CASE REPORT
ONCOLOGY

Diseases & Research

Recurrent Middle Ear Cancer: Case Report

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Abstract: Background: Middle ear cancer is clinically uncommon, representing approximately 1.5% of ear malignancies and 0.03% to 0.06% of all cancers. Recurrent cases of middle ear cancer are particularly rare. This report discusses a patient with middle ear cancer who experienced invasive growth into surrounding tissues and developed a large cancerous ulcer post-resection. Case Summary: A 72-year-old male underwent a subtotal resection of the right temporal bone in February 2021, diagnosed with squamous cell carcinoma of the middle ear. Regrettably, he did not receive follow-up medical care after surgery. In June 2022, he returned to the hospital with complaints of pus and bleeding from a mass behind his ear. Further examinations led to a diagnosis of recurrent middle ear cancer with extensive local infiltration. We initiated a combination treatment comprising targeted therapy, chemotherapy, radiotherapy, and local application of rhGM-CSF. The patient showed remarkable sensitivity to this treatment plan, evidenced by a significant reduction in the mass and discharge behind the ear within a week. After two cycles of combined targeted therapy and chemotherapy, the treatment's effectiveness was assessed as PR (partial response) via magnetic resonance imaging. As of August 2023, the patient remains in stable condition. Conclusion: For such a recurrent middle ear cancer with giant cancerous ulcer, we suggest do not neglect local treatment while giving anti-tumor treatment.

Keywords: Recurrent; Middle ear cancer; Giant cancerous ulcer; rhGM-CSF.

Introduction

The patient was admitted to hospital in February 2021 with a six-month history of recurrent pus discharge in the right ear. A CT scan revealed soft tissue shadows in the right external auditory canal and bone resorption in the mastoid area, suggesting a malignant tumor. On February 24, 2021, he underwent subtotal resection of the right temporal bone and abdominal wall fat-filling. Postoperative pathology confirmed squamous carcinoma. Unfortunately, the patient did not partake in postoperative follow-up, and thus did not undergo subsequent examinations or adjuvant therapy.

Case Presentation

Chief complaints

The patient complained of subcutaneous mass behind the ear with repeated pus and bleeding (Fig. 1).

History of present illness

In February 2021, the patient was referred to our hospital after complaining of persistent pus discharge in the right ear for six months. A CT scan indicated soft tissue shadows in the right external auditory canal, as well as bone resorption and degradation in the mastoid region which implying cancer. On February 24, 2021, a subtotal excision of the right temporal bone and abdominal wall fat filling operations were conducted. Squamous cell cancer was confirmed with postoperative pathology. Unfortunately, the patient did not return for follow-up appointments following the surgery, and no postoperative tests or adjuvant treatment were performed.

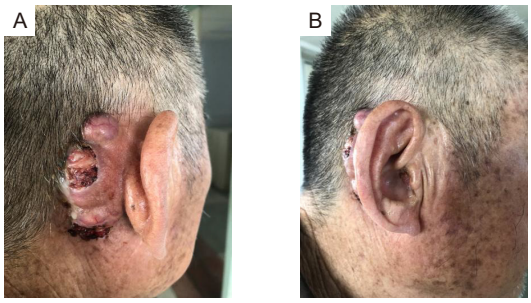

Fig. 1. The condition of the right ear at the first visit.
A. Back.
B. Side.

History of past illness

The patient had chronic suppurative otitis media with long-term recurrent episodes, hypertension, coronary heart disease, and atrial fibrillation.

Personal and family history

No special personal history, no familial genetic disease.

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Physical examination
The patient presents multiple subcutaneous masses behind the ear, which have merged into a larger mass. There is also recurrent pus discharge and bleeding observed.

Laboratory examinations
Routine blood tests, microbiology examinations, and coagulation profiles were essentially normal. Tumor markers, including alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9, were all within normal ranges.

Imaging examinations
Magnetic resonance imaging (MRI) revealed lesions in the right mastoid, middle ear, outer ear, right nasopharynx, parapharyngeal space, and right cerebellar horn. These are considered to be recurrent lesions. Involvement was also noted in the right temporal bone, pterygoid sinus, and right temporal lobe (refer to Fig. 2).

