Utility of Tc-99m-labeled levofloxacin as an infection-imaging agent in musculoskeletal infections

Pakistan Journal of Nuclear Medicine
Volume 10(1):13–19

Pakistan Society of Nuclear Medicine
contact@psnmed.com
https://pjnmed.com

Ayesha Ammar[1*], Shazia Fatima[1], Kahkashan Bahsir Mir[1], Sadaf Butt[1], Sadaf Batool[1], Muhammad Adnan Saeed[1], Noreen Marwat[1], Naseer Ahmed[1]

ABSTRACT

Background: The purpose of this study is to ascertain the utility of Technetium (Tc)-99m-labeled levofloxacin in diagnosing musculoskeletal infections and also to observe its biodistribution in the human body. Patients who were referred with the clinical suspicion of having osteomyelitis underwent Tc-99m levofloxacin imaging.

Methods: Tc-99m-labeled levofloxacin scintigraphy was carried out in 30 patients with musculoskeletal infections and the results were compared with the culture and sensitivity of suspected lesions.

Results: Fifteen patients were true-positive, 2 were false-positive, 1 was false-negative, and 12 were true-negative. The sensitivity and specificity were 93.8% and 85.7%, respectively. The positive and negative predictive values were 88.2% and 92.3%, respectively. The biodistribution studies revealed that 7.74% ± 0.42% of the injected dose at 1 hour decreased to 5.45% ± 0.37% at 2 hours, and to 2.49% ± 0.55% at 4 hours. The liver showed a mean uptake value of 5.58% of injected activity at 1 hour, which decreased to 3.52% ± 0.30% and 2.00% ± 0.5 0% at 2 and 4 hours, respectively. The activity in the bladder increased from the mean percentage uptake value of 5.45% ± 0.84% at 1 hour to 20.00% ± 3.67% at 2 hours and 39.67% ± 4.23% at 4 hours. The results of Student's *t*-test showed significant differences in the uptake values of infected and noninfected sites. Chi-square results confirmed strong association between osteomyelitis and Tc 99m Levofloxacin uptake.

Conclusion: Tc-99m-labeled levofloxacin has the potential of simulating an infection-imaging agent.

Keywords: 99mTc levofloxacin, musculoskeletal infections, nuclear medicine.

Received: 14 September 2019 **Accepted:** 20 May 2020
Type of Article: ORIGINAL ARTICLE
https://doi.org/10.24911/PJNMed.175-1568470299

Correspondence to: Ayesha Ammar
*Nuclear Medicine, Oncology & Radiotherapy Institute (NORI), Islamabad, Pakistan.
Email: ayesha-ammar@hotmail.com
Full list of author information is available at the end of the article.

Introduction

Levofloxacin is an isomer of ciprofloxacin. It specifically binds to the DNA gyrase and inhibits the formation of bacterial colonies. The main aim of our study is to develop and formulate a ready-to-use kit for diagnosing infections, as previously reported by Shimpi et al [1]. Levofloxacin was reduced with the use of stannous ion as the reducing agent, and the reported results were the same. This study was carried out on mice, and the target to nontarget ratio was calculated. One biodistribution study reported that there was a major difference in the uptake values in major organs and in infected muscles [1]. The study objective of El-Ghany [2] was to prepare a kit which can be easily formulated having a long shelf life and which can easily discriminate between infection and sterile inflammation, having specific activity of binding to a specific target in the infectious foci and showing high accumulation in the abscess. It can bind to a variety of microorganisms without binding to the host cell and it is safe and well tolerated by patients with both kidney and liver impairments.

Our main aim was to assess the utility of Technetium (Tc)-99m levofloxacin as an infection-imaging agent in musculoskeletal infection and also to evaluate the biodistribution of Tc-99m levofloxacin.

