ORIGINAL ARTICLE

Diagnostic value of ^{99m}Tc-HMPAO-labeled leukocytes scintigraphy in suspicion of post-sternotomy mediastinitis relapse

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Background. The diagnostic value of radiolabeled white blood cells (WBCs) scintigraphy in mediastinitis is well established, but data in the specific context of relapse are lacking. The present study aimed at evaluation of the diagnostic value of WBCs scintigraphy in suspicion of mediastinitis relapse after prior surgical revision.

Methods and Results. Multiple planar incidences of the chest were acquired 4 and 20 hours after injection of labeled WBC in 43 patients. In case of non-conclusive scintigraphy, a second scan was performed 2-3 weeks after the first one. The diagnosis of infection was based on positive bacteriological results; otherwise patients were followed up for at least 1 year. Out of 39 analyzable patients, 17 (44%) were diagnosed with mediastinitis relapse. After the first scan, 32 of 39 were correctly classified, 2 were false positive, and 5 were not conclusive. After completion of an additional scan in the latter 5 patients, 36 of 39 were correctly classified and 3 were false positive (100% sensitivity, 86% specificity, 85% positive predictive value, and 100% negative predictive value).

Conclusions. In the specific context of suspicion of mediastinitis relapse, the optimal diagnostic value was achieved by repeating the scan when the first one was not conclusive. In this context, a negative WBC scintigraphy was able to rule out infection, with potential major impact on therapeutic management in patients with poor clinical status. (J Nucl Cardiol 2015;22:123–9.)

Key Words: Infection · leukocyte labeling · 99m Tc-HMPAO · mediastinitis

INTRODUCTION

Mediastinitis is defined as deep wound infection associated with sternal osteomyelitis with or without infected retrosternal space that requires surgical debridement.[1] It is one of the most serious complications after surgery for coronary artery bypass and/or valvular

surgery. Its overall incidence is relatively low, between 1% and 3% of patients that underwent cardiac surgery, but its mortality is estimated to vary between 10% and 25%.[2] Even in the absence of fatal outcome, the occurrence of mediastinitis is associated with high morbidity and prolonged hospitalization.[3]–[11] Despite appropriate antibiotic therapy and surgical removal of infected and necrotic tissue and debridement, infection may relapse in a substantial number of patients. In a series of 60 patients diagnosed with staphylococcal post-sternotomy mediastinitis reported by Upton et al, the rate of relapse was 18% after an initial treatment.[12] Subsequent management of such patients in poor condition due to prolonged stay in intensive care unit (ICU) requires additional high-risk surgery followed by open-packing technique, and is associated with a poor outcome.[9,13,14] Indication for surgery needs therefore to rely on strong evidence of infection relapse, in a context of inflammatory remodeling that may be intense in the weeks following surgical revision.

The value of ^{99m}Tc-HMPAO-labeled leukocytes (white blood cell, WBC) scintigraphy is well established in the diagnosis of infection of soft tissues and bones. This technique also proved to be highly sensitive and specific in mediastinitis.[15]–[18] However, data regarding the value of WBC scintigraphy in the specific context of relapse of mediastinitis are lacking. Therefore, the aim of the present study was to prospectively evaluate the diagnostic value of WBC scintigraphy in suspicion of mediastinitis relapse after a prior surgical revision.

PATIENTS AND METHODS

Design of the Study

Patients were prospectively included in the study if they met the following selection criteria. Inclusion criteria were: (1) suspicion of mediastinitis relapse and (2) history of surgical debridement within the previous 6 months. The suspicion of mediastinitis relapse could be based on persistent or recurrent fever and/or persistent purulent flow discharge; and/or positive bacterial Redon catheters cultures; and/or persistent biological inflammatory syndrome. Exclusion criteria were: (1) indication for urgent surgery and (2) ventilator-dependant patient or contraindication to patient mobilization. The study was approved by the local ethics committee and all patients gave their informed consent.

Then, WBC scintigraphy was performed as part of the diagnostic work-up. In case of non-conclusive WBC scintigraphy and if urgent surgery was not indicated, a second scan was performed 2-3 weeks after the first one while clinical, biological, and pathological monitoring were maintained.