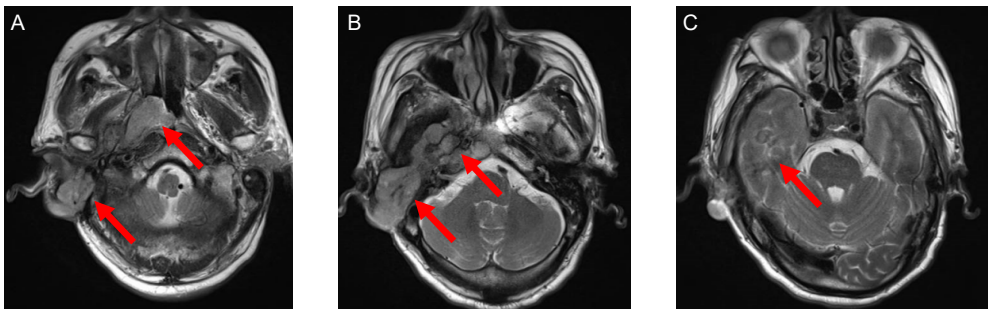

Fig. 2. Magnetic resonance imaging before treatment (June 24, 2022).
A. Lesions in outer ear and right nasopharynx.
B. Lesions in middle ear and outer ear.
C. Lesions in right temporal lobe.

The final diagnosis
The final diagnosis is a postoperative recurrence of right middle ear cancer, grade 3 hypertension (high risk), coronary artery disease, and atrial fibrillation.

Treatment Method

Initially, the patient underwent two cycles of chemotherapy in combination with targeted therapy. This regimen included docetaxel, cisplatin, and an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Concurrently, we addressed the cancerous ulcer with local treatment. Given the lack of established treatments for cancerous ulcers, our approach was guided by protocols typically used for radiation mucositis.

According to the Guidelines for the Prevention and Treatment of Acute Mucositis Associated with Head and Neck Radiotherapy (the 2022 edition), recombinant human granulocyte/macrophage-stimulating factor (GM-CSF) is recommended for managing mucositis induced by head and neck radiotherapy[1]. In the initial week, the ulcer was treated as follows: it was first cleansed with saline, then disinfected with povidone-iodine, followed by another saline rinse. Subsequently, 400 μg of rhGM-CSF dry powder was applied directly to the affected area.

A week later, we dissolved 400 μg of the dry powder in 30 to 50 mL of saline. This solution was soaked into gauze and applied to the ulcer for 15-30 minutes, at least four times daily. Additionally, gauze soaked in the same solution was used to pack the pus-filled cavities.

One week after starting the treatment, we observed an unexpected and significant reduction in both the size of the mass and the ulcerated surface behind the ear, accompanied by a marked decrease in exudation (see Fig. 3). Following two cycles of treatment, we assessed the efficacy of treatment plan with MRI and noticed a large partial response (PR) (Fig. 4). We then proceeded with an additional cycle of the original treatment regimen. After three cycles of targeted therapy, stable disease (SD) was confirmed via CT scan.

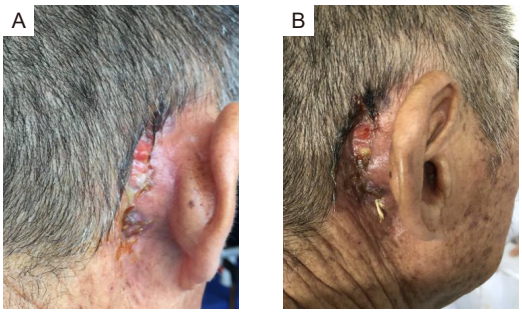

Fig. 3. The condition of the ear after local treatment.
A. One week later.
B. Two weeks later.

Subsequent to three cycles of chemotherapy, we convened a multidisciplinary team to review the case. The consensus among the participating experts was that the patient had responded well to the first two cycles of treatment, but the third cycle did not yield significant tumor regression, indicating that the efficacy had plateaued. Therefore, the recommended next step was to initiate local radiotherapy to control disease progression. Given the patient's unsatisfactory health conditions, concurrent chemotherapy was deemed potentially inadvisable.

The patient underwent volumetric arc intensity-modulated radiation therapy (IMRT) with the following protocol: Gross Tumor Volume (GTV) was defined as the residual tumor identified by CT and MR imaging. The Clinical Target Volume (CTV) in-

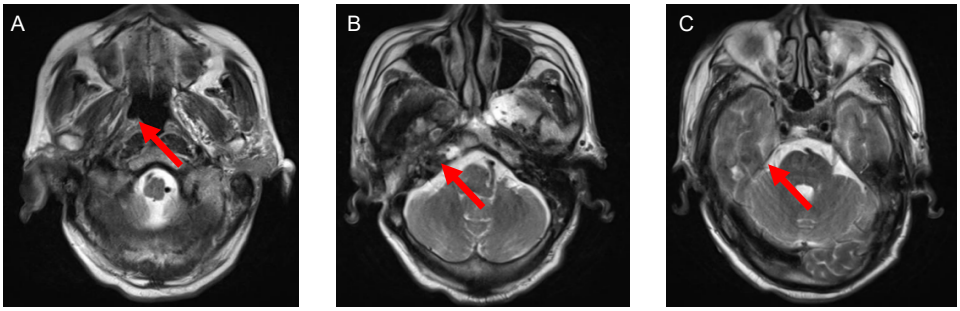

Fig. 4. Resonance imaging after treatment (August 9, 2022).
A. Lesions in outer ear and right nasopharynx were significantly reduced.
B. Lesions in middle ear and outer ear were significantly reduced.
C. Lesions in right temporal lobe were reduced.