Material and Methods

This study was conducted in at the nuclear medicine department of Nuclear Medicine, Oncology & Radiotherapy Institute (NORI). Ethical approval was granted by the Research Training and Monitoring Cell (RTMC) of NORI, in January 2011, RTMC 3/1-150-2011, and informed consent was obtained from the patients. A total of 30 patients were included in this study and 19 were male and 11 were female, as shown in Table 1. Approximately, 5–10 mg of levofloxacin was used and stannous ion was used as the reducing agent. Radiochemical purity on the instant thin-layer chromatography (ITLC) scanner having stationary and mobile phases was checked using the double strip method. After checking for radiochemical purity, the patients were injected. Imaging was carried out on a dual-headed gamma camera. The processing and quantitative analysis were carried out using Xeleris® software. The patients

included in the study were those who were referred to our center with the clinical suspicion of having musculoskeletal infection, who were not on antibiotics within 10 days of the study, after a history of trauma, or having no minor surgical procedure within 7 days of the study. Patients who were pregnant, breast feeding, with any evidence of bleeding diathesis or coagulation, and comorbid conditions, such as hepatic or renal failure, were excluded.

After Tc-99m levofloxacin was injected, blood flow and blood pool images were taken immediately to observe the flow and distribution of radiopharmaceuticals. Delayed images of the region of interest were taken at 1, 2, and 4 hours, as shown in Figure 1. In addition, we obtained the whole body images to see the biodistribution at 1, 2, and 4 hours. In order to observe the biodistribution of Tc-99m levofloxacin, the regions of interest were drawn in the anterior and posterior views around the whole body, liver, kidneys, and bladder, as shown in Figure 2. Percentage uptake by different organs with reference to the whole body was calculated using the following formula:

Percentage uptake = counts in the sp organ/whole body counts × 100.

If there was concordance between the results of the three-phase bone scan and Tc-99m levofloxacin, the diagnosis of osteomyelitis would be confirmed. The images were analyzed qualitatively and quantitatively and were divided into four groups based on tracer avidity. Group 1 showed no radiotracer uptake, group 2 showed mild radiotracer uptake, group 3 showed moderate radiotracer uptake, and group 4 showed a marked increase in radiotracer uptakes (Table 2). For analysis, we compared the uptake at the site of pathology with the radiotracer uptake in the kidney and liver. We divided it based on the visual scale of 0–3, with group 1 showing no uptake, group 2 showing uptake less than the liver, group 3 showing uptake greater than the liver but lesser than the kidney, and group 4 showing uptake greater than the kidney. A score of 0 and 1, group 1 and 2, was considered as negative uptake scan, while a score above that was considered as positive uptake scan. The uptake pattern in our study population is according to the visual scoring system given

Table 1. *Characteristics of the study population.*

1	Total male patients	19
2	Total female patients	11
3	Mean age (years)	27.5 ± 13.8
4	Median height (cm)	133.2 ± 8.8
5	Median weight (kg)	45.7 ± 7.1

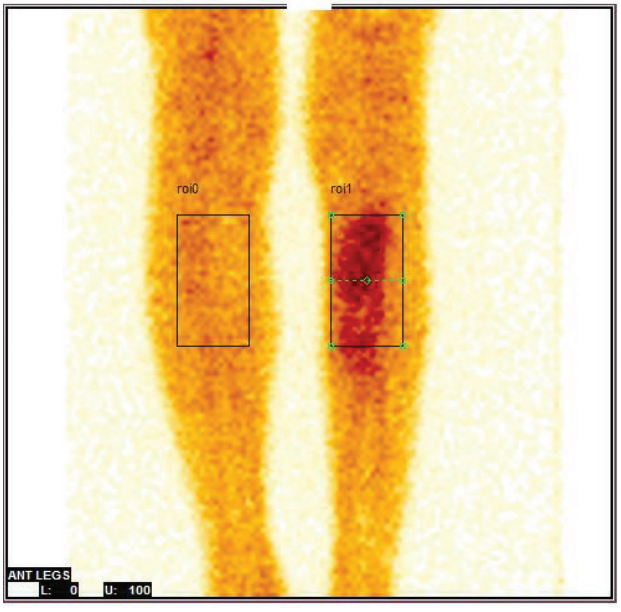

Figure 1. *Image showing the region of interest drawn on the static 1-hour image.*