Initial diagnosis of mediastinitis relapse and therapeutic management were agreed upon by consensus during an interdisciplinary meeting[8]–[10] where experts were not blinded to

WBC scintigraphy results: (1) if a patient was diagnosed with mediastinitis relapse, an additional debridement was performed; (2) if surgery was deemed not realizable due to the poor clinical status of the patient, medical treatment only was maintained using appropriate and prolonged antibiotic therapy with a strict clinical, biological, and pathological monitoring; (3) if a patient was not diagnosed with mediastinitis relapse, antibiotic therapy was withdrawn and clinical follow-up was undertaken.

The final diagnosis of mediastinitis relapse was based on positive bacteriological results of direct examination and culture of either surgical material, or transcutaneous needle aspirates of the deep mediastinum. Positive bacterial Redon catheters cultures were not considered for the diagnosis of mediastinitis. Conversely, the final exclusion of mediastinitis relapse was assessed after a follow-up of at least 1 year to exclude a late relapse. According to the study design, WBC may have influenced the initial diagnostic and therapeutic decision. However, the reference standard remained independent of the therapeutic option, so that the result of WBC scintigraphy did not influence the final diagnosis.

Patients

Forty three consecutive patients (32 males, mean age 66 ± 10 years) with a history of mediastinitis following thoracic surgery for coronary artery bypass, valve replacement or both (Table 1), and suspected of mediastinitis relapse were included (Table 2). The first debridement had been performed within a median delay of 16 days (range 5-54 days) after initial cardiac surgery. Among the 43 patients, 9 had already been surgically treated twice for mediastinitis (median delay between the second and third surgery 19 days [range 3-53] days). After debridement, patients had a closed-drainage aspiration using Redon drain catheters and were admitted to an intensive care unit but none needed prolonged mechanical ventilation. When microbiological cultures of Redon catheters aspirates were negative and the volume of effluent was inferior to 20 cc/24 hours, catheters were progressively withdrawn until complete removal usually between day 15 and day 20 after debridement. Appropriate intravenous antibiotic treatment based on available microbiological data (Table 3) was systematically started before surgical debridement and maintained for at least 6 weeks.[8,10]

In 26 patients (67%), WBC scintigraphy was performed while they were still under the 6-week period of antibiotic therapy following the debridement (median delay 20 days; range 12-48). In the remaining 13 patients, when suspicion of relapse occurred after discontinuation of antibiotic therapy, a probabilistic antibiotic regimen was undertaken and WBC scintigraphy was performed as part of the diagnostic work-up. In this case, the delay was shorter (median 5 days; range 2-15). In the group of 5 patients who underwent repeat studies, unchanged antibiotic regimen has been maintained between scans.

Cell Labeling

Polymorphonuclear cells (PMNs) from 50 mL of fresh venous blood anticoagulated with heparin were isolated, and

Table 1. Study population (N = 44)

Age (year)	66 ± 10
Males, N (%)	32 (73)
Initial surgery	
Coronary bypass, N (%)	28 (64)
Valve replacement, N (%)	12 (27)
Coronary bypass and valve replacement, N (%)	4 (9)

Table 2. Inclusion criteria

Criteria	N (%)*
Positive Redon culture	17 (40%)
Sternal wound inflammation	8 (19%)
Persistent purulent flow discharge	7 (16%)
Sternal dehiscence	3 (7%)
Persistent fever/biological inflammatory syndrome	12 (28%)

*Total >100% since some patients may have presented more than 1 criterion

Table 3. Main causative microorganisms (N = 39)

