

Management of Malignant Otitis Externa with Hyperbaric Oxygen Therapy: A case series of 20 patients

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Abstract

Malignant otitis externa (MOE) is an aggressive infection of the external auditory canal (EAC) which primarily affects diabetic patients. Some literature supports the effectiveness of hyperbaric oxygen therapy (HBOT) as a treatment modality for MOE. A case series was conducted of all patients diagnosed with MOE and treated with HBOT at the Said Bin Sultan Naval Base Poly Clinic in Oman between January 2014 and December 2019. A total of 20 patients were included in the series. Overall, 100% of the participants presented with persistent ear discharge, 95% with ear pain, and 75% with granulation in the EAC; moreover, 100% showed abnormally high levels of inflammatory markers and abnormal computed tomography findings. Patients underwent an average of 29 ± 8.9 HBOT sessions. Overall, 19 patients (95%) were considered cured by the end of the treatment. The use of HBOT in the management of MOE appears promising and may cure MOE.

Keywords: Otorhinolaryngologic Diseases; Otitis Externa; External Auditory Canal; Hyperbaric Oxygenation; Diabetes Complications; Oman.

Introduction

Malignant otitis externa (MOE) is an invasive infection of the external auditory canal (EAC) and base of the skull.¹⁻³ It is termed malignant because it behaves and spreads like a malignancy.¹ The infection predominantly affects patients with primary or secondary immunodeficiency, such as

older people with diabetes (in 90% of cases), patients undergoing radio- or chemotherapy, those with human immunodeficiency virus infections, and children with malnutrition.⁴ Multiple bacterial and fungal organisms have been identified as causes of MOE; however, *Pseudomonas aeruginosa* is the most common causative agent.^{2,4}

Patients with MOE usually present with persistent otalgia, otorrhea, and hearing loss.^{5,6} The disease can be complicated by severe osteomyelitis of the temporal bone, palsy of the cranial VII–XII nerves (particularly the facial nerve), and involvement of the blood vessels and soft tissues. In addition, death can occur due to extensive osteomyelitis of the skull and disseminated septic thromboemboli of the brain.^{5,6} A diagnosis of MOE is made from a combination of clinical, laboratory, and radiological findings and nuclear imaging.² Computed tomography (CT) and magnetic resonance imaging (MRI) scans are used to determine the anatomical extent of the disease. Radioisotope imaging using technetium-99/gallium-67 is a very sensitive but non-specific test that is usually used to monitor treatment response as it detects actively dividing cells.⁴

Treatment of MOE requires the prolonged use of local or systemic antibiotics—with ear swabs guiding the choice of antimicrobial therapy—as well as diabetes control measures and repeated debridement of the necrotic tissue; in some cases, aggressive surgical management may be necessary.^{1,5} Hyperbaric oxygen therapy (HBOT) involves the intermittent breathing of 100% oxygen while under conditions in which the ambient pressure is greater than atmospheric pressure. Although HBOT has been considered as an adjunctive therapy in the treatment of various infectious and inflammatory diseases, this modality is not yet indicated for use in MOE.³ However, there are reports in the literature supporting the beneficial effect of HBOT in the management of MOE cases which share similar characteristics to obstinate osteomyelitis and necrotizing inflammation.^{2–12}

At the Said Bin Sultan Naval Base Poly Clinic in Oman, HBOT has been offered as an outpatient-based service since 1979. Treatment consists of multiple sessions in which the patient is exposed to a pressure of 2.4 atmospheres absolute. A single daily session lasts for 90 minutes and involves three periods of pure oxygen breathing for 25 minutes at a time, interspersed by three 5-minute intervals of air breathing. The total number of treatment sessions required is individually

prescribed according to each patient's clinical manifestations and response to treatment. The aim of this case series was to determine the effectiveness of HBOT as an adjuvant therapy for patients with MOE and to identify factors affecting treatment outcomes.

Case series

Between January 2014 and December 2019, a total of 26 patients with MOE were referred for adjuvant HBOT to the Hyperbaric Medicine Unit of Said Bin Sultan Naval Base Poly Clinic due to worsening of the disease following the failure of conventional treatment (i.e., antibiotic therapy with or without concurrent surgery). Six patients were excluded from the series as they did not complete the total number of recommended HBOT sessions for various reasons, including four patients who faced logistical and transportation difficulties and two patients who were lost to follow-up. Treatment outcome was classified into four categories: died of disease (DOD), died of other causes (DOC), cured with no evidence of disease, and alive but with refractory disease. The latter category was applied in cases in which there was incomplete resolution of the otalgia, otorrhea, or granulation tissue.