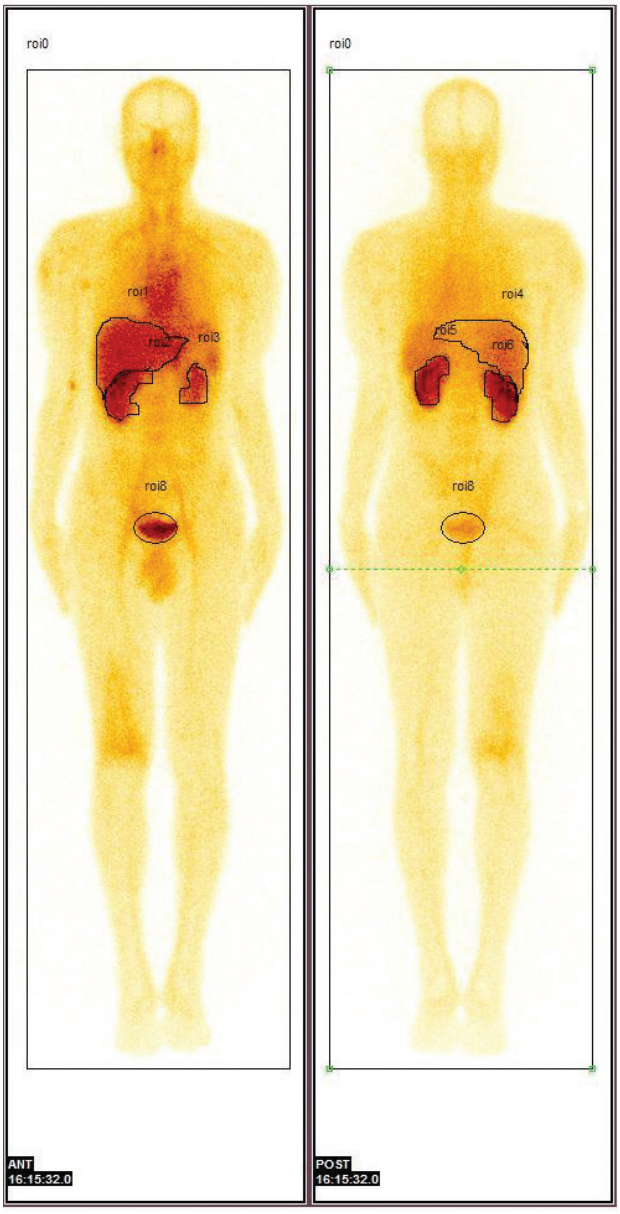

Figure 2. *Regions of interest on the whole body and different organs for biodistribution.*

in Table 2. Scans were analyzed quantitatively by drawing the regions of interest on the target side and another copy of that was pasted on the non-target side. The readings were taken at 1, 2, and 4 hours. The data were statistically analyzed on MS Excel and Statistical Package for the Social Sciences. The significance of difference in positive and negative scan results was tested using the nonparametric chi-squared test; p-value < 0.05 was considered significant.

Results

Radiochemical purity

The chemical purity of the test was tested using ITLC, and the labeling efficiency was greater than 96% and the free technetium was found to be less than 1%, even after 4 hours of its formation.

Quantitative data results

The biodistribution of Tc-99m levofloxacin was assessed scintographically. The whole body images of patients were taken at 1, 2, and 4 hours. There was gradual excretion of the radiotracer via the kidneys. Renal activity decreased from a mean percentage uptake value of 7.74% ± 0.42% of the injected dose at 1 hour to 5.45% ± 0.37% at 2 hours and to 2.24% ± 0.55% at 4 hours. The liver showed a mean percentage uptake value of 5.58% of the injected activity at 1 hour, which gradually decreased to 3.52% ± 0.30% and 2.00% ± 0.50% at 2 and 4 hours, respectively. The activity in the bladder increased from a mean percentage uptake value of 5.45% ± 0.84% at 1 hour to 20.00% ± 3.67% at 2, and at 4 hours, the value increased to 39.67% ± 4.23%. For quantitative analysis, the target to nontarget ratio was calculated at 1, 2, and 4 hours. Means and standard deviations were also calculated. For patients who were positive on levofloxacin scan, their mean and standard deviation at 1 hour was 2.41 ± 0.28, at 2 hours was 2.72 ± 0.29, and at 4 hours was 2.40 ± 0.24. For patients who were negative on levofloxacin scan, their mean and standard deviations at 1 hour was 1.09 ± 0.08, at 2 hours was 1.05 ± 0.05, and at 4 hours was 1.07 ± 0.07, as shown in Figure 3.