Microorganism	N (%)
Methicillin-resistant *Staphylococcus aureus*	18
Methicillin susceptible *Staphylococcus aureus*	6
Coagulase negative Staphylococci	8
Other (Gram negative bacilli, enterococcus)	6
Unidentified (16S rRNA PCR positive)	1

labeled with 320 MBq of freshly prepared ^{99m}Tc-HMPAO (Ceretec®, Amersham, Les Ulis, France) according to recommendations.[19] Upon reconstitution of the HMPAO kit with ^{99m}Tc-pertechnetate from a fresh generator eluate (within 30 min of elution) a lipophilic complex is formed. Freshly prepared ^{99m}Tc-HMPAO (1 mL, approximately 750-1000 MBq) in saline solution was added to the isolated granulocytes and incubated for 15 min at room temperature. After centrifugation, the supernatant containing unbound ^{99m}Tc-HMPAO was removed, and the amount of radioactivity was measured in the pellet and in the supernatant to calculate the labeling efficiency. Labeling efficiency was evaluated from the ratio of labeled cell to total radioactivity and was always superior to 90%. To avoid degradation of the radiopharmaceutical and radiation damage to labeled cells, ^{99m}Tc-HMPAO-labeled PMNs were injected as soon as possible, but not later than 30 min after labeling.

SCINTIGRAPHY

Image Acquisition

Patients referred to scintigraphy were in poor clinical status, which necessitated a rapid completion of image acquisition. Consequently, we decided to prioritize multiple planar incidences rather than SPECT/CT. In our experience, oblique views additionally to anterior view allowed to differentiate between superficial and deep sternal wound infections. After injection of 110-185 MBq of ^{99m}Tc-HMPAO-labeled PMNs, anterior, posterior, and right and left anterior oblique views of the chest were acquired with a double-head gamma camera (DST, SMV, Buc, France) equipped with high resolution parallel-hole collimators with a 256×256 matrix. Energy window was centered on the 140 keV photopeak of ^{99m}Tc, with a 20% window. Ten minutes acquisitions were performed at 4 hours, and 15 min acquisitions at 24 hour. The median delay between the last debridement and WBC scintigraphy was 25 days (range 8-116).

Image Analysis

Abnormal uptake scoring was used on 4 and 24 hours images: 0 = no abnormal uptake, 1 = equivocal (faint), 2 = moderate, 3 = intense uptake. The kinetics of accumulation between 4 and 24 hours images was also considered: an increase in uptake or size over time was considered as infection, whereas a decrease in uptake or size was considered as inflammation.

The scintigraphy was considered negative when no focal abnormal accumulation of cells was detectable at 4 and 24 hours or when abnormal uptake was present at 4 hours but decreased at 24 hours (scored as 0/0 or 1/0). The scan was considered non-conclusive when faint or moderate uptake was present at 4 hours after injection without increase at 24 hours (1/1 or 2/1).

The scan was considered positive when intense or moderate focal uptake was present at 4 hours, with stable or increased intensity at 24 hours (scored 3/3, 2/3, 2/2 or 1/2).

In addition to the daily analysis of scans, all the scintigraphic images were retrospectively interpreted in an off-site blinded reading session by 2 senior readers experienced with radiolabeled leukocytes scintigraphy (RL and CLV) in order to assess interobserver agreement. They rated each scan in 3 mutually exclusive categories: positive, negative, or non-conclusive.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation except delays that were expressed as median and range. Categorical variables were expressed as percentages. Sensitivity, specificity, positive predictive value, and negative predictive value of WBC planar scintigraphy were calculated according to the final diagnosis of mediastinitis and expressed with the relative 95% confidence interval. Interobserver agreement has been assessed by use of weighted Kappa

coefficient. Statistical analysis was performed using Medcalc software (version 12.1.0). A value of $P < 0.05$ was considered significant.

RESULTS

Patients

Out of the 43 patients, 4 patients, all with negative scans, were excluded from statistical analysis: 2 had an initial favorable clinical course but were lost to follow-up before 1 year, and 2 had also initial favorable clinical course but died before the first year of a cause unrelated to mediastinitis.

Overall, 39 patients were considered for analysis. Main clinical characteristics are shown in Tables 1 and 2. Mediastinitis relapse has been confirmed in 17 patients (44%): 8 by surgery, 9 by positive cultures of needle aspirations, and/or biopsies. Among these latter 9 patients, 4 died during the first month of follow-up due to the worsening of the infection. Twenty two patients (56%) were considered negative for mediastinitis relapse after a mean follow-up of two years.

