



Usefulness of ^{99m}Tc -HMPAO leukocyte scintigraphy in necrotizing external otitis/skull base osteomyelitis

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ABSTRACT

Necrotizing external otitis (NEO) is a rare but serious disease of the skull base (osteomyelitis). Immunosuppressed, and elderly patients are most commonly affected. The most common pathogen is *Pseudomonas aeruginosa*. Early diagnosis is crucial for the prognosis. To establish the diagnosis, both positive imaging findings, and clinical criteria are required to be met. Imaging is used during follow-up to monitor a potential recurrence due to its high risk, even after successful treatment. The use of radiological or nuclear medicine methods (scintigraphy) in the management of NEO is not currently standardised. We report a series of 5 patients with necrotizing external otitis/otogenic skull base osteomyelitis over a period of 12 years (2012-2024). In all patients, ^{99m}Tc -HMPAO (hexa-methyl-propylene-amine-oxime) labelled autologous leukocyte scintigraphy was used to diagnose, to monitor therapy response and for a follow-up. The primary diagnosis of necrotizing otitis was confirmed by scintigraphy in all cases (positive predictive value of 100%). In monitoring of treatment response, true negative scintigraphic findings were observed in two cases, two findings were false-negative (negative predictive value of 50%), and one case was found to be a false-positive. In a follow-up, the recurrence of the disease was truly detected or ruled out by subsequent scintigraphy in all subjects. Technetium-99m-labelled leukocyte scintigraphy is a convenient and reliable method, especially for diagnosing, and follow-up of necrotizing external otitis/otogenic skull base osteomyelitis. In terms of monitoring treatment response, further studies could be suggested for improving the estimated low negative predictive value.

KEYWORDS

necrotizing external otitis, malignant external otitis, skull base osteomyelitis, otitis externa, chronic suppurative otitis media, leukocyte scintigraphy.

1 Introduction

Necrotizing external otitis (NEO) is rare but potentially life-threatening infectious inflammatory process. It most commonly originates in the external ear canal and gradually spreads to the soft tissues and bones of the skull base.

The disease primarily affects older patients, especially those with diabetes or with diseases that cause immunosuppression, such as advanced stages of malignancy, post-transplant conditions, chronic renal failure, AIDS (acquired immunodeficiency syndrome), etc.

A definitive diagnosis is based on the patient's medical history, clinical presentation, positive microbiological culture, most commonly showing *Pseudomonas aeruginosa* (Guerrero-Espejo et al., 2017) and a positive imaging finding (Cohen and Friedman, 1987). The disease requires a long-term antibiotic (ATB)/antimicrobial therapy.

Despite being assessed as cured, patients with NEO, or otogenic

skull base osteomyelitis (SBO), are at a high risk of disease recurrence (recurrence rate of 7-27%) (Martel et al., 2000; Hariga et al., 2010; Le Clerc 2014; Prasad et al., 2014; Shavit et al., 2016; Rozenblum-Beddok et al., 2018; Marina et al., 2019; Arsovic et al., 2020; van der Meer et al., 2022). It most commonly occurs in cases, when an antibiotic treatment is prematurely terminated (Hariga et al., 2010; Pulcini et al., 2012). Since a recurrence of the disease has been described from 1 to 12 months after the discontinuation of antimicrobial therapy (Franco-Vidal et al., 2007, Le Clerc et al., 2014; Shavit et al., 2016; Rozenblum-Beddok et al., 2018), a regular follow-up of the patient on clinical, laboratory and imaging criteria is recommended for at least 6 months (Franco-Vidal et al., 2007; Courson et al., 2014; van der Meer et al., 2022).

The research is conducted on an optimal imaging method for establishing the diagnosis, for monitoring the disease activity and for assessing response to treatment.

Currently, both radiological methods - computed tomography (CT) and magnetic resonance imaging (MRI), as well as nuclear

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medicine methods (scintigraphy) are used in the management of NEO. Each modality has its advantages and limitations. The choice of imaging is also influenced by factors such as availability of a various modality and subjective preferences (Cooper et al., 2018).

The main advantage of radiological methods is a high-resolution visualization of intricate anatomical details. CT allows high-resolution imaging of bone structures and is very effective for detecting changes in bone tissue. MRI has superior ability to visualize soft tissue and structures. This is important in diagnosing NEO, because although the disease primarily affects the bone, the changes are more often seen in soft tissues of the skull base rather than in the bone marrow (Karantanas et al., 2003; Kwon et al., 2006). CT is widely used due to its availability (Chawdhary et al., 2017; Cooper et al., 2018), despite the fact, that MRI is superior to CT, both in the primary diagnosis and in monitoring the disease activity (Seabold et al., 1995; Mejzlik et al., 2019). The limitations of MRI are persistent soft tissue changes even after an acute resolution of infection; i.e. false-positive findings (Cherko et al., 2016; Morales et al., 2019). Despite these limitations, both CT and MR are accurate tools for imaging complications of NEO/ skull base osteomyelitis, such as abscesses, extensive bone destruction, and intracranial involvement (Morales et al., 2019).

Scintigraphy, as the method for dynamic monitoring of pathological process activity, is considered the gold standard for diagnosing necrotizing external otitis since establishing the diagnostic criteria for NEO in 1987 by Cohen and Friedman (Cohen and Friedman, 1987). Previously used types of scintigraphy based on the principle of detecting pathological changes in bone metabolism or inflammatory processes in tissues have evolved into the use of bone scintigraphy with ^{99m}Tc -MDP (methylenediphosphonate) in the primary diagnosis of the disease (Seabold et al., 1995; Weber et al., 1995), and scintigraphy with ^{67}Ga -citrate in monitoring the response to treatment (Garty et al.,

1985). However, the results of recently published meta-analysis focusing on the use of these two types of scintigraphy do not support their routine use in the management of NEO, due to relatively low sensitivity and presumed low specificity (Moss et al., 2020).

New scintigraphy methods, which are based on labelling autologous white blood cells with radiopharmaceuticals, demonstrate high sensitivity and specificity in detecting occult inflammatory processes (Epstein et al., 1992). Due to the lower radiation dose, scintigraphy using technetium 99m , ^{99m}Tc -HMPAO (hexa-methyl-propylene-amine-oxime) labelled autologous leukocytes is now preferred diagnostic imaging (Bruni et al., 2008; Arsovic et al., 2020). This two-phase examination method combined with SPECT/CT (single photon emission computed tomography/computed tomography) provides a three-dimensional image and allow sufficient anatomical information of a lesion. In the diagnosis of NEO/skull base osteomyelitis the method has a sensitivity of 93-100% (Rozenblum-Beddok et al., 2018; Vion et al., 2020) and a negative predictive value of 88% (Rozenblum-Beddok et al., 2018;), and a sensitivity of 86% and a specificity of 75% in case of monitoring the response to treatment, respectively (Vion et al., 2020).

The aim of this study was to report a single centre's experience in using ^{99m}Tc -labelled autologous leukocyte scintigraphy in necrotizing external otitis/otogenic skull base osteomyelitis.

2 Patients and Methods

This retrospective study was conducted between 1/2012 and 8/2023 at the tertiary referral centre. Five patients suspected of having necrotizing external otitis/otogenic skull base osteomyelitis by fulfilling the obligatory and occasional criteria of NEO were enrolled in the study (Table A.1; A.2). Malignancy was ruled out by biopsies in all cases. The patients underwent ^{99m}Tc -HMPAO-

Table A.1 Obligatory criteria for the diagnosis of necrotizing external otitis in patients suggested by Cohen and Friedman [2].

Obligatory criteria						
Patient	Pain	Exudate	Edema	Granulations	Microabscess	Positive scintigraphy
1.	+	+	+	+	-	+
2.	+	+	-	+	-	+
3.	+	+	+	+	-	+
4.	+	+	-	- ^(*)	+	+
5.	+	+	+	+	-	+

* A middle ear polyp in the tympanic membrane perforation in chronic suppurative otitis media.

Table A.2 Occasional criteria for the diagnosis of necrotizing external otitis in patients suggested by Cohen and Friedman [2].

Occasional criteria					
Patient	Diabetes mellitus	Immunosuppression	<i>Pseudomonas aeruginosa</i>	Cranial nerve involvement	Radiograph ^(***)
1.	+	-	+	+	-
2.	+	-	+	+	-
3.	+	+ ^(*)	+	+	-
4.	-	-	-	+	-
5.	+	+ ^(**)	+	+	-

* Chronic renal failure (multifactorial etiology).

** Immunosuppressants (condition after kidney transplantation).

*** Obsolete imaging method.

labelled autologous leukocyte scintigraphy. The diagnostic scintigraphy was performed before treatment or within 7 days after the initiation of antibiotic treatment (Fig.1-5). Subsequent scintigraphic examination was used to therapy response monitoring over the course of antibiotics. The same modality method was used for a follow-up imaging.