The final confirmation of osteomyelitis was carried out by culture and sensitivity of the affected area. True-positives, true-negatives, false-positives, and false-negatives were calculated by comparing the scintigraphic data with the gold standard techniques. Based on the results of culture and sensitivity, 16 patients (53.3%) out of the total study population had osteomyelitis, while 14 patients (46.6%) had negative results for any infection. Out of the total 30 patients, on levofloxacin scintigraphy, 15 were true-positive, 2 were false-positive, 1 was false-negative,

Table 2. *Radiotracer uptake patterns in study population.*

SCALE	UPTAKE LEVELS	NO. OF PATIENTS	PERCENTAGE
0	Showing no uptake	8	26.7%
1	Showing uptake less than liver	5	23.3%
2	Equal to liver and less than kidney	15	50%
3	Equal to kidney	2	6.7%

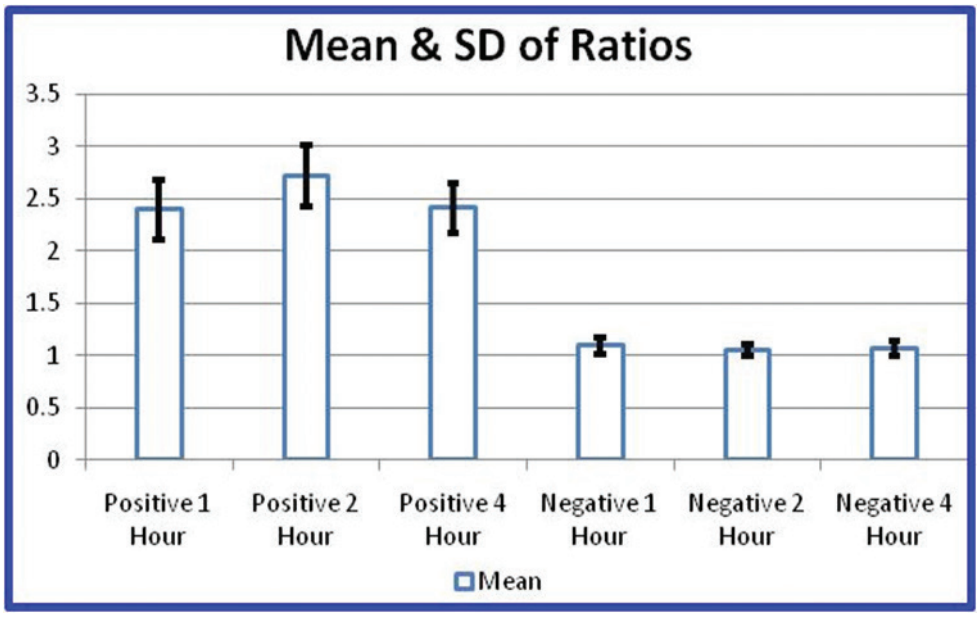

Figure 3. *Means of the target to nontarget ratio in positive and negative scans.*

and 12 were true-negative. Out of the 17 patients who were positive on levofloxacin scintigraphy, 12 patients (70.58%) were positive for *Staphylococcus aureus* and 5 patients (23. 64%) were positive for *Escherichia coli* on culture sensitivity. Out of the 13 negative patients on levofloxacin scanning, 12 (92.3%) had an unremarkable culture and sensitivity results. Only one patient had a positive culture.

Qualitative analysis

Based on radiotracer uptake, patients were categorized into positive and negative groups, and 17 patients were considered positive and 13 were considered negative.

Student's *t*-test showed that there is significant difference in the target the nontarget ratios between positive and negative levofloxacin scanning at various time intervals (Table 4).

Discussion

Infectious diseases are a major source of mortality and morbidity in underdeveloped countries. Early diagnosis and localization of infections would stall mortality and morbidity and complications, like sepsis, bone deformity, and chronicity. The most reliable method for early diagnosis of an infection is the analysis of microbiological samples taken from the lesion [4]. The procedure is usually invasive and may be difficult or even impossible to carry out in many cases. On the other hand, conventional anatomical imaging modalities, such as plain radiography, ultrasonography, and computed tomography (CT), are useful only after abscess formation, which is a later manifestation of the infection.