WBC Scintigraphy Results

Interobserver agreement assessed by weighted Kappa coefficient was 0.73. In the 17 patients diagnosed with mediastinitis relapse, the first scan was considered positive in 16 and non-conclusive in one. In this latter patient, a second scintigraphy has been performed 2 weeks later and was positive; the patient underwent a surgical debridement 2 days after this last scintigraphy confirming the diagnosis of sternal osteomyelitis.

In the 22 patients diagnosed with no mediastinitis relapse, scintigraphy was considered negative in 16, non-conclusive in 4, and positive in 2 patients. In the 4 patients with non-conclusive results, a second scintigraphy has been performed (between 2 and 3 weeks after the first one) and considered negative in 3 and positive in one.

In summary, diagnosis performance of WBC scintigraphy based on the first scan only showed: 16 true positive, 2 false positive, 16 true negative, and 5 non-conclusive scans. Accordingly, 32 of 39 patients were correctly classified corresponding to 94% (95% CI 71%-100%) sensitivity, 73% (95% CI 50%-89%) specificity, 73% (95% CI 50%-89%) positive predictive value, and 94% (95% CI 94%-100%) negative predictive value.

Diagnosis performance of WBC scintigraphy based on both scans, including the additional scan performed in 5 patients when the first one was considered non-conclusive, was: 17 true positive, 3 false positive, 19 true negative, and no false negative. Accordingly, 36 of 39 patients were correctly classified corresponding to 100% (95% CI 80%-100%) sensitivity, 86% (95% CI 65%-97%) specificity, 85% (95% CI 62%-97%) positive predictive value, and 100% (95% CI 82%-100%) negative predictive value.

Of note, in the false positive/non-conclusive groups, the delay between the last surgery and scintigraphy was relatively short: median 10 days (range 5-16 days), with a sternal dehiscence or pseudarthrosis in all patients. Relevant examples of positive and negative scans are shown in Figures 1 and 2.

DISCUSSION

The present study takes place in the specific context of suspicion of mediastinitis relapse, occurring usually early after a previous surgical revision. In this context of important tissue inflammation due to iterative surgeries, the diagnosis of infection is very challenging, particularly with morphological imaging. Additionally, the impact of diagnosis on outcomes is major, due to the patients' poor clinical status and the mortality associated with additional high-risk surgery. Consequently, a reliable imaging technique is required for diagnosis of persistent or recurrent sternal osteomyelitis and potential mediastinal extension. In the present single center study, with a limited number of patients, the negative predictive value of WBC scintigraphy was excellent, reaching 94% after a first scan and 100% if an additional scan was performed when the first one was non-conclusive. Accordingly, WBC scintigraphy may be regarded as a gatekeeper for unnecessary re-debridement or prolonged use of antibiotics when the scan is normal.