The clinical data of the patients included the age, sex, medical history, clinical findings, diabetes and immunodeficiency disorders, and microbiology culture results. The facial nerve (CN VII) function was scored by House-Brackmann scale (I-VI) (House and Brackmann, 1985). The headache was scored by Numerical Rating Scale (NRS) (1-10) (Breivik, 2008).

3 Leukocyte Scintigraphy

Planar and SPECT/CT images centered on the head and neck regions were performed using a hybrid gamma camera (GE Discovery NM/CT 670, GE HealthCare, Chicago, USA). Images were obtained 4 hours and 24 hours after intravenous injection of 600 MBq^{99m}Tc-labelled leukocytes. Three-dimensional images (3D) were reconstructed using Ordered Subset Expectation Maximization (OSEM) algorithm. CT scans were performed immediately after SPECT.

3.1 Scanning parameters:

Static acquisition: 256x256 matrix, LEHR collimator, energy window 140.5 keV $\pm$ 10% (window width), acquisition time in 4 hrs: 200 s, in 24 hrs: 2015 s.

Tomographic acquisition: 128x128 matrix, 60 projections of 6 deg, LEHR collimator, energy window 140.5 keV $\pm$ 10% (window width) with pulse height analyser, OSEM RR 4x12 reconstruction, acquisition time in 4 hrs: 35 s/projection (total 17.5 min), in 24 hrs: 85 s/projection (total 42.5 min).

3.2 Imaging data analysis

^{99m}Tc-HMPAO (hexa-methyl-propylene-amine-oxime) labelled autologous leukocytes scintigraphy images were analysed by an experienced nuclear medicine physician. Visual analysis was performed to evaluate the accumulation of labelled leukocytes in delayed (4 h post-injection) and late (24 h post-injection) planar scintigraphy images and in fused SPECT/CT images.

Scintigraphy was considered positive when a focal labelled leukocyte uptake was observed in both delayed and late images of the skull (base) bones/soft tissues, either increasing in time or increasing in size.

The response to treatment by a scintigraphy scan was assessed by comparing the ^{99m}Tc-leukocyte uptake with the results from previous scans. The three mechanisms of uptake were considered: decrease, constant, and increase.

Scintigraphy finding was considered negative if there was no leukocyte uptake on the delayed and late images.

4 Results

The mean age of the five patients was 67 (51-84) years, all were male. All patients had positive ^{99m}Tc-HMPAO leukocyte scintigraphy, and all were confirmed as a true positive through clinical symptoms and laboratory parameters (sensitivity of 100%). Four patients were diagnosed with necrotizing external otitis (Pt 1, 2, 3, 5), and one patient with otogenic skull base osteomyelitis (Pt 4). The baseline clinical characteristics of the study patients are shown in Tables A, B and C1-5.

4.1 Clinical presentation

Otalgia and ear discharge were present in all patients, while swelling and granulation tissue in the external ear canal was present in 4 of them. Pathological findings in the ear canal were absent in one patient due to skull base osteomyelitis originating from chronic suppurative otitis media. Cephalgia was the predominant complaint in all cases, including two cases of very severe intensity, requiring opioid analgesics. All patients had cranial nerve involvement. In 100% of the patients the facial nerve (CN VII) was involved. In addition, one patient suffered from unilateral vagal nerve (CN X) palsy, and another patient suffered from the unilateral abducens nerve (CN VI), the unilateral glossopharyngeal (CN IX) and the bilateral hypoglossal nerve (CN XII) dysfunctions (Table B).

4.2 Histology

Results of soft tissue biopsies taken from the ear canals in 4 patients and from the middle ear in one confirmed nonspecific granulation tissue

4.3 Comorbidities in patients

Four patients were treated for diabetes mellitus. Of these, two suffered from co-occurring immunodeficiency disorders (Table A.2).

4.4 Microbiological analysis

The causative pathogen of NEO was identified as *Pseudomonas aeruginosa* in four cases. In one patient a polymicrobial infection (*Staphylococcus aureus*, *Campylobacter rectus*, *Streptococcus oralis*) was detected.

4.5 Duration of symptoms

The mean duration of symptoms until the definitive diagnosis of NEO was established by ^{99m}Technetium-labelled white blood cell scintigraphy was 189 (30 - 639) days, with a median of 78 days (Tables C1-5).

4.6 Therapy protocol

All 5 patients received targeted intravenous antibiotic (ATB) therapy. In four cases NEO was initially managed using combination of two ATBs and in one case using monotherapy (Tables C.1-5). One of the patients underwent middle ear surgery due to complications (multiple abscesses) (Pt 4).

Treatment of the patients included ear canal debridement with the application of local anti-inflammatory agents and ATBs. In patients with diabetes, thorough glycaemic compensation was attempted.

4.7 Duration and courses of antibiotic therapy

The duration of the initial inpatient intravenous antibiotic course ranged from 23 to 46 (mean 39) days (Tables C.1-5). One patient achieved a complete remission of the disease after this course of medication (Pt 4). In other four patients, ATB therapy has been continued due to persistence of the disease: patient 1 continued to receive an oral step-down therapy; patient 2 continued to receive a combination therapy (sequential oral and oral step-down therapy); patient 3 continued to receive an intravenous ATB therapy, and patient 5 continued to receive a combination therapy (intravenous and oral antibiotic therapy) (Tables C.1-5). The antibiotic treatment modifications in patients with recurrence of the disease (Pts 3, 5) are shown in tables C.1-5. The shortest duration

Table B Clinical characteristics of patients (neurological symptoms).

Pt [*]	Age	Side	Pretreatment/ Posttreatment CN VII function (HB score) **		Pretreatment/ Posttreatment other CN function		Pretreatment/ Posttreatment cephalgia (NRS)***	
1.	73	right	HB V/VI	HB V/V	normal	normal	moderate (NRS 5- 6)	no pain (NRS 0)
2.	78	left	HB II/II	HB I/I	CN X: paresis	CN X: paresis	severe (NRS 7)	severe (NRS 7)
3.	84	right	HB VI/VI	HB VI/VI****	normal	normal	extreme (NRS 8)	severe (NRS 7)
4.	51	left	HB I/III	HB I/I	CN VI: ipsilateral paresis CN IX: contralateral paresis CN XII: bilateral paresis normal	CN VI: normal CN IX: normal CN XII: normal	moderate (NRS 4)	very severe (NRS 8)
			HB III/VI	HB I/I	normal	normal		
5.	50	right	HB IV/V (during the recurrence)	HB V/V (after the recurrence)	CN IX: ipsilateral paresis CN X: ipsilateral paresis CN XII: ipsilateral paresis (during the recurrence)	CN IX: normal CN X: normal CN XII: normal	mild (NRS 2-3)	no pain (NRS 0)

^{*}Pt (patient).

** House Brackmann score, upwards (superior)/outwards (lateral) facial movement (I-VI) [30].

*** NRS-numerical pain rating scale (0-10) [30].

****After the 13th month of treatment.

Table C.1 Clinical characteristics of patient No.1.

Pt [*]	Duration of symptoms (days)	Etiology/ Diagnosis/ Pathogen	ATB treatment (inpatient)/ (outpatient)	Scintigraphy (interval and result)	Type of scintigraphy imaging	Outcome
1	38	external otitis/ necrotizing external otitis/ <i>Ps. aeruginosa</i>	Ciprofloxacin (800 mg/day) + Gentamicin (160 mg/day) (parenteral therapy) Ciprofloxacin (1000 mg/day) (oral therapy) Note: therapy termination	1. at diagnosis, positive 2. after 8 weeks, positive (slight decrease in uptake) 3. after 6.5 weeks, negative 4. after 32weeks, negative	diagnostic monitor treatment response follow-up	cured non- recurrence

^{*} Pt (patient).

Table C.2 Clinical characteristics of patient No.2.

Pt [*]	Duration of symptoms (days)	Etiology/ Diagnosis/ Pathogen	ATB treatment (inpatient)/ (outpatient)	Scintigraphy (interval and result)	Type of scintigraphy imaging	Outcome
2	639	external otitis/ central skull base osteomyelitis/ <i>Ps. aeruginosa</i>	Ceftazidime (2000 mg/day) + Ciprofloxacin(800 mg/day) (parenteral therapy) Clindamycin (900 mg/day) + Ciprofloxacin (1000 mg/day) (oral therapy) Piperacillin/tazobactam (13,5gr/day) + Sulfamethoxazole/trimethoprim (1600/320 mg/day) (parenteral therapy) note: therapy discontinuation (prevention of full development of adverse reactions)	1. at diagnosis, positive 2. after 6 weeks, positive (slight decrease in uptake) 3. after 6 weeks, positive (increase in uptake) 4. after 13.5 weeks, positive (slight decrease in uptake) 5. after 40 weeks, negative 6. after 42 weeks, negative	diagnostic monitor treatment response follow-up	cured non-recurrence

^{*} Pt (patient).