Ethical approval for this case series analysis was obtained from both the Forces Medical Services Medical Ethics Committee (#FMS-MEC 005/2020) and the Ministry of Health (#MoH/CSR/20/23816). Data were collected from the medical records system of the referring hospitals, as well as the in-house medical records system of the Said Bin Sultan Naval Base Poly Clinic. Relevant information was collected using a data collection sheet and entered for statistical analysis. Overall, the mean age of the patients was 64.6 years and the mean follow-up period was 14.1 months. The patients underwent an average of 29 ± 8.9 HBOT sessions (range: 13–51 sessions). All of the patients were diabetic.

Case 1

A 63-year-old male with known uncontrolled diabetes and hypertension presented with a six-week history of persistent right ear pain and discharge. An ear swab culture showed no growth. Radiological imaging confirmed mastoiditis and temporal bone osteomyelitis. He received ciprofloxacin and ceftazidime for 47 days before HBOT and underwent a tympanomastoidectomy. The patient experienced a full recovery following 27 sessions of HBOT.

Case 2

A 56-year-old female with known uncontrolled diabetes, hypertension, and chronic kidney disease (CKD) presented with persistent right ear pain, discharge, and right-sided facial nerve palsy of more than two weeks' duration. An ear swab culture was negative. Mastoiditis was observed during radiological imaging. She was prescribed a prolonged course of ciprofloxacin and piperacillin/tazobactam for 17 days before undergoing 25 sessions of HBOT, after which the MOE resolved completely. However, the facial nerve palsy persisted.

Case 3

A 64-year-old female with uncontrolled diabetes, hypertension, and CKD presented with a three-year history of persistent left ear pain and discharge. Investigations revealed the growth of *P. aeruginosa* from an ear swab culture. Mastoiditis was observed during a CT and Gallium-67 scan see figure 1. She received ciprofloxacin for 124 days and underwent 44 sessions of HBOT resulting in disease resolution see figure 2. The patient developed bilateral middle ear barotrauma as a side-effect of the HBOT, which was treated successfully with a nasal decongestant.

Case 4

A 64-year-old male with known uncontrolled diabetes and hypertension presented with a three-month history of persistent left ear pain and discharge. *P. aeruginosa* was isolated from an ear swab culture and a CT scan confirmed mastoiditis and temporal bone osteomyelitis. Ceftazidime and piperacillin/tazobactam were prescribed for 84 days before referral to HBOT. The patient underwent 27 sessions of HBOT and was cured with no evidence of disease.

Case 5

A 71-year-old male with known uncontrolled diabetes, hypertension, and CKD presented with a six-week history of persistent right ear pain and discharge. An ear swab culture was negative. Mastoiditis and temporal bone osteomyelitis were seen during radiological imaging. He received ceftazidime and ciprofloxacin for 45 days before referral to HBOT. Complete resolution of the MOE occurred after 25 sessions of HBOT.

Case 6

A 39-year-old female with controlled diabetes presented with a three-week history of persistent left ear pain and discharge. An ear swab culture revealed growth of *P. aeruginosa*. The disease was complicated by temporal bone osteomyelitis. The patient was prescribed a prolonged course of ciprofloxacin and piperacillin/tazobactam for 24 days before HBOT started. She underwent 30 sessions of HBOT, after which she had a full recovery.

Case 7

An 81-year-old male with uncontrolled diabetes presented with a six-month history of persistent left ear pain and discharge. An ear swab culture showed *Klebsiella pneumoniae* and *Proteus mirabilis* isolates. The MOE was complicated by mastoiditis, bone osteomyelitis of the skull base, jugular foramen syndrome, and cerebral vein and transverse sinus thrombosis. The patient received piperacillin/tazobactam and ciprofloxacin for 184 days before starting HBOT. He underwent 27 sessions of HBOT and recovered completely.

Case 8

A 62-year-old male with uncontrolled diabetes presented with persistent right ear pain, discharge, and impaired hearing of six weeks' duration. An ear swab culture showed mixed growth of *P. aeruginosa* and *Staphylococcus aureus*. He received ceftazidime and meropenem for 43 days then referred for HBOT. He underwent 17 sessions of HBOT and was subsequently cured of the disease.

