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Role of Nuclear Imaging and Intraoperative Frozen Section in Patients with Late Prosthetic Joint Infections

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Abstract

Background: Differential diagnosis of prosthetic joint infection and aseptic loosening can be not easy. The American Academy of orthopaedic Surgeons has recently published guidelines to perform a correct diagnosis using clinical findings, inflammatory markers, and microbiological cultures. In uncertain cases radionuclide imaging, frozen section and histopathology can be useful.

Methods: Retrospective analysis of a cohort of patients with prosthetic joint infection examined with technetium-99-labeled-leukocyte, frozen section and histopathology.

Results: A cohort of 30 patients was evaluated in the period 2010-2012. Before surgery, technetium-99-labeled-leukocyte imaging was performed in 25 cases (in the remaining 5, infection was documented by the presence of a sinus tract). The nuclear scan was negative in 3 patients and positive in the other 22. Patients with negative scan were treated with one stage exchange. Patients with documented infection were treated with resection arthroplasty (2 cases) or two-stage exchange (25 cases). Frozen section examination, performed during removal arthroprosthesis, was negative in 4 cases (3 patients undergoing one stage exchange and one false negative) and positive in 26 cases. Histological findings were in agreement with frozen section. A failure for persistence of infection (culture positive) was documented in 3/25 two stage exchange. Radionuclide scan was repeated before spacer removal in 20/25 two stage. It was negative in 16 (one false negative), positive in 4 cases (2 true positive in patients with persistence of infection, 2 false positive in patients with cultures negative). During prosthesis replacement frozen section and permanent histopathology was repeated with some discordant results for persistence of inflammation in patients with documented resolution of infection.

Conclusions: In our experience technetium-99-labeled-leukocyte imaging associated with intraoperative frozen section examination, have guided a correct management of patients with suspect prosthetic joint infections. In 2 stage exchange the sensibility seems better during first step (prosthesis removal) than during prosthesis replacement.

Keywords: Infection; Arthroplasty; Nuclear imaging; Histological diagnosis

Abbreviations: PJI: Prosthetic Joint Infections; ESR: Erythrocyte Sedimentation Rate; CRP: C - Reactive Protein; AAOS: American Academy of Orthopaedic Surgeons; PET: Positron Emission Tomography (FDG-PET), WBC: White Blood Cells; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Introduction

Prosthetic joint infections (PJI) represent a not frequent (1-2%) but severe complication of arthroplasty [1]. In relation to the time of onset after surgery, PJI are classified as "early", in the first 3 months, "delayed", between 3 months and 2 years or "late", more than 2 years after surgery [2]. PJI remain a diagnostic challenge and a hard management for the clinician [3]. For these reasons the American Academy of Orthopaedic Surgeons (AAOS) has recently published guidelines to perform a correct diagnosis [4]. The gold standard is represented by microbiological identification of the pathogen [5] with cultures of specimens obtained during arthrocentesis, tissue biopsy or surgery. Clinical symptoms and signs can only suggest a diagnosis. Fever is described in severe septic syndrome but when infection is restricted to periprosthetic tissue, pain can be the only symptom as in the aseptic loosening. Laboratory tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be within the normal range or slightly elevated. Imagine techniques can be employed, but plain radiograph is not specific and can mimic an aseptic loosing, computed tomography scan and magnetic resonance can have strong artefacts due to the metal component. Several nuclear medicine techniques have been proposed to define more clearly diagnosis in dubious cases [6]. While bone scintigraphy can be falsely positive for years after surgery because of bone remodeling, radio labeling of autologous peripheral white blood cells (WBC) scintigraphy is more sensitive and specific. When revision is performed, frozen section and histopathologic analysis of periprosthetic tissue can differentiate PJI or aseptic loosing. An area of connective tissue, called periprosthetic membrane, is interjected between prosthesis and bone and its composition is different in aseptic loosing and infection. A probable infection is suggested by acknowledgement in periprosthetic tissue of acute inflammatory cells, defined as the presence of more than 5 neutrophil granulocytes (PMN) in at least 5 high power fields (400X). Permanent histology of periprosthetic membranes identify four different patterns: type I with presence of infiltration predominantly

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due to macrophages and multinuclear giant cells, type II and type III with predominant inflammatory cells and granulocytes, and type IV that is considered undetermined [7]. Lesions of the type II and III are typical of periprosthetic infections.

We report a small cohort of late PJI evaluated with radionuclide scan, frozen section and permanent histopathological section in a tertiary care center for therapy of bone infections in Italy.

Patients and Methods

We retrospectively evaluated a cohort of late PJI, observed from January 2010 to December 2012 at the Infectious Diseases and Septic Orthopedic Unit of S. Maria Misericordia, Albenga and Santa Corona Hospital, Pietra Ligure (Savona), Italy.