Table C.3 Clinical characteristics of patient No.3.

Pt	Duration of symptoms (days)	Etiology/Diagnosis/Pathogen	ATB treatment (inpatient)/(outpatient)	Scintigraphy (interval and result)	Type of scintigraphy imaging	Outcome
2	30	external otitis/ necrotizing external otitis/ <i>Ps .aeruginosa</i>	Ceftazidime (2gr/day) (parenteral therapy) Ceftazidime (2gr/day) (parenteral therapy) Ceftazidime(2gr/day) (parenteral therapy) note: therapy termination	1. at diagnosis, positive 2. after 6 weeks, positive (slight decrease in uptake) 3. after 5 weeks, mild positive (decrease in uptake) 4. after 11. weeks, negative	diagnostic monitor treatment response note: false negative	
			Ceftazidime (2gr/day)(parenteral therapy) Ceftazidime (2gr/day) (parenteral therapy) Ceftazidime (2gr/day) (parenteral therapy)	5.after 10.5 weeks, positive (increase uptake in different localization) 6. after 10.5 weeks, positive (increase uptake in different localization) 7. after 10. week, positive	follow-up monitor treatment response	died

Pt (patient).

Table C.4 Clinical characteristics of patient No.4.

Pt	Duration of symptoms (days)	Etiology/ Diagnosis/ Pathogen	ATB treatment (inpatient)/(outpatient)	Scintigraphy (interval and result)	Type of scintigraphy imaging	Outcome
4	157	CSOM ⁺ / skull base osteomyelitis/ <i>Staphylococcus aureus</i> , <i>Campylobacter rectus</i> , <i>Streptococcus oralis</i>	Ceftazidime (6gr/day) + Linezolid (1200 mg/day) (parenteral therapy) note: therapy termination	1. at diagnosis, positive 2. after 6 weeks, negative 3. after 13.5 weeks, negative 4. after 32 weeks, negative	diagnostic monitor treatment response follow-up	cured non-recurrence

Pt (patient).

⁺CSOM (chronic suppurative otitis media).

of the treatment was 28 days. The longest therapy lasted 267 days.

4.8 Scintigraphy in monitoring therapy response and follow-up

Monitoring scan was performed after the so-called therapeutic time window of 72 hours in week 6-8 (average 7). One patient showed a negative finding on the scintigraphy (Pt 4). In four patients with positive scintigraphy, subsequent imaging was repeated after another 5-7 weeks (Pts 1, 2, 3, 5). Among them, in 2 scintigraphy remains positive (Pt 2, 3) and a further scintigraphy was performed after 10-14 weeks.

Scintigraphy detected a shift of an active infection focus in 2 patients. In the first case (Pt 5), the infection moved twice; during the initial ATB course and subsequently during the recurrence (Fig. 5.) In the second case (Pt 3) the infection moved two times during the recurrence (Fig. 3).

After a negative leukocyte scan and discontinuation of treatment, scintigraphy was used to follow-up the patients and the examinations were performed in 3 to 10 months.

The disease relapsed in two patients, one (Pt3) and two (Pt 5) months after discontinuation of the treatment based on a negative leukocyte scan (false negative), respectively. The negative predictive value of scintigraphy was of 50%. The presenting new symptoms were headache in one (Pt 3) and multiple cranial nerves palsies in the other patient (Pt 5).

One scintigraphic finding, performed in another patient (Pt 2) two weeks after discontinuing the treatment, was considered as a false positive, as the following scintigraphy scan was completely negative, and the patient remained asymptomatic (Fig.2).

The follow-up for our patients were done through regular clinical examination conducting every month, or in occurrence of a new onset of symptom. In that case, leukocyte scintigraphy was also performed. The mean follow-up period of the patients was 10 (8-12) months.

4.9 Persistent neurological symptoms

Two of the four cured patients continued to experience persistent severe headaches and required moderate opioid analgesia. One patient had a mild cephalgia, another one was completely free of a headache (Table B).

Facial nerve (CN VII) palsy of severe degree of impairment persisted in three patients. In two cases of mild degree dysfunction there was a complete restoration of the function. Vagal nerve (CN X) dysfunction endured in one patient. Other involved cranial nerves, CN IX, CN X, CN XII in one, and CN VI, CN IX, CN XII in the other patient completely restored their function (Table B).

4.10 Outcome

Four patients were completely cured. One patient died during the 13th month of the treatment. The cause of the death has been found to be multifactorial (chronic renal failure, neurodegenerative disorders, epilepsy, necrotizing external otitis, and complicated traumatic injury).

5 Discussion

Necrotizing external otitis and osteomyelitis of the skull base are serious complications of external otitis, or rarely of chronic

Table C.5 Clinical characteristics of patient No.5.

Pt*	Duration of symptoms (days)	Etiology/ Diagnosis/ Pathogen	ATB treatment (inpatient)/(outpatient)	Scintigraphy (interval and result)	Type of scintigraphy imaging	Outcome	
5	78	external otitis/ necrotizing external otitis/ <i>Ps. aeruginosa</i>	Ceftazidime (6gr/day) + Ciprofloxacin (800 mg/day) (parenteral therapy)	1. at diagnosis, positive	diagnostic	cured	
			Ceftazidime (6gr/day) (parenteral therapy) + Ciprofloxacin (1000 mg/day) (oral therapy)	2. after 6,5 weeks, positive (decrease in uptake in primary location, increase in uptake in different localization)	monitor treatment response		
			note: therapy termination	3. after 6 weeks, negative	note: false negative		
			Cefepime (4gr/day) (parenteral therapy) + Ciprofloxacin (1000 mg/day) (oral therapy)	4. after 10 weeks, positive (increase in uptake in primary localization)	follow-up		
			Cefepime(4gr/day) (parenteral therapy) + Ciprofloxacin(1000 mg- 500 mg/day) (oral therapy) **	5. after 10 weeks, positive (decrease in uptake)	monitor treatment response		
			Cefepime (4gr/day) (parenteral therapy) + Ciprofloxacin (500 mg/day) (oral therapy) ***	6. after 7 weeks, positive (decrease in uptake)			
			note: therapy termination	7. after 10 weeks, negative	follow-up		non- recurrence
				8. after 12 weeks, negative			

* Pt (patient).

** Ciprofloxacin dose reduction due to adverse event (renal-transplant hypoperfusion).

*** Ciprofloxacin dose reduction due to adverse effect (peripheral neuropathy).

suppurative otitis media (Prasad et al., 2014; Arsovic et al., 2020). The different pathogenesis and pathophysiology of the disease and patterns of spread, manifested by diverse clinical manifestations that may be absent in different high-risk, immunosuppressed patient groups, make the diagnosis particularly difficult (Franco-Vidal et al., 2007; Guevara et al., 2013; Mahdyouun et al., 2013).

The diagnosis is based on meeting the obligatory and occasional criteria presented in the 1980s (Cohen and Friedman, 1987). They include clinical and laboratory parameters. The distribution of causative pathogens has changed over time. Imaging methods have evolved with the development of diverse modalities. They play a major role in diagnosis, monitoring the response to treatment, and follow-up, since both clinical and laboratory inflammatory parameters may not reliably determine the course of the disease.

The new generation of highly sensitive nuclear medicine methods (scintigraphy), based on labelling autologous leukocytes with radiopharmaceuticals are used in detecting occult inflammatory processes (Epstein et al., 1992). Of them, scintigraphy using ^{99m}Tc-HMPAO-labelled leukocytes, having a benefit from a lower radiation dose, is now preferred for the diagnosis of necrotizing external otitis (Rozenblum-Beddok et al. 2018; Arsovic et al., 2020). This two-stage examination method enables very good anatomical localization of the lesion. Moreover, the use of the same tracer component provides comparable uptake mechanism (Rozenblum-

Beddok et al. 2018).

Our patient cohort consisted of males only, with three patients over 70 years old and two middle-aged, which is consistent with the literature (Hatch et al., 2018; Cheng et al., 2019; Ijaz et al. 2022).

Three of our patients with necrotizing otitis presented with ear discharge, edema, and granulations in the ear canal. Mahdyouun et al. reported these typical findings in 42 to 100% of cases (Mahdyouun et al., 2013). In another patient, edema and granulations have been present previously, but were absent due to intensive debridement. One patient completely lacked pathological ear canal conditions because the skull base osteomyelitis developed from chronic suppurative otitis media (CSOM). The disease manifested by tympanic membrane perforation, chronic ear discharge, and an aural polyp. Similar cases of skull base osteomyelitis arising from CSOM were described by Sokołowski et al. (Sokołowski et al., 2019).