Case 9

A 62-year-old male with known controlled diabetes and hypertension presented with a history of persistent right discharge and impaired hearing of more than two weeks' duration. *P. aeruginosa* was isolated from an ear swab culture. An MRI showed osteomyelitis of the skull base. The patient received a prolonged course of piperacillin/tazobactam for 15 days before HBOT initiated. After undergoing 27 sessions of HBOT, full resolution of the disease was observed.

Case 10

A 71-year-old female with controlled diabetes and hypertension presented with persistent left ear pain and discharge of more than two weeks' duration. An ear swab culture was negative. However,

a CT scan confirmed extension of the infection to the infratemporal fossa and parapharyngeal space. The patient received ciprofloxacin and ceftazidime for 17 days then HBOT started. She made a full recovery after 25 HBOT sessions.

Case 11

An 85-year-old female with uncontrolled diabetes and hypertension presented with a six-month history of persistent left ear pain and discharge. An ear swab culture revealed multi-drug-resistant (MDR) *P. aeruginosa*. Both CT and gallium-67 scans confirmed temporal bone osteomyelitis. She received Colistin for 168 days. Despite 51 sessions of HBOT, the disease persisted until the patient's death as a result of a myocardial infarction after six months of treatment. Beforehand, the patient had developed bilateral middle ear barotrauma as a side-effect of HBOT which was treated successfully with a nasal decongestant.

Case 12

A 65-year-old male with known uncontrolled diabetes and hypertension presented with a four-month history of persistent left ear pain and discharge. An ear swab culture revealed *P. aeruginosa* isolates. Mastoiditis and temporal bone and skull base osteomyelitis were observed during an MRI scan. The patient received a prolonged course of piperacillin/tazobactam for 134 days before undergoing 29 sessions of HBOT. He subsequently made a full recovery.

Case 13

A 60-year-old male with uncontrolled diabetes and hypertension presented with a four-month history of persistent right ear pain and discharge. An ear swab culture showed no growth. Both CT and gallium-67 imaging confirmed temporal bone osteomyelitis. The patient received piperacillin/tazobactam for 122 days and underwent a cortical mastoidectomy. He received 31 sessions of HBOT before making a full recovery.

Case 14

A 69-year-old male with controlled diabetes presented with persistent left ear pain and discharge of six weeks' duration. An ear swab culture showed *P. aeruginosa* and *Aspergillus flavus*. Both MRI and technetium-99 imaging confirmed temporal bone osteomyelitis and involvement of the

temporomandibular joint. He received ceftazidime, ciprofloxacin, and clotrimazole for 40 days. He underwent 16 sessions of HBOT, after which he was cured with no evidence of disease.

Case 15

A 77-year-old female with known controlled diabetes and hypertension presented with a five-week history of persistent left ear pain, discharge, and left-sided facial nerve palsy. An ear swab culture was negative. However, a CT scan confirmed skull base and temporal bone osteomyelitis, internal jugular vein compression, and involvement of the retropharyngeal space. The patient received caspofungin and ceftazidime for 39 days. She underwent 33 sessions of HBOT with full resolution of both the MOE and the facial nerve palsy.

Case 16

A 59-year-old male with uncontrolled diabetes and hypertension presented with a history of persistent left ear pain, discharge, and left-sided facial nerve palsy of six weeks' duration. An ear swab culture was negative. He received ceftazidime and ciprofloxacin for 42 days. Complete resolution of the MOE was achieved after 29 sessions of HBOT; however, no improvement was noted with regards to the facial nerve palsy.

Case 17

A 60-year-old female with known uncontrolled diabetes and hypertension presented with a four-month history of persistent right ear pain, discharge, and right-sided facial nerve palsy. An ear swab culture showed beta-hemolytic group B *Streptococcus* (GBS). A CT scan confirmed temporal bone osteomyelitis. She received ceftazidime, piperacillin/tazobactam, and meropenem for 125 days. The patient underwent a total of 40 sessions of HBOT which resulted in the complete resolution of the MOE and partial improvement of the facial nerve palsy.

Case 18

A 55-year-old female with uncontrolled diabetes and hypertension presented with persistent left ear pain and discharge of six weeks' duration. *P. aeruginosa* was isolated from an ear swab culture. A CT scan revealed mastoiditis and the formation of a cholesteatoma. The patient received

ceftazidime and ciprofloxacin for 41 days. She underwent 27 sessions of HBOT and was cured of the disease.