Previous studies evaluating WBC scintigraphy in the diagnosis of deep sternal wound infection reported consistent results with a sensitivity between 86% and 100%, and a specificity between 89% and 97%.[15-18,20] After the first scan, our study showed sensitivity and specificity slightly lower compared to that reported by Cooper et al[16] and Quirce et al[18] despite similar imaging procedure and analysis criteria. The relative lack of sensitivity may be related to the decreased ability of radiolabeled leukocytes to migrate through scar tissue and reach infected sites following a surgical revision. On the other hand, surgical removal of infected and necrotic tissue and debridement, although mandatory for promoting the healing process, is likely to induce a transient but marked inflammatory phase which probably underlies false positive scans or non-conclusive pattern as reported in some patients of the present study. Indeed, all false positive and non-conclusive scans were performed within 2 weeks following revision surgery. However, performing a second scan when the first one is not conclusive proved to be useful in the present study: it allowed to improve both sensitivity and
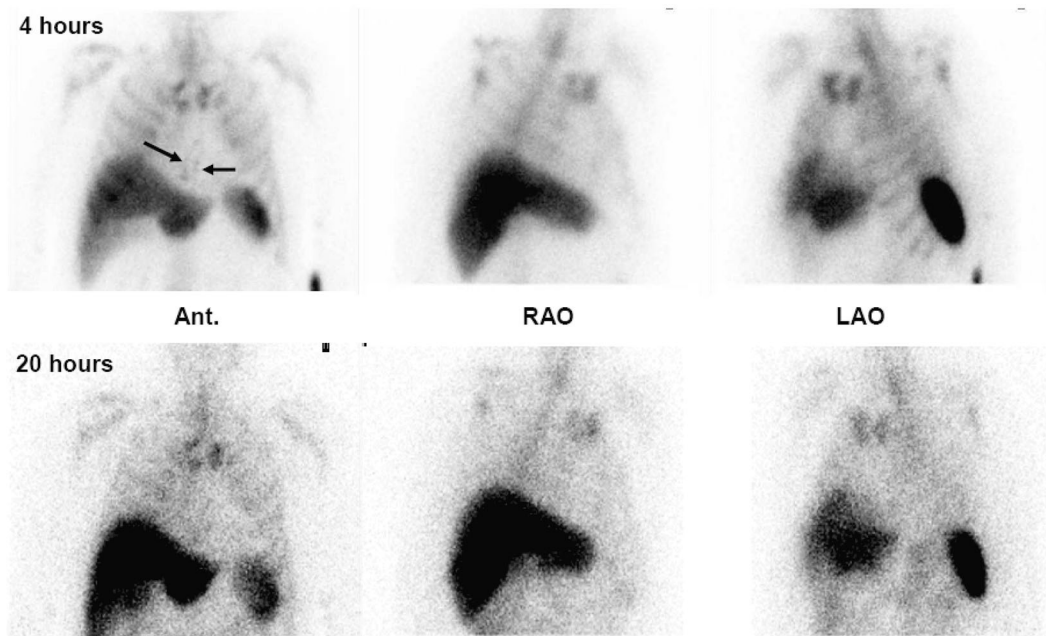
Figure 1. ^{99m}Tc-labeled white blood cells scintigraphy in a 76 year-old man with a history of aorta valve replacement and coronary bypass graft on the left anterior descending coronary artery. Three weeks after surgery, he was diagnosed with methicillin-resistant Staphylococcus aureus postoperative mediastinitis, and treated by surgical debridement and drainage with Redon catheters. After 4 weeks of appropriate antibiotic therapy, mediastinitis relapse was suspected on persistent elevated C-reactive protein and a raise of leukocytes blood counts. WBC scintigraphy showed a very faint uptake on the edges of the sternal wound (*arrows* 4 h), decreasing on late images performed 20 h after leukocytes reinjection. The scan was considered negative and no event occurred during follow-up. *Ant.*, Anterior view; *RAO*, right anterior oblique; *LAO*, left anterior oblique.

specificity to levels similar to those reported in a first episode of mediastinitis.[16,18]

A limitation of our study was related to the absence of SPECT or SPECT/CT in the imaging procedure. Due to prolonged stay in ICU, patients included in the present study were in poor clinical status, and most of them unable to undergo a long imaging procedure. This forced us to keep the imaging time as short as possible without compromising neither image quality or diagnostic value. Consequently, we decided to perform multiple planar incidences of the chest instead of suboptimal tomographic acquisitions. Indeed, in the setting of sternal osteomyelitis, a study suggested that planar images were more relevant in the assessment of sternal uptake than SPECT.[21] The authors reported normal planar and SPECT patterns of thoracic distribution of ^{99m}Tc-HMPAO in 20 patients who had undergone a previous median sternotomy, without infectious complications at follow-up. The sternal uptake was homogeneous in five patients and heterogeneous in 15 patients. Planar views were considered better for the assessment of sternal uptake, but SPECT views were superior for the direct visualization of the mediastinum by eliminating overlapping sternal uptake.[21]

Recently an alternative approach was proposed for imaging infection using[18] FDG PET.[18] FDG accumulates in metabolically active cells, including activated leukocytes at the site of infection, enabling imaging of inflammatory processes.[22] There is now a large body of evidence supporting the usefulness of[18] FDG in infection, particularly due to its high negative predictive value.[23,24] However, thus far, no study reported on[18] FDG PET diagnostic value in post-sternotomy mediastinitis. To this regard, an alternative approach would be to match technical advances of PET with specificity of infection targeting through PMNs migration. A preliminary work by Bhargava et al reported on feasibility of human leukocyte labeling with Cu-64,[25] which 12 hours half-life seems optimal for delayed acquisitions.