Neurological symptoms in our entire cohort included cephalgia, which was mostly of severe to very severe intensity getting worse at night. This symptom is reported as the most common in patients with NEO (Hariga et al., 2010; Mahdyouun et al., 2013; Marina et al., 2019). All our patients suffered from facial nerve paresis. Three patients showed mild, while remaining two patients had severe palsy at the time of diagnosis. Other authors reported a slightly lower percentage of facial nerve neuropathy in their series (16-38%) (Chen et al., 2010; Hariga et al., 2010; Pulcini et al., 2012;

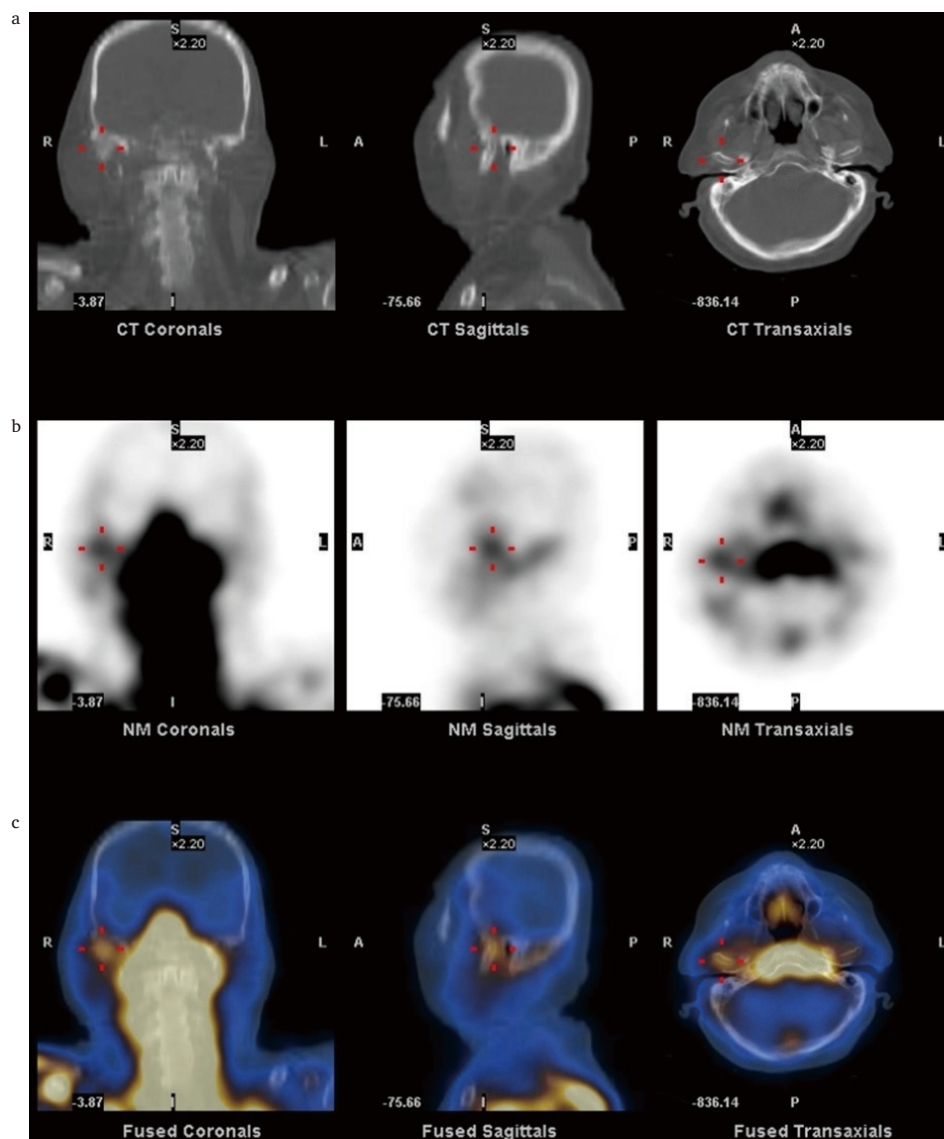


Figure 1 ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy; a (CT); b (SPECT); c (SPECT/CT).

Pre-treatment diagnosis of necrotizing external otitis of 73-year-old male with insulin-dependent type 2 diabetes and peripheral angiopathy (patient No.1).

On delayed (4 h post-injection) and late (24 h post-injection) planar scintigraphy images and on fused SPECT/CT images a higher accumulation of labelled leukocytes is visible in the following areas: in the inferior wall of the cartilaginous and bony part of the ear canal on the right, in the mastoid process on the right with a maximum on its inferior surface, and in the stylomastoid foramen area on the right.

Hatch et al., 2018; Marina et al., 2019; Dabiri et al., 2020; Jung et al., 2021; van der Meer et al., 2022). The occurrence of other CN palsies increased the incidence of neuropathy up to 44% (Jung et al., 2021). In three patients, other cranial nerves were also affected. The patient with extensive central skull base osteomyelitis exhibited the most severe CNs involvement at onset (ipsilateral CN VI palsy, contralateral CN IX, and bilateral CN XII palsy). In another patient, the multiple CNs paresis (ipsilateral CN IX, CN X, and CN XII) developed during the recurrence of the NEO. One patient had long lasting unilateral CN X dysfunction. Other authors report lower cranial nerve neuropathies (CN IX, CN X, CN XI), ipsilateral or bilateral, in cases with extension of NEO to the central base of the skull (Saha et al., 2013; Silveira et al., 2020; van der Meer et al., 2022).

The time from symptom onset to diagnosis of necrotizing external otitis ranged from 4 to 11 weeks in three patients with external otitis. The patient with CSOM was referred after 22 weeks

of conservative outpatient treatment due to multiple cranial nerves paresis. Glikson et al. reported a mean duration of 6 weeks (Glikson et al., 2017), whereas other authors reported duration from 10 to 14 weeks (Franco-Vidal et al., 2007; Vourexakis et al., 2010; Ganheva and Kuthubutheen, 2013; Guevara et al., 2013; Mahdyoune et al., 2013). In one patient, it took 639 days to establish the diagnosis. He was initially inappropriately treated for recurrent chronic otitis externa at another ENT institution. Similar cases of the diagnostic dilemma of necrotizing external otitis/central skull base osteomyelitis with average 7-month duration of symptoms are described by Jacobsen et al. (Jacobsen et al., 2010).

Microbial etiology of NEO was identified in all patients. In four of them, *Pseudomonas aeruginosa*, and in one patient three bacterial pathogens were detected. Targeted combined antibiotic therapy, consisted of quinolones and third generation cephalosporins or aminoglycosides as determined by a result of quantitative ATB susceptibility including minimum inhibitory concentration

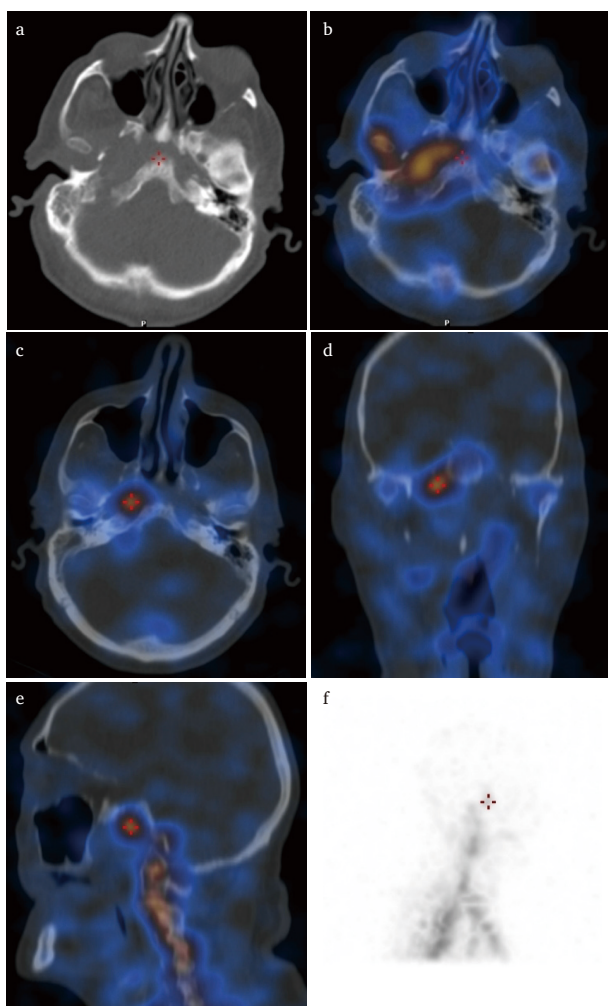


Figure 2 ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy; a (CT); b, c, d, e (SPECT/CT); f (planar scintigraphy).

Pre-treatment diagnosis (a, b), treatment response monitoring (c, d, e, f) of central skull base osteomyelitis of 78-year-old male with insulin-dependent type 2 diabetes (patient No.2).

On delayed (4 h post-injection) and late (24 h post-injection) planar scintigraphy images and on fused SPECT/CT images, a higher accumulation of labelled leukocytes is visible in the following areas: in the petrous apex on the right, and in the soft tissue of the nasopharynx (a, b).