Case 19

A 64-year-old male with controlled diabetes and hypertension presented with a four-week history of persistent right ear pain and discharge. An ear swab culture showed growth of *P. aeruginosa* and *P. mirabilis*. Mastoiditis was observed on CT imaging. The patient received ceftazidime and ciprofloxacin for 27 days and underwent 13 sessions of HBOT, with full recovery confirmed upon follow-up.

Case 20

A 62-year-old female with uncontrolled diabetes and hypertension presented with a two-month history of persistent right ear pain and discharge. An ear swab culture showed *P. aeruginosa* isolates. A CT scan confirmed temporal bone osteomyelitis. She received ceftazidime for 61 days and had 33 sessions of HBOT, resulting in a full recovery.

Discussion

According to a recent systematic review, the most common symptom of MOE is otorrhea (84.1%), followed by otalgia (77.3%), while common signs of disease in the EAC include granulation tissue (59.1%) and edema (27.3%).¹⁰ Similarly, all of the patients in our case series had chronic otorrhea, with severe otalgia reported in 95% of patients, granulation tissue in 75%, and edema of the EAC in 35%. Usually, the disease originates in the EAC and spreads through the osseocartilaginous junction to the soft tissues beneath the temporal bone.^{9,12} Spreading infection can lead to various complications, such as skull base osteomyelitis; furthermore, progressive osteomyelitis can result in cranial polyneuropathy.^{1,5} In our series, 70%, 25%, and 5% of the patients had stage 2, stage 3a, and stage 4 disease, respectively [Table 1].¹³

Previous research indicates that facial nerve palsy in MOE is associated with a poorer prognosis.³ However, other researchers have failed to show an association between involvement of the cranial nerves and survival.^{6,11} Similarly, Mani *et al.* found no significant difference in the survival of MOE patients with and those without facial paralysis.¹⁴ In the present case series, four patients

(20%) had palsy of the VII cranial nerve; subsequently, by the end of the follow-up period, two of the patients showed no improvement, one had experienced partial recovery, and the final patient had recovered completely. Another case series reported facial nerve palsy in four MOE patients (60%); of these, three underwent HBOT after conventional medical treatment failed, with improvement noted in two patients.⁵ These findings support the theory that not all facial nerve function recovers in MOE patients even when there is no evidence of continuing infection.³

One of the patients in our series had palsy of multiple cranial nerves, including the glossopharyngeal (IX), vagus (X), spinal accessory (XI), and hypoglossal (XII) nerves. Together, palsy of the former three cranial nerves is known collectively as jugular foramen syndrome. Nevertheless, despite the involvement of multiple cranial nerves, the patient improved and was disease-free after receiving adjunctive HBOT. This supports previous findings indicating that multiple cranial nerve involvement is not linked to survival.¹¹

A marked elevation in erythrocyte sedimentation rate (ESR) is a useful marker to support a diagnosis of MOE and monitor therapeutic response.^{2,5} In our series, 95% of patients had high ESRs upon presentation; moreover, while one patient had no documented ESR, his C-reactive protein levels were high. Subsequently, among the 15 patients for whom follow-up ESR measurements were collected, 14 returned to normal levels following HBOT. The remaining patient remained symptomatic for MOE with persistently high ESRs during the following six months of follow-up until DOC. Another case series investigating patients with MOE reported that serial ESR measurements correlated well with the patients' condition; moreover, following HBOT, all patients improved clinically with a reduction in ESR.⁸

Although *P. aeruginosa* is the most commonly isolated organism in MOE, other researchers have reported an increasing frequency of other causative organisms.³ One study identified *P. aeruginosa* in 11 patients (55%) and *S. aureus* in three patients (12%).² Our analysis showed *P. aeruginosa* isolates in 11 (44%) swab cultures, with *P. mirabilis*, *K. pneumoniae*, *S. aureus* and GBS isolated in several other cases. *A. flavus* was identified in a single patient in our series; this is a pathogen very rarely isolated in MOE.² In addition, we identified one patient with a mixed bacterial and fungal infection and seven patients with negative swab cultures. However, most patients in the

current case series received oral empiric antibiotics prior to being seen at referring hospitals; Harris *et al.* found that bacteria were less often detected in culture-based tests collected after antibiotic use.¹⁵ In addition, some cultures may have been reported as negative due to the absence of data prior to admission.