For each patient the following data were retrospectively collected: age, sex, prosthetic joint affected, results of the diagnostic and follow up workup, and type of intervention. In particular, the diagnostic workup called for the following procedures:

1) Clinical history, physical examination, plain radiograph and evaluation of serum markers of inflammation (ESR normal < 20 mm/1st h, CPR normal <0.75 mg/dl);
2) Technetium-99-labeled-leukocyte imaging, that in particular cases was associated with positron emission tomography (FDG-PET). All tests were performed after suspension of antibiotic treatment from at least 2 weeks;
3) Frozen section histopathology of samples taken during surgery, with results given within 90 minutes from sampling: test is considered negative if <5 neutrophil granulocytes 400X magnification (high-power field) are detected, positive if >5 PMN are observed;
4) Histological definitive examination of samples taken during surgery classified according to the consensus classification of the periprosthetic interface membrane [7];
5) Culture of at least 3 samples from the suspected infected area, with at least 2 positive samples with the same pathogen in the case of common skin bacteria isolation [8].

When both radionuclide test and frozen section were negative for infection a one stage prosthesis exchange was performed. In case of positive tests or when the results were not conclusive a two stage intervention strategy with spacer insertion was carried out. Antibiotic treatment was prescribed, according with isolated pathogens for 8 weeks. Technetium-99-labeled-leukocyte imaging was repeated before replacement. Frozen section and histopathology examination was repeated during spacer removal and prosthesis replacement. Also in this case at least 3 intraoperative samples were sent for microbiological cultures.

The performance of the diagnostic tests was evaluated calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) by means of Dag_Stat 98.xls spreadsheet running on Microsoft Excel 2011 for Macintosh (Microsoft Corp., Seattle, WA, USA) [9].

Results

During the study period, 30 patients with a painful prosthesis were identified: 19 hips and 11 knees PJI in 17 female and 13 males, with a mean age of 65 years (range 32-85). At time of first observation ESR and CRP were evaluated (mean ESR 59 mm/1st h, range 6-111; mean CRP 3.3 mg/dl, range 0.33-34).

Table 1 reports on results of different tests performed to identify the presence of late-onset prosthetic joint infection. Technetium-99-labeled-leukocyte scan was performed before surgery in 25 out of 30 cases (example in Figure 1), while in the remaining 5, radionuclide scan was not performed because of infection was proved by the presence of a secreting fistula (Table 1, Panel A). All the prosthetic joints were removed and patients underwent frozen section examination, histopathology and cultures. The combinations of radionuclide scan and fresh frozen sections have guided surgical management: one-stage, two-stage prosthetic joint replacement or Girdlestone procedure.

Both radionuclide scan and frozen section of intra-operative

Panel A*: *data at time of first intervention (remotion arthroprosthesis) (n=30)	**Positive**	**Negative**
Radionuclide (n=25)	22 (88%)	3 (12%)
Fresh frozen section (n=30)	26 (87%)	4 (13%) One false negative
Histopathology (n=30) Type I Type II-III Type IV	23 (77%)	2 (7%) 5 (16%) Four false negative
Cultures (n=30)	23 (77%)	7 (23%) (3 aseptic loosing, 4 not microbiologically documented infections)
Panel B*: *data at time of remotion spacer and prosthesis reimplantation in "two stage exchange" (n=25)		
Radionuclide (n=20)	4 (20%) Two false positive	16 (80%) One false negative
Fresh frozen section (n=25)	3 (12%)	22 (88%)
Histopathology (n=25) Type I Type II-III Type IV	7 (28%)	7 (28%) 11 (44%)
Cultures (n=25)	3 (12%) Failure for persistence of infection	22 (88%)

Table 1: Results of diagnostic work up.

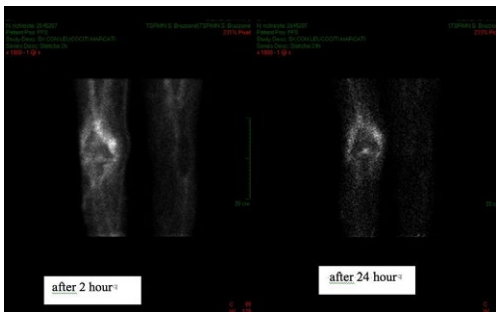

Figure 1: WBC scintigraphy in knee prosthetic joint infection. Persistent uptake in imaging at 24 h after injection.

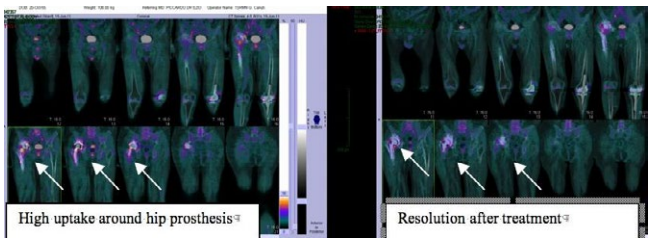

Figure 2: TC-PET: Uptake around hip prosthesis in a patient with severe infection. Negative test after treatment.

samples resulted negative in 3 cases, therefore the diagnosis was of aseptic loosing and patients underwent a one-stage prosthetic joint replacement. The accuracy of this diagnosis was confirmed by negative cultures of the 3 surgery samples. Follow up was also negative for relapse of infection after one year.

