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Original

Discordance between labelled white blood cell scintigraphy and bone scan following suspicion of bone infection: What should be done about it?

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Abstract

BACKGROUND: Bone infection is a common issue in infectiology. The gold standard for evaluating bone infection is the white blood cell (WBC) scan. In our practice the WBC scan is coupled with a bone scan. Discordances in the results of these two examinations are a common occurrence in daily practice. We decided to investigate the meaning of these discordances. Materials and methods: Two hundred and ninety-six 99mTc-HMPAO-labelled white blood cells (WBC) and 99mTc-HMDP bone scanning (BS) examinations were performed in our department between 1997 and 2003 for evaluation of bone infection. Out of these 296 examinations, a first rating extracted 54 scans that were considered discordant. These 54 scans were reviewed by three observers. Clinical and paraclinical data were obtained for all the cases definitely considered as discordant by all three observers. RESULTS: The observers finally retained 18 cases as discordant from the initial 296 (6.1%). Thirteen patients were not infected, and five patients were considered infected based on clinical follow-up or bacteriological and histological data. For the 17 patients with WBC–, BS+, 4 (23.5%) were infected.
CONCLUSION: Our study shows that in the vast majority (17 out of 18), discordances consist of a negative WBC scan with a positive bone scan. In these cases the accuracy of the WBC scan is diminished as 23.5% of the patients with a negative WBC and a positive bone scan are infected.
Key words: white-blood-cell scintigraphy, bone scintigraphy, bone infection, discordances

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Introduction

Bone infection is a common occurrence in infectiology; the management of bone infected patients is a complex issue that requires long therapy. When patients are suspected to have bone infection, the clinician relies heavily on paraclinical examinations and on imagery procedures in particular to ascertain a diagnosis.

However, no examination achieves 100 percent accuracy. Therefore, a large number of teams are working on this field, trying to increase the performance of these examinations.

A PubMed search with the words 'bone infection and scintigraphy' finds more than 280 entries for the last 5 years only.

On top of nuclear medicine, other imaging modalities such as MRI scanning, CT scanning, and ultrasound are being performed and evaluated.

Despite this growing field of research, autologous leukocytes (AL) labelled in vitro with 111-In or 99m-Tc (also known as white blood cell scintigraphy — WBC) are still considered the gold standard for infection imaging [1].

Nevertheless, many studies show marked differences in sensitivity, specificity, and accuracy for WBC. Moreover, its interpretation

is quite often difficult. To facilitate interpretation and to obtain more information the WBC is usually performed after or at the same time as a bone scan (BS).

We have focused our interest on a very practical matter, which happens to be a common occurrence in daily practice: the discordance between a positive bone scan and a negative autologous leukocyte scan, or between a positive autologous leukocyte scan and a negative bone scan.

Material and methods

Study population

In this retrospective study, we included patients who had a discordance between their WBC scintigraphy and their bone scan in our institution between 1997 and 2003. Two hundred and ninety-six WBC scans were performed in this period. A first rating was made at the time of the examination by the initial observer. From this first rating we extracted, out of 296 examinations, 54 cases of discordance. For these 54 cases, both WBC and bone scintigraphy were reviewed by 3 independent and trained observers. The observers were told about clinical history and the site which was suspected of infection; bone and WBC scans were interpreted together. If there was no late imaging or if some elements were missing, the cases were systematically ruled out. Each examined bone site was staged between –1 and 2. Lack of radiotracer uptake was represented by a score of –1, 0 represented physiological uptake, 1 was moderate increase of uptake, and 2 was marked increased of uptake. Examinations in which the ratings for the WBC and bone scintigraphy did not match were called discordant, i.e. 2 versus 0 or 2 versus –1. Any other situation was not considered as discordant. The examinations were finally considered as discordant if the three observers agreed on the rating for both the WBC and the bone scans. Clinical and paraclinical data were then gathered to see if the examined site was infected or not.

In the event of surgery, the bone site was considered infected if at least two deep bacteria cultures grew with the same bacteria or if there was microscopic evidence of infection. The bone site was considered uninfected if bacteriological samples were negative and if there was no histological sign of infection. Concerning patients who did not go through surgery, the clinical outcome was determined by follow up for at least one year after the imaging procedure. On the basis of clinical parameters, we considered as not infected those patients for whom antibiotic treatment was not required at the end of follow-up. On the other hand, we considered as infected those patients who required an antibiotic therapy during follow-up.

^{99m}Tc-HMPAO leukocyte scintigraphy

Blood samples were collected for leukocyte labelling. The leukocyte fractions were labelled with ^{99m}Tc-HMPAO using a dose of 740 MBq (20 mCi) and standard techniques [1] .The leukocytes were reinjected intravenously into each patient with a delay of no more than 3 hours; the administered activity ranged from 185 to 550 MBq (5–14.86 mCi). Labelled fractions viability was controlled using the trypan blue test.