(MIC), was initiated in all but one patient with necrotizing otitis caused by *Pseudomonas aeruginosa*. This intensified ATB approach in NEO was recommended by Pulcini et al., who demonstrated a significantly better response to treatment and a reduction in hospitalisation time with the initial combination of two ATBs (ceftazidime and ciprofloxacin) for susceptible *Pseudomonas sp.* strains (Pulcini et al., 2012). In one patient we couldn't administer a combination of 2 antimicrobial agents due to a severe renal insufficiency. He was treated by a single-agent antimicrobial therapy (ceftazidime) and the renal dosage adjustment has been made. Although the combination therapy is not considered to be more effective than monotherapy by some authors (Frost et al., 2021), that reduced therapy regimen probably contributed to a poor prognosis in our patient. Another patient with skull base osteomyelitis caused by *Staphylococcus aureus*, *Campylobacter rectus*, and *Streptococcus oralis* received a combination therapy (third generation cephalosporin and linezolid).

Surgery was performed in only one patient in our study,

because CT and MRI scans revealed multiple temporal space abscesses and intra-temporal abscess at the diagnosis of NEO. Other authors described the same indication for surgery (Alva et al., 2009; Nawas et al., 2013; Prasad et al., 2014). Another reported criteria, such as inadequate response to treatment, progressive facial nerve paresis, persistent ear discharge, or osteolytic changes of the temporal bone (Peleg et al., 2007; Saha et al., 2013; Meizlik et al., 2019).

In all of our patients with suspected NEO/skull base osteomyelitis, a ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy gave a positive result. The diagnostic sensitivity of the method was 100% in our cohort. Consistent very high sensitivity rates were reported by Vion et al. (100%) (Vion et al., 2020), and by Rozenblum-Beddok et al. (93%) (Rozenblum-Beddok et al., 2018). Recent meta-analysis with a focus on diagnostic performance of traditional scintigraphy methods found the pooled sensitivity of ^{99m}Tc -MDP (methylene diphosphonate) scintigraphy of 85%, and pooled sensitivity of ^{67}Ga -citrate scintigraphy of 71% in detecting NEO (Moss et al., 2020).

In monitoring response to treatment, the first labelled leukocyte scintigraphy scan was performed on average 6 weeks after initiation of the therapy. Franco-Vidal et al., LeClerc et al., Van Kroonenburgh et al., each using different imaging modalities reported 4, 6 and 8 weeks, respectively (Franco-Vidal et al., 2007; Le Clerc et al., 2014; van Kroonenburgh et al., 2018). In the case of positive scintigraphy finding on treatment monitoring scan, we continued antibiotic therapy until the next examination, which was performed again after 6 weeks. When further positivity was revealed, we repeated the scan after 12 weeks. If any of these findings was negative, the therapy was discontinued. Follow-up scintigraphic examinations were then performed individually (Tables C.1-C.5); in patient 1 to verify the negativity of the result due to persistent facial nerve paresis; in patient 2 to confirm the negative scintigraphic finding, that was achieved despite the discontinuing of therapy, and in patient 4 to verify the negative scan first, then for a headache progression and recurrent middle ear infections of the affected (operated) ear with persistent tympanic membrane perforation. Follow-up scintigraphy scans in these cases were true negative. In the available literature, the follow-up includes physical examination, laboratory tests, and an imaging monitoring. Follow-up is recommended at least 1 year after termination of the treatment (Marina et al., 2019; Hasnaoui et al., 2021). Most papers don't specify the follow-up intervals in detail (van Kroonenburgh et al., 2018; Auinger et al., 2021). The authors who used ^{99m}Tc -labelled leukocytes in the management of necrotizing otitis, performed follow-up scintigraphy only in patients presented with new symptoms (Rozenblum-Beddok et al., 2018). This management was applied in our cohort in two patients, in which a recurrence occurred 1 and 2 months after the termination of the initial course of antimicrobial therapy, respectively. In one patient, the clinical manifestation included headache localized in the ipsilateral temporal region. The other one suffered from speech disorder, dysphagia, and ipsilateral impairment of the facial function. The scintigraphy was true positive in detection of recurrence of the disease in the localizations that differed from the primary lesions in both cases. In addition, a subsequent scintigraphy detected a further shift of the inflammatory lesion to the central skull base in both. Similar cases of an early recurrence with an interval from 2 to 8 weeks are mentioned in the other studies (Hariga et al., 2010; Pulcini et al., 2012). But, in contrast to our study, in the study of Pulcini et al. it was caused by a reduction of therapy duration in all patients (Pulcini et al., 2012).

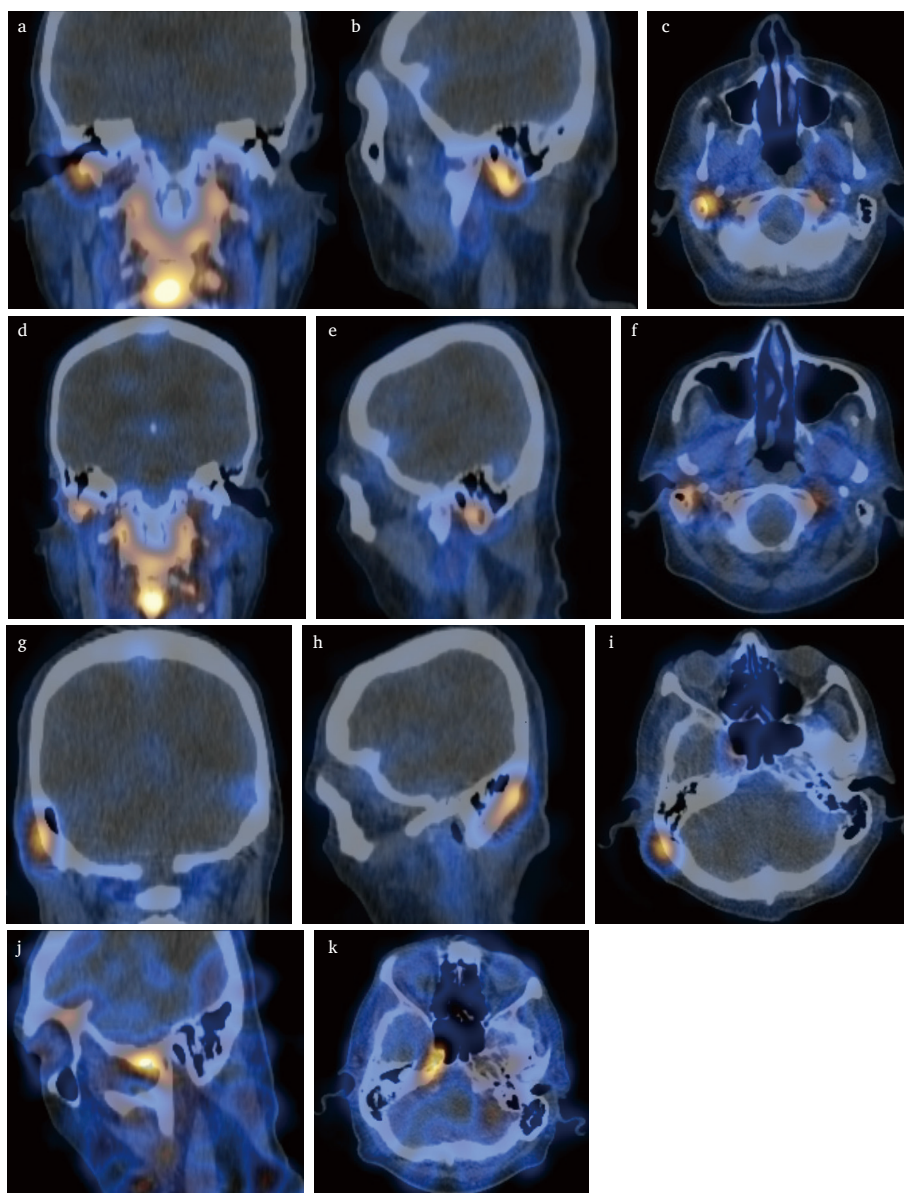


Figure 3 ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy; a, b, c, d, e, f, g, h, i, j, k (SPET/CT).

Pre-treatment diagnosis (a, b, c), treatment response monitoring (d, e, f, j, k), and follow-up (g, h, i) of necrotizing external otitis of 84-year-old male with insulin-dependent type 2 diabetes, with hemodialysis-dependent chronic renal insufficiency caused by a combination of hypertension, diabetic vascular nephropathy and chronic tubulointerstitial nephritis, and with severe polymorbidity (patient No.3).

On delayed (4 h post-injection) and late (24 h post-injection) fused SPECT/CT images, a higher accumulation of labelled leukocytes is visible in the following areas: in the inferior wall of the cartilaginous and bony part of the ear canal on the right, in the mastoid process on the right with a maximum on its inferior surface, and in the stylomastoid foramen area on the right (a, b, c).