Standard X-ray is the initial modality for the investigation of suspected osteomyelitis. It shows the abnormality

Table 3. *Sensitivity and specificity of Tc-99m levofloxacin.*

POSITIVE PREDICTIVE VALUE (PPV) & NEGATIVE PREDICTIVE VALUE (NPV) TEST		ACUTE OSTEOMYELITIS		
		PRESENT	ABSENT	TOTAL
Levo scan	Positive	15	2	17
	Negative	1	12	13
	Total	16	14	30
a	Results Grid	True-positive	15	50.0%
b		False-positive	2	6.7%
c		False-negative	1	3.3%
d		True-negative	12	40.0%
		Sensitivity		93.8%
		Specificity		85.7%
		PPV		88.2%
		NPV		92.3%

Table 4. *Chi-squared test states that levofloxacin scintigraphy results truly depict the presence or absence of osteomyelitis.*

CHI-SQUARED TEST						
NULL HYPOTHESIS		NO RELATIONSHIP BETWEEN ACUTE OSTEOMYELITIS AND LEVO SCAN				
Chi-square						
		Total (ad–bc)^2		950,520	19.20	
		(a+b)(c+d)(a+c)(b+d)		49,504		
Detailed calculations						
Cell	O (Obs value)	E (Exp value)	O–E	(O–E)^2	(O–E)^2/E	Chi-square
a	15	9.1	5.9	35.20	3.9	19.20
b	2	7.9	–5.9	35.20	4.4	
c	1	6.9	–5.9	35.20	5.1	
d	12	6.1	5.9	35.20	5.80	
Degrees of freedom		(No. of Rows–1) × (No. of Columns–1)			1	
Significance level		5%			3.84	
		1%			6.64	
		0.1%			10.83	
Result		It has been proved that there is a strong correlation between acute osteomyelitis and Levo Scan even at 0.1% significance. Hence, with 0.1% chance of being wrong, it can be stated that Levo Scan is a good indicator of acute osteomyelitis.				

only when 40%–50% of the bone density is lost. Normal X-rays do not exclude osteomyelitis [5].

On ultrasound, the initial finding would be deep soft tissue swelling, which is also an accurate sign of early osteomyelitis, and it remains and stays there throughout the process of inflammation. This can be easily discriminated from cellulitis. CT and MRI, despite being highly sensitive and sophisticated, are modalities that lack specificity for infections, especially in early phases when the anatomic structures have not yet been altered. Magnetic resonance imaging (MRI) aids in delineating the sinus tracts and soft tissue abscesses and helps in discriminating between osteomyelitis and cellulitis and by disclosing the extent of intramedullary involvement [6,7].

Radionuclide studies, in fact, have been used for detecting and localizing infections for nearly half a century. Many scintigraphy-imaging agents, such as gallium-67, radiolabeled leukocytes, human immunoglobulin, dextran, and peptides, have been reported for detecting and localizing infectious lesions. Although these agents have been proved useful, they have some drawbacks primarily because of their inability to differentiate between inflamed and infected lesions. Tc-99m-labeled methylene diphosphonate bone scan has a sensitivity of 90% and specificity of 75%. Its limitations are reduced specificity in a bone with preexisting conditions of the bone, such as fractures, orthopedic hardware, or in cases of arthropathy [5,8].

In-111-labeled leukocytes is in use for many decades, for radiotracer uptake and localization of infection, after the labeling process. It is lipophilic in nature with a long half-life. Its laborious preparation and labeling technique hinders its use routinely. Gallium(Ga)-67 citrate is one of the first radiopharmaceuticals developed for imaging infections. However, Ga-67 has an unfavorable physical characteristic for gamma camera imaging and gives high radiation exposure. Hence, it is not widely used, and has been superseded by Tc-99m-labeled pharmaceuticals, which have more favorable properties as infection-imaging agents [9,10],