The ^{99m}Tc-HMPAO-labelled WBC images were acquired in anterior and posterior view of the suspected region at two different time points after injection: 4 hours (early) and 20 hours (late).

Table 1. The results of bone scintigraphy

	WBC+ BS–	WBC– BS+
Infection	1	4
No infection	0	13

WBC+ — positive white blood cell scintigraphy; WBC– — negative white blood cell scintigraphy; BS– — negative bone scan; BS+ — positive bone scan

Bone scan

Using standard techniques, 2- or 3- phase bone scans were performed. The administered activity ranged from 555 to 740 MBq (15–20 mCi).

Results

Fifty-four out of 296 examinations were considered as discordant by the initial observer (18.2%). The three independent and trained observers finally retained 18 (6.1%) cases as discordant out of the 296.

The sex ratio was 2/1 (female/male). Mean age at the time of examination was 52.8 years (15–73). Median follow-up after the scans was 43 months (12–84).

Out of the 18 patients investigated, 7 (38.9%) had a suspicion of prosthetic infection, 1 had a suspicion of infection on osteosynthesis material, 9 (50%) had a suspicion of infection after orthopaedic surgery without foreign body, and 1 had a suspicion of chronic osteomyelitis.

We differentiated two kinds of discordances: negative WBC scintigraphy with positive bone scans, and positive WBC scintigraphy with negative bone scans. In 17 out of the 18 discordances it was a negative WBC scintigraphy with a positive bone scan. In one case it was a positive WBC scintigraphy with a negative bone scan (Table 1).

For this one case with a positive WBC scan there was a bacteriologically-proven infection; the WBC scan was positive for soft tissues near the femur whereas the bone examination showed no uptake of radiotracer. Our first impression was that there was an abscess without bone infection, but the histological examination came back positive for bone infection. Therefore, this case was considered a false negative bone scan.

In 13 cases there was no sign of infection following the scintigraphic investigation. Twice multiple bacteriological samples came back negative, and in 11 cases clinical follow-up showed a decrease or disappearance of symptoms without the need for antibiotic therapy.

In 5 cases there were signs of infection: bacteriological and histological proof in three cases and in the other two cases antibiotic therapy substantially improved the symptoms.

In the 17 WBC– BS+ there were 4 patients presenting infection. This means that the probability of infection in a situation of discordance with a negative WBC scan and a positive bone scan is 23%.

Discussion

Our study shows that the probability of infection in patients with a positive bone scan and a negative WBC scan is nearly 1 in 4.

Despite its acknowledged status as the gold standard procedure for infection, WBC is far from being 100% accurate.

In our study, four infected patients had a negative WBC scan. One of them had a spondylodiscitis. It is well known that WBC scans have a poor sensitivity in spine infection [5]. However, in the three other cases infection was located in the limbs.

Another possible explanation for false negativity is chronic infection. With chronicity the granulocyte response decreases and the inflammatory process is dominated by macrophages and other mononuclear cells [6].

Since we are confronted with poor performance of WBC scans in some situations, we should look for better examinations in specific situations.

99mTc-labelled ciprofloxacin (Infecton, Draximage, Quebec, Canada) is a fluoroquinolone analogue with a specific binding to bacterial DNA gyrase that is present in all viable bacteria. It has shown better results than standard WBC scan for spine infection [7] and could be an alternative to WBC in this indication.

99mTc-labeled antistage specific embryonic antigen-1 (anti-SSEA-1) monoclonal IgM class antibodies, known as LeuTech (Mallinckrodt, Hazelwood, MO), binds specifically to the CD-15 antigen epitope on the cell membrane of activated neutrophils with very high affinity (*K*d_10_11 mol/l). LeuTech has shown very high sensitivity, specificity, and positive predictive value for the detection of infection and has successfully identified osteomyelitis and post-surgical infection [8].

When there is a suspicion of periprosthetic infection, autologous labelled leukocytes combined with bone marrow imaging is the modality of choice and provides an accuracy of 90% [9].

18-FDG PET is being extensively studied as a marker for inflammation and infection [10]. 18-FDG can trace the increased glucose metabolism of inflammatory cells (PMNs, lymphocytes, macrophages) at sites of infection and inflammation. On top of the advantages provided by the higher resolution of PET, 18-FDG PET has demonstrated significant diagnostic potential in soft tissue and bone infection [11]. 18-FDG is also a marker of chronic inflammation and could replace WBC in this indication.

Conclusions

In the presence of a negative WBC and a positive bone scan, the nuclear medicine specialist should be wary of false negative results, which occur in nearly 1 in 4 cases, in our experience. We recommend performing early and late imaging in bone scans and to confront results with other imaging modalities as well as with clinical and biological data, in close collaboration with the clinician.

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