When MOE was first described, it had a poor prognosis with a >50% mortality rate.⁹ Since that time, the mortality rate has improved considerably, an improvement largely attributable to advances in treatment.¹¹ A number of antimicrobial regimes for MOE have been documented in the literature, including prolonged courses of ciprofloxacin, meropenem, piperacillin/tazobactam, ceftazidime, and gentamicin.^{1,3} The recommended duration of antibiotic use in MOE treatment is 6 weeks and sometimes it is continued for several months depends on the improvement on imaging and physical examination due to poor perfusion of diseased area.^{1,9} The specific choice of antibiotic depends upon hospital policy and microbiological cultures. Most of the patients in our case series received ciprofloxacin followed by ceftazidime as strong anti-pseudomonal agents. Oral ciprofloxacin is the preferred first line of treatment for MOE in an outpatient setting; however, due to the increased use of this drug, there is concern regarding the possibility of antibiotic resistance in *Pseudomonas*-associated infections. Nevertheless, such patients do not have an increased risk of disease-specific mortality.^{1,11}

In our case series, one patient was found to have a *Pseudomonas*-associated infection which was resistant to multiple drugs, including ciprofloxacin. Although a swab culture sensitivity assessment informed the use of colistin, the patient did not show any improvement and DOC within six months as a result of a myocardial infarction. Colistin has been reported to be an effective treatment for various infections caused by MDR *P. aeruginosa*, including in one case of bilateral MOE.¹¹ Unfortunately, the patient in this case subsequently DOC one year after diagnosis with no change in his chronic infection despite a prolonged antibiotic regimen.¹¹

To the best of our knowledge, no previous research has yet investigated the therapeutic value of HBOT in MOE caused by MDR *P. aeruginosa*. The underlying theoretical principle of HBOT relies on the increase in oxygen supply and arterial oxygen tension.⁸ Inside the hyperbaric chamber, under typical therapeutic conditions, levels of partial pressure of oxygen dissolved in

plasma can become greater than 20 times that of those observed when breathing room air at normal atmospheric pressure. The theory of action is that HBOT causes a decrease in the production of local nitric oxide by the endothelial cells, thereby leading to vasoconstriction and a decrease in edema of the damaged tissues. Moreover, increased arterial oxygen tension promotes modulation of a number of growth factors, proliferation of fibroblasts, activation of neoangiogenesis, and improved osteoblastic activity leading to enhanced healing.^{3,9}

Oxygen also has antibacterial effects at the infection site. As neutrophils and macrophages enter these environments to kill bacteria, they consume large amounts of oxygen which is then utilized by these cells to produce reactive oxygen species (ROS). These ROS can kill bacteria through membrane disruption and protein denaturation. Therefore, HBOT can enhance the response of the immune system to the infection. Interestingly, HBOT has even been found to increase the antibacterial effectiveness of certain antibiotics, such as aminoglycosides.^{4,6} Thus, employing HBOT for conditions which share a similar pathophysiology appears logical.⁸ Indeed, 95% of the patients in our series were treated successfully with HBOT, with no DOD cases and only one patient who DOC.

Nevertheless, MOE is an uncommon disease that is difficult to diagnose; moreover, HBOT can be extremely slow and accessibility to hyperbaric chambers is often restricted. These limitations hinder the ability of researchers to conduct prospective, randomized, double-blind clinical trials to confirm the safety and efficacy of HBOT as a treatment modality for MOE.⁴ This may explain why most related publications in this area are based on the authors' own practice and experiences. In a retrospective study, Amaro *et al.* demonstrated disease resolution in 16 patients with MOE who received HBOT in conjunction with antibiotics after all other treatments had failed.³ The researchers reported that the duration of hospitalization prior to HBOT was significantly longer than the time between initiation of HBOT and cure ($p = 0.028$).³ In our study, the length of receiving treatment in the referring hospital prior to receiving HBOT was significantly associated with the number of HBOT sessions required for full recovery ($p = 0.029$). These findings point toward the need for the early initiation of HBOT.

Side-effects of HBOT include ear barotrauma, sinus squeeze, dental problems, seizures, claustrophobia, and pulmonary oxygen toxicity; however, such effects are generally either very rare or transient in nature.¹⁶ In our case series, two patients reported middle ear barotrauma. Both were found to have had an upper respiratory tract infection prior to the therapeutic session which made it difficult for them to equalize their ear pressure. They were treated with nasal decongestants and resumed HBOT treatment during their following scheduled sessions. Nasal decongestants have been shown to be effective in preventing middle ear barotrauma.¹⁷

Conclusion

The use of HBOT as an adjuvant therapy in the management of MOE appears promising. Overall, 95% of the patients in this case series were considered cured by the end of the treatment. Early initiation of this treatment modality could prevent severe complications and reduce mortality associated with the disease. Moreover, early treatment may lessen the number of therapeutic sessions required for complete recovery, thereby reducing the need for prolonged hospitalization and related costs.