A large multicenter trial inducting 879 patients has proved Tc-99m-labeled ciprofloxacin's high sensitivity and efficacy as an infection-imaging agent. However, previously reported data about the specificity of Tc-99m ciprofloxacin for infection are contradictory [13,16]. Moreover, proposed emerging bacterial resistance against this antimicrobial agent has led to the recruitment of many other quinolones as infection-imaging agent. Levofloxacin is the fourth generation of quinolone antibiotics that has activity against a wide range of Gram-negative and Gram-positive microorganisms, including *Streptococcus pneumonia*, and multidrug-resistant strains. Levofloxacin showed widespread distribution into body tissues and it was stereo chemically stable in plasma and urine. Levofloxacin undergoes limited metabolism in humans and is excreted as an unchanged drug in the urine that is used safely in patients with impaired renal functions and hepatic insufficiency. Many *in-vivo* and preclinical studies have been conducted to observe the efficacy of the Tc-99m Levofloxacin as an infection-imaging agent. This study was undertaken to observe utility of Tc-99m-labeled levofloxacin as an infection-imaging agent and also to observe its biodistribution pattern in the human body [21].

A scintigraphic method was used to determine biodistribution. The results revealed gradual excretion of the tracer via the kidneys, with a percentage of the administered dose of 7.74% ± 0.42% of the injected dose at 1 hour decreasing to 5 and to 2.49% ± 0.55% at 4 hours. A similar pattern was observed in liver activity. Tracer accumulated gradually in the urinary bladder, with the same parameter values of 5.45% ± 0.84% of the injected dose at 1 hour decreasing to 39.67% ± 4.23% at 4 hours. A similar pattern of distribution was observed for Tc-99m ciprofloxacin [1] and in animal model studies of levofloxacin. The difference of percentage observed by El-Ghany et al. [2] is most likely due to the difference size of animal and human tissue and the different amounts of the levofloxacin used.

The kit was prepared and also evaluated for quality control. Radiochemical purity was tested before injecting the patient and it was found to be more than 96% radiochemically pure. Complex remained at the base line, while free pertechnetate moved upward and was concordance with the studies in [2,3]

The scintigrams were interpreted as positive or negative based on the visual analysis technique. They were considered positive for infection when Tc-99m levofloxacin tracer uptake was more in the pathological side when compared to the healthy side. For tracer avidity, we divided them into four groups: group 1 with no uptake, group 2 with uptake equal to the liver, group 3 with uptake more than the liver, and in group 4 uptake was equal to the kidney. We took the first two groups as negative and the last two as positive. Eight had no radiotracer uptake, with a percentage of 26.67%, and five had an uptake lesser than the liver, constituting 23.33% of the study population. Fifteen had tracer avidity more than the liver, comprising 50%, while only two patients fell in group 4 had tracer uptakes equal to the kidney. These are also analyzed by Sarda et al. [15,16] on visual score and according to them those who showed radiotracer uptake were given a positive score and those with no tracer uptake are given negative score. Visual score (0–3) was used to categorize studies as positive or negative, with scores of 0 (minimal or no uptake; equivalent to soft tissue) and 1 (mild; less uptake than in liver) being considered as negative and scores of 2 (moderate; uptake greater than or equal to that in the liver) and 3 (intense; uptake greater than or equal to that in the kidneys) being considered as positive [2].

The target to nontarget ratios for every patient were calculated at 1, 2, and 4 hours. The highest target to nontarget ratio was in the 2-hours image. The ratio of the target to nontarget ratio was far more in infection than inflammation. These results were further confirmed because most of the patients were infected with *E. coli* and *S. aureus*, which were the causative agents in most of the cases. The studies carried out by El-Ghany et al. [2] showed that the target to nontarget ratio was significant at 24 hours postinjection, whereas in our study the target to nontarget ratio was highest at 2 hours. This proves that we can tell a patient much earlier if he is having an infection or not. From the data, it can be calculated that there were 15 true-positive, 12 false-negative, 2 false-positive, and only 1 is true-negative. From the data, the sensitivity turned out to be 93.8%, specificity was 85.7% with a positive predictive value of 88.9%, and NPV value was 92.8%. So our study with 88.9% can certainly say that a person is having a musculoskeletal infection, and with 92.8% guarantee we can say that a patient is not having a musculoskeletal infection. When we compared our results with studies labeled with ciprofloxacin in Singapore [13,14], their results for the infected prosthesis were 47 true-positives, 33 true-negatives, 5 false-positives, and 11 false-negatives, giving a sensitivity of 81% and specificity of 87%. The positive and negative predictive values were 90% and 75%, respectively. The largest trial study of Tc-99m-labeled ciprofloxacin that included about 900 patients, was conducted in the framework of an International Atomic Energy Agency (IAEA) coordinated research project [20]. In this study, the overall sensitivity was 87.6%, while the specificity was 81.7% [13,14,19].