NEW KNOWLEDGE GAINED

WBC scintigraphy provides specific assessment of infection relapse after surgical debridement of post-sternotomy mediastinitis. The diagnostic value seems optimal as soon as 2 weeks after revision surgery.
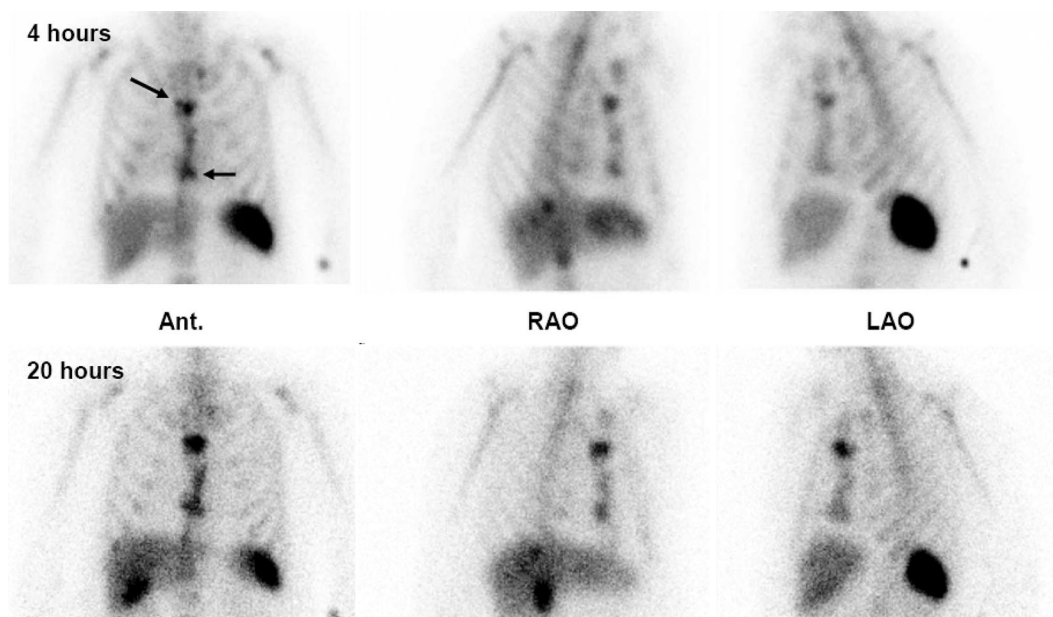
Figure 2. ^{99m}Tc-labeled white blood cells scintigraphy in a 58 year-old woman with a history of diabetes mellitus and coronary bypass graft. Two weeks after surgery she presented pus draining from the scar. Needle aspirates culture was positive for Staphylococcus epidermidis. She was treated by surgical debridement and drainage with Redon catheters. After 6 weeks of appropriate antibiotic therapy, she developed low grade fever associated with local signs of inflammation of the scar. WBC scintigraphy showed a marked uptake of the whole sternum (*arrows* 4 h), increasing on late images performed 20 h after leukocytes reinjection. The diagnosis of mediastinitis relapse was confirmed by culture of samples taken during surgical re-debridement positive for methicillin-resistant Staphylococcus aureus. *Ant.*, Anterior view; *RAO*, right anterior oblique; *LAO*, left anterior oblique.

CONCLUSION

In the specific context of suspicion of post-sternotomy mediastinitis relapse after a prior surgical revision, our study showed that the diagnostic value of WBC scintigraphy was slightly lower than that reported in the setting of the initial episode of mediastinitis. However, the diagnostic value was improved by repeating the scan after 2-3 weeks when the first one was not conclusive. In this context, WBC scintigraphy was able to rule out infection when the scan was negative and may be regarded as a gatekeeper for unnecessary re-debridement or prolonged use of antibiotics.

Disclosures

None.

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