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Table 1: Disease staging of malignant otitis externa. ¹³

Stage	Description
1	Clinical evidence of MOE with infection of the soft tissues beyond the EAC, but negative TC-99 bone scan findings
2	Soft tissue infection beyond the EAC with positive Tc-99 bone scan findings
3a	As above, but with paralysis of a single cranial nerve
3b	As above, but with paralysis of multiple cranial nerves
4	Meningitis, empyema, sinus thrombosis, or brain abscesses

MOE = malignant otitis externa; EAC = external auditory canal; Tc-99 = technetium-99.

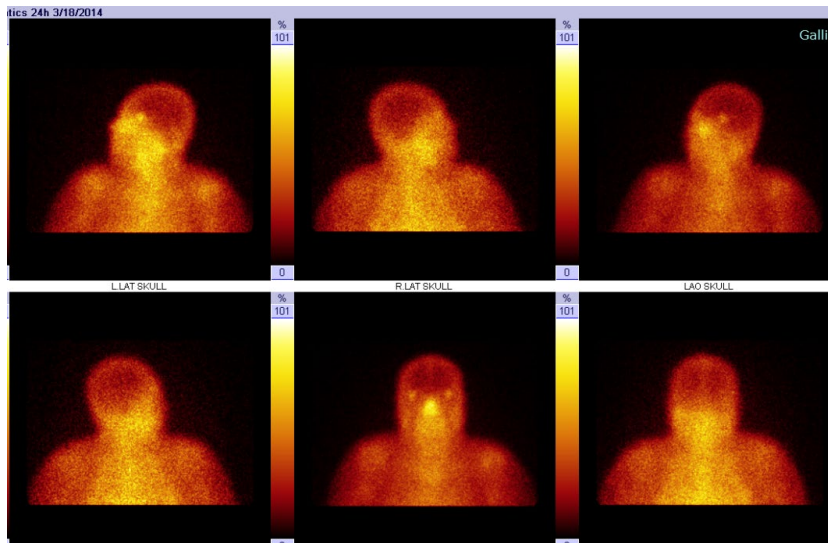


Figure 1: case 3, before HBOT treatment: Gallium-67 Scintigraphy, showing focal area of increased tracer uptake in the left ear region including the left sphenoid bone with extension to the left mastoid process. Suggestive of active left otitis. (Date: 18/3/2014)

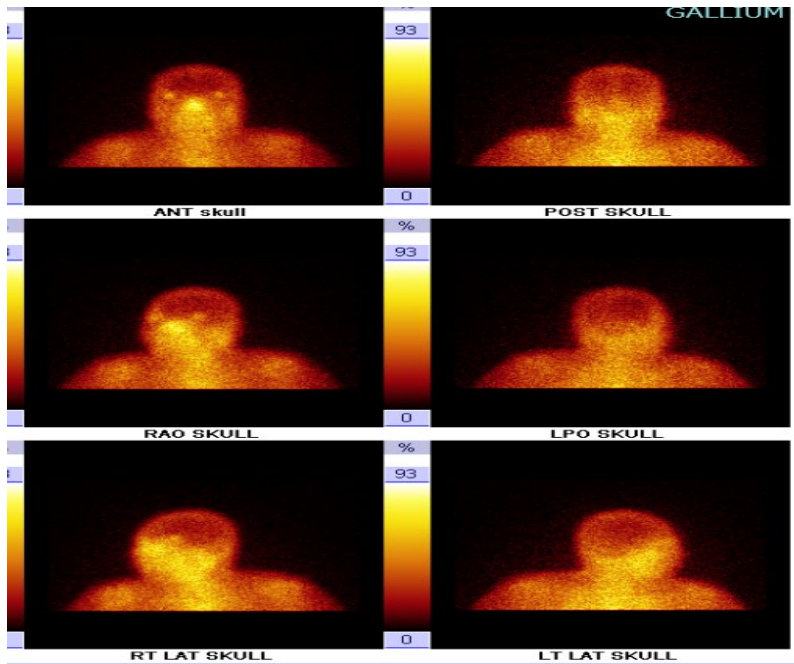


Figure 2: case 3, after HBOT treatment: Gallium-67 Scintigraphy: showed: Normal radiotracer uptake in the skull. (Date: 13/4/2015)