Regarding the results of false-positivity, a case of a patient with a persistently increased target to nontarget ratio at 1, 2, and at 4 hours showed that *S. aureus* was the root cause of infection. But to our knowledge, the biopsy of the patient proved to be osteogenic sarcoma. Therefore, we assume that the reason behind this is that she is having an acute infection superimposed on sarcoma. Similar to this was a case of a patient who showed a persistently increased target to nontarget ratio at 1, 2, and 4 hours, and his culture and sensitivity showed the presence of microorganisms. His biopsy turned out to be chronic nonspecific osteomyelitis. This may be because the patient was having an acute chronic infection. The only case of a false-negative patient did not show any radiotracer uptake at the site of prosthesis. His bone scan showed increased radiotracer uptake at the site of prosthesis. His culture and sensitivity showed the presence of methicillin-resistant *Staphylococcus aureus*, which may be the reason that it is not showing any radiotracer uptake.

Conclusion

The development of new radiotracers for the diagnosing infections will help clinicians to monitor the response and success of antimicrobial therapy for infections with multidrug-resistant pathogens. The specific and fast accumulation of Tc-99m-labeled antibiotics and antimicrobial peptides has become the choice for infection-imaging agent and they have now been successfully applied in clinical settings. Their further evaluation with different types of infections in humans will determine the future of these promising compounds. Infection imaging with radiopharmaceuticals is unique, considering that neither CT nor MRI is able to detect microorganisms, as such, and monitor the effect of antimicrobial therapy based on the number of bacteria because they are the anatomical modalities, whereas our field is the functional imaging. Therefore, we can conclude that regarding our results, Tc-99m-labeled levofloxacin can be used as an infection-imaging agent, which is an effective imaging agent.

List of Abbreviations

CT	computed tomography
Ga	Gallium
IAEA	International Atomic Energy Agency
ITLC	instant thin-layer chromatography
MRI	magnetic resonance imaging
MS excel	Microsoft excel
NPV	Negative predictive value
PPV	Positive predictive value
Tc	Technetium

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Informed written consent was taken from all the patients included in this study.

Ethical approval

Ethical approval was granted by the RTMC of Nuclear Medicine, Oncology and Radiotherapy Institute via ref no RTMC 3/1-150-2011/NORI-ERC-10/1, dated: January 2011.

Author details

Ayesha Ammar[1*], Shazia Fatima[1], Kahkashan Bahsir Mir[1], Sadaf Butt[1], Sadaf Batool[1], Muhammad Adnan Saeed[1], Noreen Marwat[1], Naseer Ahmed[1]

1. Nuclear Medicine, Oncology & Radiotherapy Institute (NORI), Islamabad, Pakistan

References

1. Shimpi. HH, Nair N. 99mTc labeled levofloxacin: an agent for infection imaging. Indian J Nucl Med. 2003;18:16.
2. El-Ghany EA, Amin AM, El-Kawy OA, Amin M. Technetium-99m labeling and freeze-dried kit formulation of levofloxacin (L-Flox): a novel agent for detecting sites of infection. J Labelled Comp Radiopharm. 2007;50:25–31. https://doi.org/10.1002/jlcr.1153
3. Naqvi S, Ishfaq M, Khan Z, Nagra S,Bukhari I,Hussain A, et al. 99mTc labeled levofloxacin as an infection imaging agent: a novel method for labeling levofloxacin using

