PMNs per high-powered field) or -negative group (<five PMNs). A relapse was defined as the occurrence of PJI. Median follow-up was 51 months (range, 32–80 months) following second-stage revision surgery.
Results: Intraoperative histopathological revealed that 8.0% of cases were PMNs-positive. Postoperative histopathological examination revealed that 28.0% of cases were PMNs-positive. 28.0% of cases showed discrepancy between the PMNs-positivity. Intraclass correlation coefficient indicates poor reproducibility. Infection relapse after revision surgery occurred in two cases (8.0%); both relapse cases were from the PMNs-negative group. There was no statistical relationship between the presence of PMNs in periprosthetic tissue by intraoperative or postoperative histopathological examination and relapse of infection.
Conclusions: Our findings showed that intraoperative histopathological examination could not predict the relapse of infection. Intraoperative histopathological examination promotes overdiagnosis of the requirement for re-implantation of antibiotic-impregnated cement and prolonged treatment periods.
Level of evidence: Level III, diagnostic study

Introduction

Periprosthetic joint infection (PJI) is one of the most common and intractable complications following total joint arthroplasty.[1] PJI is treated with either a one-stage exchange operation or a two-stage exchange using an antibiotic-impregnated cement spacer.[2,3] When the infection is not abrogated, re-exchange of antibiotic-impregnated cement spacer is conducted. Infection persistence is diagnosed by a combination of clinical presentation, blood tests, culture, and histological examinations.[4,5] Musculoskeletal Infection

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Society reported that accumulation of polymorphonuclear leukocytes (PMNs) in tissues is a minor criterion for diagnosis of persistent infection.[5] In addition, intraoperative histopathological examination is reportedly useful for diagnosing persistent infection during second-stage revision surgery.[6–8] However, we experienced several cases with discrepancy between the PMNs-positivity of intraoperative frozen sections compared with postoperative hematoxylin and eosin (HE)-stained sections in second-stage revision surgery. These PMNs positive cases did not relapse PJI after second-stage revision surgery. We hypothesized that although intraoperative PMNs-positivity can detect infection persistence,[7,9,10] PMNs-positivity cannot predict the relapse of PJI after revision arthroplasty following first stage antibiotic-impregnated cement spacer replacement. Therefore, we retrospectively compared the PMNs-positivity in periprosthetic tissues by examining intraoperative or postoperative HE sections, and compared the results of clinical follow-up with these histopathological results.

Methods

Patients

This study is a single center retrospective study. This study was based on the data of 25 patients who had been hospitalized in the Department of Orthopaedic Surgery of Kagoshima University hospital from October 2006 to October 2014. All of two stage revision surgery patients who were performed intraoperative histopathological examinations were included in this study. Prosthesis removal for treatment of PJI was done in 8 bipolar hip arthroplasty (BHA) patients, 10 total hip arthroplasty (THA) patients, and 7 total knee arthroplasty (TKA) patients. There were 14 women and 11 men, with a mean age of 67.0 years (range, 37–83 years). Before removal of the prosthesis or after revision arthroplasty, a diagnosis of PJI was made based on clinical presentation, laboratory data, and diagnostic imaging, as recommended by the Infectious Diseases Society of America.[8,11]

First-stage surgery involved prosthesis removal, debridement, irrigation, and placement of antibiotic-impregnated spacer. Intravenous antibiotics were administered for 4–6 weeks following first-stage surgery. The abrogation of PJI was assessed after a 2-week drug-free period. Second-stage revision surgery was indicated in patients who did not demonstrate local heat, tenderness, elevation of C-reactive protein (CRP), and elevation of erythrocyte sedimentation rate. Following a 2–3 months placement of antibiotic-impregnated spacer period, second-stage revision surgery was performed. Median follow-up was 51 months (range, 32–80 months) following second second-stage revision surgery.

Intra- and post-operative histopathological examinations

The cement spacer was impregnated with 2.5–10% vancomycin combined with 0–5.0% amikacin sulfate. A cement spacer mold (Biomet Orthopedics, USA) or handmade cement spacer was used. Following prosthesis removal, intravenous antibiotics were administered for 4–6 weeks. When methicillin-resistant *Staphylococcus* or methicillin-resistant *Staphylococcus aureus* (MRSA) was detected, vancomycin or teicoplanin were used; cefazolin was used for all other cases after drug susceptibility testing. Antibiotics were intravenously administered twice daily. All patients were allowed to use a wheelchair and to move their affected joints between operations. Hip and knee joints were allowed mobilization. Between three and seven periprosthetic specimens (median, three) were collected from each patient during each second-stage revision surgery; intraoperative, postoperative histopathological evaluation and bacterial culture was performed on these specimens using blood agar medium and BTB agar. Culture duration was 7 days. Detection of bacterial strain was performed by mass spectrometry using VITEK MS (BioMérieux, Lyon, France). Previous studies reported that five PMNs per high-powered field (HPF) was a suitable diagnostic threshold for diagnosis of PJI[12]; therefore, we regarded cases with five PMNs per HPF in more than five fields as PJI positive. We divided the patients into the PMNs-positive group (≥five PMNs per HPF) and the PMNs-negative group (<five PMNs per HPF). Manifestation of PJI following second-stage revision surgery was identified as a relapse of infection. All histopathological examinations were performed by skilled pathologists who were blinded to the grouping data.

Statistical analysis

The intraclass correlation coefficient assessment was performed to examine the reproducibility between intra- and postoperative histopathological examinations. Fisher's exact test was performed to evaluate the differences between groups. All statistical analyses were performed using BellCurve for Excel 2015 (Social Survey Research Information Co. (SSRI), Ltd, Osaka, Japan) which is an add-in software for Excel (Microsoft, Redmond, USA).

Results

The intraclass correlation coefficient indicates very poor reproducibility of PMNs-positivity between intraoperative and postoperative histopathological examinations.

The individualized data are outlined in Table 1. Intraoperative histopathological examination of frozen sections of tissue obtained during second-stage revision surgery revealed that 8.0% of cases (2/25) were PMNs-positive. In contrast, postoperative histopathological examinations of HE sections revealed that 28.0% of cases (7/25) were PMNs-positive (Tables 1 and 2). Seven cases (28.0%) showed discrepancy between the results of intraoperative and postoperative HE histopathological examinations (red characters in Table 1). The intraclass correlation coefficient indicate very poor reproducibility of intraoperative and postoperative histopathological examinations (0.116: −0.233–0.462) ($p = 0.267$) (Table 1). In addition, Fisher's exact test showed that there was no statistical relationship between PMNs-positivity in intra- and postoperative histopathological examinations (Table 2).

There was no statistical relationship between accumulation of PMNs in intraoperative or postoperative histopathological examinations and relapse of infection.

The proportion of infection relapse was 8.0% (2/25). In one case of relapse, PJI was abrogated by third-stage irrigation and debridement; the other case of relapse had the revision THA removed. All cases of infection relapse were from the PMNs-negative group as defined by intra- and postoperative histopathological findings. Fisher's exact test revealed no statistical relationship between PMNs-positivity in intra- or postoperative histopathological examinations and relapse of infection (Table 3).

There was no statistical relationship between accumulation of PMNs in intraoperative or postoperative histopathological examinations and detection of bacteria.

Pathogenic bacteria were detected in samples obtained during second-stage revision surgery in three cases, including two cases of coagulase-negative staphylococci and one of methicillin-resistant *Staphylococcus aureus*. The causative agent in one case of infection relapse was detected as methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) in a sample obtained during second-stage revision surgery, while there was no specific bacteria detected in the other infection relapse case. The three cases in which bacteria were detected were from the

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