In the context of scintigraphy monitoring the therapy response, we observed two false-negative results. Both were found in above-mentioned patients who early relapsed. False-negative ^{99m}Tc -HMPAO-leukocyte scintigraphy results are also reported in the study by Rozenblum-Beddok et al., given the sensitivity and negative predictive value of 95% and 88%, respectively (Rozenblum-Beddok et al., 2018). A laboratory parameter that was found and differs from other patients was a high glycated hemoglobin level concerning all false negative cases (Rozenblum-Beddok et al., 2018). In our study, the level of one patient's glycemic control using glycated hemoglobin was poor ($\text{HbA1c} = 8.7\%$), and the other's level was good ($\text{HbA1c} = 5\%$). While the former patient responded to subsequent therapy, the latter's response to treatment was poor.

It appears to be, that several factors, such as bacterial (microbial) pathogenesis, conditions of bone and soft tissue vasculature (vasculopathy), laboratory parameters, immune response to infection and mechanism of antibiotic action probably influenced the monitor ^{99m}Tc -HMPAO-leukocyte scintigraphy performance (Rozenblum-Beddok et al., 2018).

In the available literature, there are two options described, how to reduce false negatives of scintigraphy methods in praxis. One was proposed by Benecke et al. using Ga-67 scintigraphy, who suggested repeating imaging 1 month after a negative scintigraphy scan (Benecke, 1989). Yano et al. followed recommendation and performed that scintigraphy 8 weeks after therapy termination (Yano et al., 2024). Another strategy is described by Vion et al. by combining scintigraphy methods, ^{99m}Tc -HMPAO-leukocyte

scintigraphy with 18F-FDG-PET/CT imaging, in order to confirm the absence of the disease (Vion et al., 2020).

We also noted one false-positive finding, in which the scintigraphy showed a mild accumulation of leukocytes in delayed and increasing accumulation in late images. One false-positive case was also reported by Rozenblum-Beddok et al., another by Vion et al. (Rozenblum-Beddok et al., 2018; Vion et al., 2020). There was no explanation for our patient with the false positive scan result.

In the comparison to old scintigraphy modalities, the meta-analysis's effort to investigate the specificity of ^{99m}Tc -MDP bone scintigraphy for disease resolution have failed due to low information density of such literature (Moss et al., 2020). The results for the ^{67}Ga scintigraphy were slightly favourable and specificity for disease resolution was averaged at about 60% (Moss et al., 2020).

In 2 out of 5 patients, the facial nerve function was fully restored after the treatment. In both cases, it was a mild and moderate degree of paralysis at the time of diagnosis. In other 2

patients with severe facial nerve dysfunction, its poor function persisted. In one patient, moderate to moderately severe CN VII impairment returned back to normal after the initial ATB course, however, the nerve function deteriorated during the recurrence, and persisted even after the patient healed from the disease. In the recent literature, higher recovery rates of CN VII palsy are available. Marina et al. published 67% (Marina et al., 2019) and Jung et al. in the study with relatively large sample size reported partial or complete recovery rate of 57% (Jung et al., 2021). The lower recovery rate in our study is probably related to the diagnostic delay of NEO and the degree of CN palsy (moderate severe to severe) in the majority of the patients. Other persistent symptoms presented in 2 of 5 patients included headaches of severe to very severe intensity that responded well to combination of paracetamol and opioids, and non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, respectively.

The prevalence of long-term neurological sequelae reported in the literature is about 33% (Lee et al., 2017; Jung et al., 2021), with

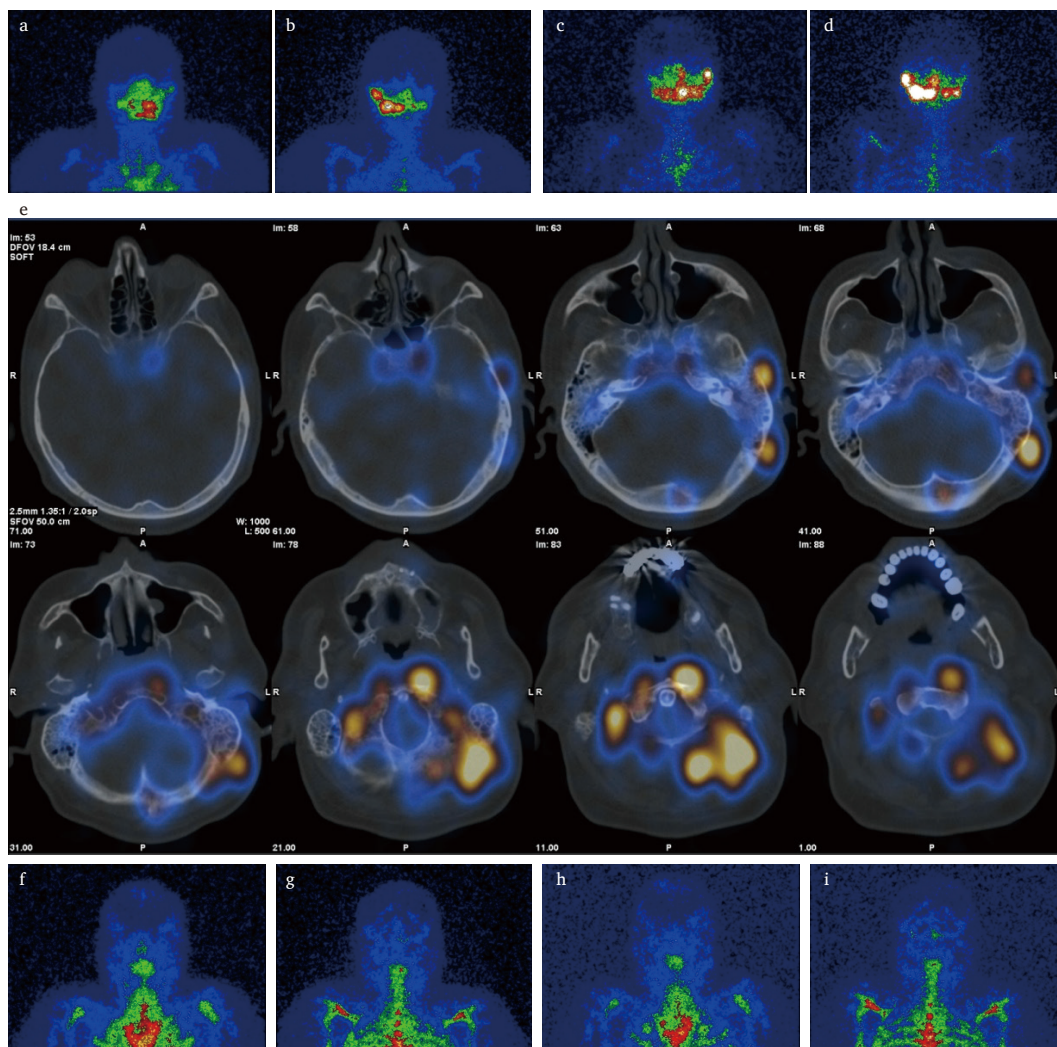


Figure 4 ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy; a, c, f, h (planar scintigraphy anterior view); b, d, g, i (planar scintigraphy posterior view); e (SPECT/CT axial plane, different levels).