cysteine·HCl as co-ligand and in vivo study. Turk J Chem. 2012;36:267–77.
4. Kumar V, Abbas A, Fausto N. Robbins and Cotran, Jon Aster. Pathologic basis of disease. 10th ed. Philadelphia, PA: Saunders; 2017.
5. Ziessman H, O'Malley J, Thrall J. Nuclear medicine: the requisites. 4th ed. Philadelphia, PA: Saunders; 2013.
6. Elgazzar AH, Abdel-Dayem HM, Clark JD, Maxon HR. Multimodality imaging of osteomyelitis. Eur J Nucl Med. 1995;22:1043–63. https://doi.org/10.1007/BF00808418
7. Elgazzar AH, Abdel-Dayem HM. Imaging skeletal infections: evolving considerations. In: Freeman LM, editor. Nuclear medicine annual. Philadelphia, PA: Lippincott Williams and Wilkins. 1999:157–91.
8. Tumeh SS, Aliabadi P, Seltzer SE, Weissman BN, McNeil BJ. Chronic osteomyelitis: the relative roles of scintigrams, plain radiographs, and transmission computed tomography. Clin Nucl Med. 1988;13:710–15. https://doi.org/10.1097/00003072-198810000-00006
9. Roca M, de Vries EFJ, Jamar F, Israel O, Signore A. Guidelines for the labelling of leucocytes with 111In-oxine. Eur J Nucl Med Mol Imaging. 2010;37:835–41.
10. Magnuson JE, Brown ML, Hauser MF, Berquist TH, Fitzgerald RH Jr, Klee GG. In-111 labeled leukocyte scintigraphy in suspectedorthopaedic prosthesis infection: comparison with other imaging modalities. Radiology. 1988;168:235–9. https://doi.org/10.1148/radiology.168.1.3380966
11. Tang JSH, Gold RH, Bassett LW, Seeger LL. Musculoskeletal infection of the extremities: evaluation with MR imaging. Radiology. 1988;166:205–9. https://doi.org/10.1148/radiology.166.1.3336680
12. Tsan MF. Mechanisms of gallium-67 accumulation in inflammatory lesions. J Nucl Med. 1985;26:88–92.
13. Britton KE, Wareham DW, Das SS, Solanki KK, Amaral H, Bhatnagar A, et al Imaging bacterial infection with (99m) Tc-ciprofloxacin (Infecton). J Clin Pathol. 2002;55(11), 817–23. https://doi.org/10.1136/jcp.55.11.817
14. Hall AV, Solanki KK, Vinjamuri S, Britton KE, Das SS. Evaluation of the efficacy of 99mTc-Infecton, a novel agent for detecting sites of infection. J Pathol. 1996;51:215–9. https://doi.org/10.1136/jcp.51.3.215
15. Sarda L, Saleh-Mghir A, Peker C, Meulemans A, Cremieux CA, Le GuludecD. Evaluation of the Tc 99m ciprofloxacin scintigraphy in a rabbit model ofstaphylococcus aureus prosthetic joint infection. J Nucl Med. 2002;43:239–24.
16. Sarda L, Cremieux A-C, Lebellec Y, Meulemans A, Lebtahi R, Hayem G, et al. Inability of 99mTc-Ciprofloxacin scintigraphy to discriminate between septic and sterile osteoarticular diseases. J Nucl Med. 2003;44:920–6.
17. Larikka MJ, Ahonen AK, Nimela O, Puronto O, Junila, JA, Hamalainen, MM, et al. Tc 99m ciprofloxacin imaging in the diagnosis of kneeprosthesis infections. Nucl Med Comm. 2002;23:167–70. https://doi.org/10.1097/00006231-200202000-00009
18. PermansK, De Winter F, Janssens L, Dumont F, Van Bree H, Dierckx R. An infected hip prosthesis in a dog diagnosed with a Tc 99mciprofloxacin scan. Vet Radiol Ultrasound. 2002;43(2):178–82. https://doi.org/10.1111/j.1740-8261.2002.tb01666.x
19. Akhtar MS, Khan ME, Khan B, Irfanullah J, Afzal MS, Khan MA, et al An imaging analysis of 99mTc-UBI (29-41) uptake in S. aureus infected thighs of rabbits on ciprofloxacin treatment. Eur J Nucl Med Mol Imaging. 2008;35:1056–64. https://doi.org/10.1007/s00259-007-0671-3
20. Development of Kits for 99mTc Radiopharmaceuticals for Infection Imaging IAEA TECDOC No. 1414-1414 92-0-111304-8, 2004.
21. Katzung BG. Basic and clinical pharmacology. 14th ed. New York, NY: McGraw-Hill Education; 2017.