A diagnosis of PJI was performed in 27 cases, 22 with a positive radionuclide scan and 5 with a secreting fistula. Frozen sections examination resulted positive in 26 cases. The only case with negative results had positive radionuclide scan and infection was confirmed by positive intraoperative cultures and histopathology (1 false negative frozen section). In 2 cases, both with positive radionuclide and fresh frozen sections, a Girdlestone procedure were performed due to the severity of infection with bone disruption. The other 25 patients performed a two-stage prosthetic joint replacement. Considering the combination of the 2 tests as a single one (radionuclide scan and frozen section), a concordant combination of the two tests had a 100% sensitivity and a 95% specificity, with a 96% correct classification rate (efficiency). The PPV resulted 75% PPV and the NPV 100%. All patients with a diagnosis of PJI (27 cases) were treated with antibiotic for 8 weeks (intravenous for at least 2 weeks).

In 20/25 patients treated with 2 stage exchange, radionuclide scan was performed also before the second step (replacement prosthesis) (Table 1, Panel B). All patients were off of antibiotic for a minimum of 2 weeks. Also at this time all patients underwent a complete diagnostic workup with frozen sections examination, histopathology and cultures. A persistence of the primary infection was documented by presence of positive cultures in 2 cases with positive scan and in 1 case with negative scintigraphy. In three patients undergoing two-stage exchange, PET was also performed and results were in agreement with technetium-99-labeled-leukocyte imaging: positive uptake before surgery, and negative after treatment (example in Figure 2).

Cultures performed at time of prosthesis removal resulted positive in the 23 (85%) of the 27 patients with a diagnosis of PJI. Single agent Gram-positive infection accounted for 17 cases (8 episodes due to methicillin-resistant *staphylococci*), while a single agent Gram-negative infection was observed in 4 (1 *S.typhimurium*, 1 Proteus and 2 *Pseudomonas aeruginosa*). In the remaining 2 cases a mixed infection was diagnosed (methicillin-susceptible *S.aureus+Corynebacterium,* coagulase-negative *Staphylococcus* + *Streptococcus*). Infections persisting after antibiotic therapy were due to methicillin-resistant coagulase-negative staphylococci in 2 cases, and methicillin-resistant *Staphylococcus* epidermidis.

Comments

Prosthetic joint replacement surgery is increasing, and as a consequence, revisions are performed more frequently than in the past [10,11]. Infections must be differentiated from aseptic mechanical loosening to choose a correct treatment. Aseptic loosening can be treated with one stage exchange, while, because of the ability of bacteria to produce slime [12], the preferred strategy in PJI is a two-stage replacement. Joint aspiration represent an excellent test for the diagnosis of PJI [4,5], but it can be difficult to perform at least in case of suspected hip arthroprosthesis infection. Therefore, diagnostic tools allowing a rapid intraoperative diagnosis of PJI, even in absence of cultures result, are needed for an efficient management of patients with suspected PJI. In the present study we report our experience on the combined use of technetium-99-labeled-leukocyte imaging and intraoperative frozen section examination to differentiate aseptic or septic prosthetic loosing. The role of radionuclide imaging in the diagnosis of PJI is still controversial [6,13,14], even if the results of these test are usually not forged by the presence of metallic hardware. Bone scintigraphy and sequential bone/gallium scintigraphy are considered unspecific while labeled leukocyte scintigraphy is the most important achievement in diagnosis of infection [6,13]. Intraoperative examination of frozen section represents a useful tool [4] with a high level of concordance with definitive histology during prosthesis removal. In spite of the quite low number of events observed, in our opinion, some important consideration can be made. The combination of the 2 tests performed at time of prosthetic joint removal had very high sensitivity and specificity with a 96% correct classification rate (efficiency). These tests allowed a correct management: one stage replacement in all cases without infection, two-stage or Girdlestone procedure in presence of PJI. The combination of the 2 tests resulted also very effective during prosthetic replacement in the two-stage procedure but in this second case we observed 2 false positive and 1 false negative radionuclide scan. Moreover, while frozen section examination was highly predictive of persistent infection, histopathology had a high number of false positive results, maybe because of local inflammation induced by the presence of the spacer.

Our data strongly support the use of technetium-99-labeled-leukocyte associated with intraoperative frozen section examination for the uncertain diagnosis of late onset PJI and for a correct decision on management strategy especially during prosthesis removal.

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