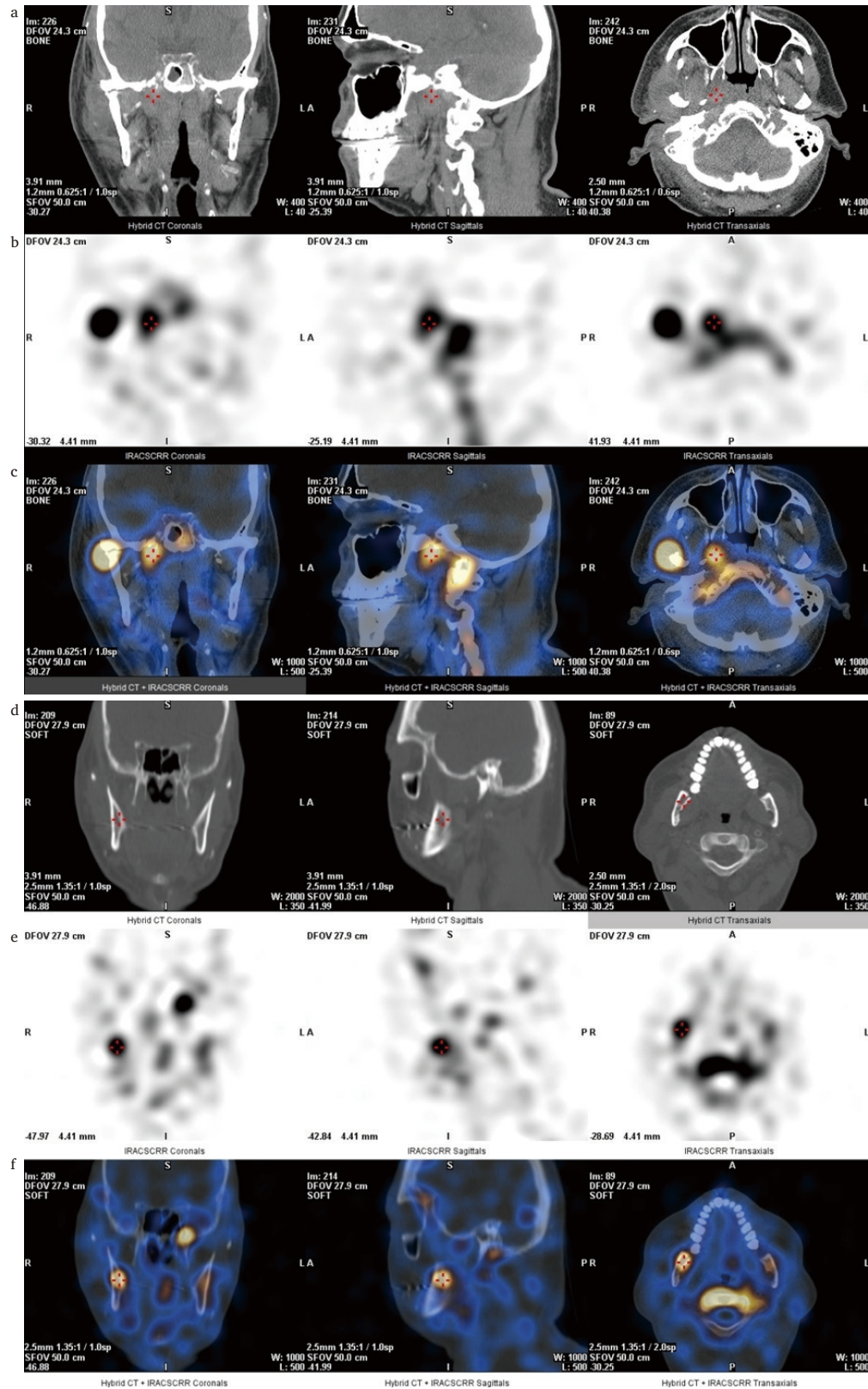
Pre-treatment diagnosis (a, b, c, d, e) and treatment response monitoring (f, g, h, i) of skull base osteomyelitis of 51-year-old male, previously healthy (patient No.4).

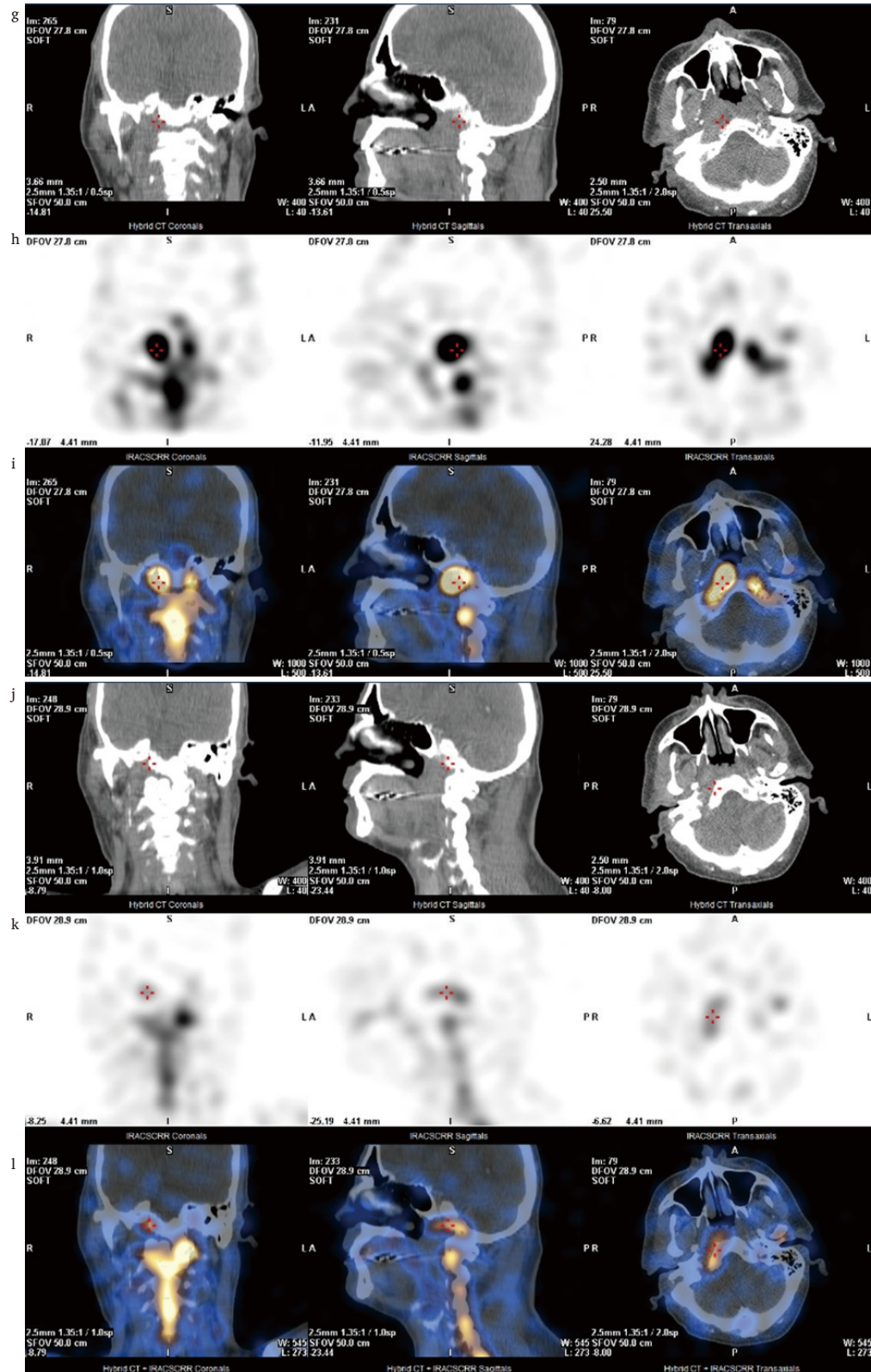
On delayed (4 h post-injection) (a, b) and late (24 h post-injection) planar scintigraphy images (c, d) and on fused SPECT/CT images (e), a higher accumulation of labelled leukocytes is visible in the following areas: in the mastoid process on the left, in the petrous bone on the left, in multiple subcutaneous infratemporal, temporal and occipital foci on the left, in the entire clivus, in the sphenoid bone, in bilateral masticatory and parapharyngeal space, bilaterally in the prevertebral muscles, in the soft tissue of the nasopharynx, in the C1 and C2 vertebrae, and in the petrous apex on the right.

the facial nerve palsy being the most common (Jung et al., 2021).

There is no consensus about the role of CN VII palsy in patient's prognosis. Some authors confirmed its negative impact on the length of treatment (Franco-Vidal et al., 2007; Guevara et al., 2013). Franco Vidal et al. and Lee et al. concluded that CN VII paresis significantly influenced survival (Franco-Vidal et al., 2007;

Lee et al., 2017). But Mani et al. didn't come to the same conclusion (Mani et al., 2007). Moreover, there is a controversy about the impact of single cranial nerve palsy vs. multiple cranial nerve palsies on mortality risk (Chen et al., 2010; Dabiri et al., 2020; Soudry et al., 2011). Study by Shavit et al. found that increased mortality risk is attributable to the combination of several factor:





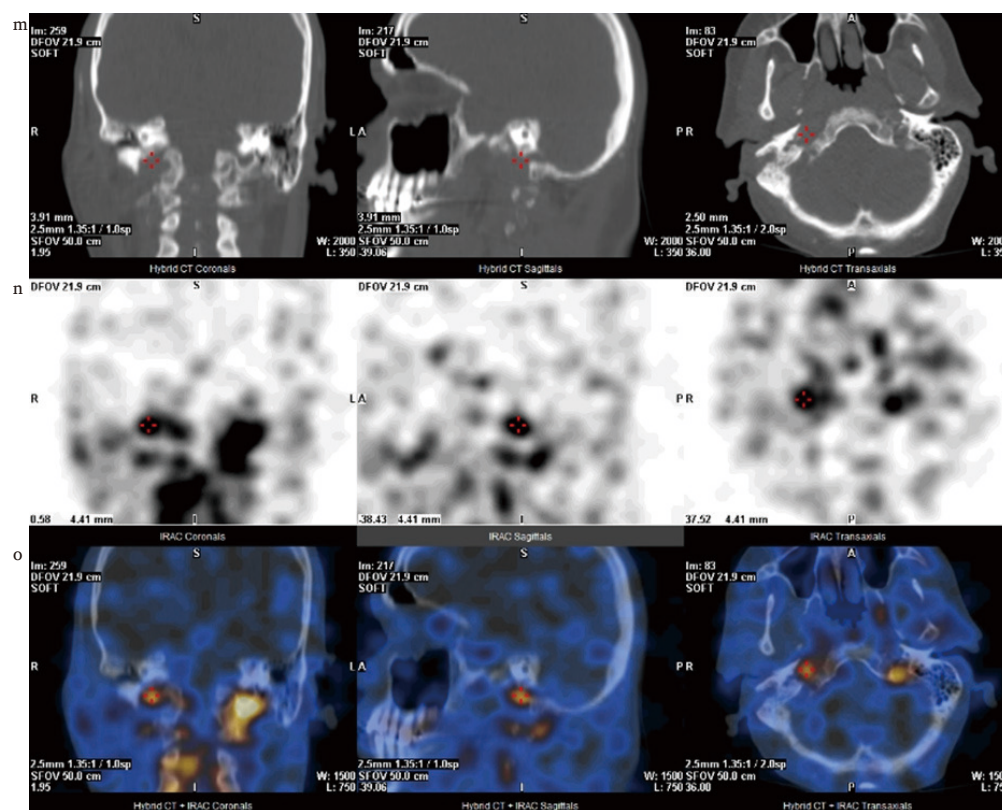


Figure 5 ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy; a, d, g, j, m (CT); b, e, h, k, n (SPECT); c, f, i, l, o (SPECT/CT).

Pre-treatment diagnosis (a, b, c), treatment response monitoring (d, e, f, j, k, l, m, n, o), and follow-up (g, h, i) of necrotizing external otitis of 50-year-old male with insulin-dependent type 2 diabetes, peripheral angiopathy, and with immunosuppression-status after kidney transplantation (patient No.5).

On delayed (4 h post-injection) and late (24 h post-injection) planar scintigraphy images and on fused SPECT/CT images, a higher accumulation of labelled leukocytes is visible in the following regions: in the temporomandibular joint with mandibular head surface erosion on the right, in the petrous apex on the right, in the clivus on the right side, and in the parapharyngeal and masticatory space on the right (note: the unspecific accumulation of leukocytes in normal bone marrow of the anterior arch of the atlas) (a, b, c).

age over 70, diabetes mellitus and facial nerve palsy or progressive changes (on bone/soft tissues) on CT (Shavit et al., 2016). Each patient in our series presented with CN VII or multiple CN palsies. Two of them with secondary immunodeficiency disorders additionally to diabetes mellitus, had the most unfavourable prognosis. In both, an early recurrence of the disease appeared, requiring a long course of antibiotics. While middle-aged patient has been cured, elderly patient has died. The mortality rate of our case series was 20%, which is at the lower end of the NEO overall all-cause mortality range of 9% to 53% (Shavit et al., 2016; Auinger et al., 2021; Jung et al., 2021; van der Meer et al., 2022).

6 Limitations

Single-center recruitment was a subject to selection (sampling) bias that affected the characteristics (i.e. overall mortality and post-treatment morbidity) of group of patients being studied. The study is based on a small sample and thus limits a statistical power mainly concerning the diagnostic accuracy of the used diagnostic method. Due to the retrospective design of the study some imbalances couldn't be avoided.

On the other hand, the focus on qualitative insights have uncovered and identified patterns of disease and themes that may not be quite evident through quantitative analysis and posed the hypothesis for future research tailored to disease imaging.

7 Conclusions

Patient No.1: in February 2012, planar and SPECT/CT imaging showed a high radiotracer uptake in the infected areas (Fig. 1a, b, c). After 8 weeks of inpatient, targeted combined antibiotic treatment, the imaging showed a decreased but persistent uptake. Following 6 weeks of outpatient treatment, scintigraphy revealed no radiotracer uptake in any areas. A follow-up scintigraphy performed 32 weeks later showed no radiotracer uptake in any regions.

Patient No.2: in June 2017, following repeated but prematurely terminated courses of targeted local and systemic antibiotic treatment and a surgical procedure (intensive debridement of the granulation tissue and bone of the ear canal, histologically benign) for unrecognized left-sided necrotizing external otitis, the disease progressed. Planar SPECT and SPECT/CT showed a high radiotracer uptake in the infected areas (Fig. 2a, b). After 6 weeks of inpatient, targeted combined antibiotic treatment, the scintigraphy showed decreased but persistent uptake. Following the patient's refusal of further inpatient treatment, intravenous antibiotics were switched to combined sequential oral and oral step-down therapy. Due to the increase in the radiotracer uptake in the scintigraphy, the patient consented to further hospitalization. Given the assumption of antimicrobial resistance of long-term antibiotic use, a switch to empirical combined intravenous antibiotic therapy was made. After 14 weeks, scintigraphy revealed mild accumulation of labelled leukocytes in the affected areas (false positive result) (Fig.

2c, d, e, f). Despite this finding, the antibiotic treatment had to be discontinued due to adverse drug reactions. A follow-up scintigraphy performed 40 weeks later showed no radiotracer uptake in any areas, indicating a negative result.

Patient No.3: In January 2020 SPECT/CT showed a high radiotracer uptake in the infected areas (Fig.3a, b, c). After 6 weeks of inpatient targeted antibiotic treatment, the imaging revealed decreased but persistent uptake (note: unspecific accumulation of leukocytes in normal vertebral bone marrow) (Fig.3d, e, f). After the continuation of outpatient treatment for 16 weeks, the scintigraphy image showed no radiotracer uptake in that, or any other area (false negative result). The antibiotic therapy was terminated. After 2.5 weeks, the patient developed a severe headache located in the temporal region/mastoid process on the right side. A follow-up scintigraphy, performed after 2.5 weeks, showed high radiotracer uptake in the mastoid cortex on the right (Fig.3g, h, i). The finding diagnosed a recurrence of the disease in a non-primary location. Outpatient targeted antibiotic treatment was resumed. After 10.5 weeks, on scintigraphy images a higher accumulation of labelled leukocytes was visible in the petrous apex on the right and in the greater wing of the sphenoid bone on the right, with no accumulation in the mastoid process (in accordance with headache resolution in that location) (Fig.3j, k). This scintigraphic finding persisted until the patient died (multifactorial etiology of the death).

Patient No.4: In January of 2021, planar scintigraphy and SPECT/CT showed high radiotracer uptake in the infected areas (Fig. 4a, b, c, d, e). After 6.5 weeks of inpatient targeted combined antibiotic treatment, the scintigraphy image showed no uptake in that, or any other area (Fig. 4f, g, h, i). The negative finding was confirmed by follow-up scintigraphy performed after 14, and 19 weeks, respectively.

Patient No.5: In February 2023, planar scintigraphy and SPECT/CT revealed high radiotracer uptake in the infected areas (Fig. 5a, b, c). After 6.5 weeks of inpatient, targeted combined antibiotic treatment, subsequent imaging showed a decrease in uptake in the primary areas, but new radiotracer uptake appeared in the mandibular ramus on the right (note: the uptake of radiotracer in the sphenoid sinus on the left is related to acute viral rhinosinusitis) (Fig.5d, e, f). After the continuation of inpatient treatment for 6 weeks, the scintigraphy image showed no radiotracer uptake in any areas (false negative result). After 51 days, the patient developed over again CN VII palsy on the right and, moreover ipsilateral cranial nerve palsies. A follow-up scintigraphy, performed after 18 days, showed significant radiotracer uptake in the petrous apex, jugular bulb area on the right, and soft tissue of the nasopharynx (Fig. 5g, h, i). The finding diagnosed a recurrence of the disease in the primary location. Inpatient antibiotic treatment was resumed and extended into outpatient care. On scintigraphy monitoring response images, performed after 10 (Fig. 5j, k, l), and 7 weeks (Fig.5m, n, o), a decrease in radiotracer uptake was found in the infected areas. After another 10 weeks a scintigraphy image showed no uptake in that, or any other area. This negative finding was confirmed by a follow-up scintigraphy performed 12 weeks later.

Necrotizing external otitis and otogenic skull base osteomyelitis remain serious, potentially life-threatening complications of external ear infection or chronic suppurative otitis media with relatively high morbidity and mortality. Early detection of the disease through imaging, followed by prompt initiation of antimicrobial therapy, is crucial for patient prognosis.

Based on our experience, ^{99m}Tc -HMPAO-labelled autologous leukocytes scintigraphy is appropriate method that establishes the

primary diagnosis of NEO, detect and rule out a disease recurrence with an adequate accuracy and reliability. However, when focusing on monitoring treatment response, the low negative predictive value limits the ability of the method to discriminate between diseased and non-diseased.

Further multicenter validation to confirm our study results should be conducted. Additional investigation could be suggested for improving estimated low negative predictive value of the method.

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Data Availability Statement

The data are available from the corresponding author on reasonable request.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital and Faculty of Medicine Palacky University Olomouc.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflict of interest.

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