cluded the right outer ear, right middle ear, right nasopharynx, parapharyngeal space, right buccal valley, and pterygoid sinus. The planning GTV (PGTV) incorporated a margin of 0.3 cm around the GTV, and the Planning Target Volume (PTV) included a 0.3 cm margin around the CTV. The radiation dosage was precisely calculated: 95% of the PGTV received a dose of 68.64 Gy, divided into 2.08 Gy per fraction over 33 fractions. Similarly, 95% of the PTV received a dose of 60.06 Gy, with 1.82 Gy per fraction over the same number of fractions (refer to Fig. 5).

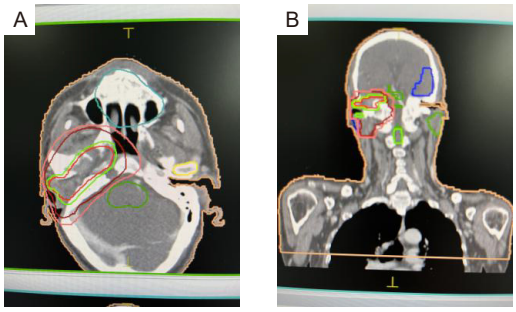

Fig. 5. Target area for radiotherapy.
A. Transverse position.
B. Sagittal position.

A post-radiotherapy CT scan indicated stable disease (SD). Following the radiation treatment, the patient was started on maintenance therapy with an anti-EGFR monoclonal antibody.

Results and follow up

The mass was largely reduced in size and the ulcer healed without exudation. The patient is now in stable condition and was last followed up in August 2023 (Fig. 6).

Discussion

The incidence of malignant tumors in the middle ear is notably low. Many patients with middle ear cancer have a long history of chronic suppurative otitis media. As suggested in previous studies, this correlation may be attributed to the metaplasia of the middle ear mucosa caused by chronic inflammation[2–4]. The patient in this report also has a history of chronic otitis media.

Malignancy in the middle ear is rare, and there is limited data available to guide clinical decisions. Its prognosis largely depends on the histological type. Squamous cell carcinoma (SCC) as the most common type of carcinoma, is associated with the poorest overall survival rates[5]. Early symptoms of this disease tend to be atypical and clinical signs are often subtle, leading to frequent misdiagnoses. The combined approach of surgery and radiotherapy is commonly employed for treating middle ear carcinoma, with the choice of surgical procedure tailored to the extent of the lesion.

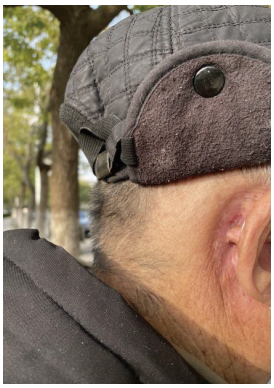

Fig. 6. The current situation (August, 2023).

A significant challenge in treating middle ear cancer is the high risk of local recurrence post-treatment, which substantially reduces patient survival rates. In this report, we discuss a case of recurrent middle ear cancer following a subtotal resection of the temporal bone. We will also share our treatment experiences and strategies that led to the successful management of this case.

In this case, selecting the appropriate first-line anti-tumor treatment was crucial. The patient presented with extensive tumor spread, a significant tumor burden, and no viable options for initial local treatment. Thus, our primary objectives were rapid tumor size reduction and patient's quality of life improvement. As per the guidelines from the Chinese Society of Clinical Oncology (CSCO), for patients with recurrent or metastatic SCC of the head and neck (R/M SCCHN) who are not candidates for surgery or radiation therapy, palliative chemotherapy in combination with anti-EGFR monoclonal antibody or Pembrolizumab is recommended.

The Keynote 048 study highlighted the role of immunotherapy in the first-line treatment of R/M SCCHN. However, this study did not include the Chinese population, and its efficacy is contingent on PD-L1 expression. In terms of local control, immunotherapy does not surpass targeted treatment. Furthermore, subgroup analyses indicated that the Pembrolizumab and Pembrolizumab plus chemotherapy regimens did not demonstrate significant overall survival (OS) benefits compared to the EXTREME regimen in the subgroup with incurable, only recurrent SCCHN. Additionally, progression-free survival (PFS) was lower than that observed with the EXTREME regimen[6,7].

In 2020, the combination of anti-EGFR monoclonal antibody and chemotherapy was approved for the first-line treatment of R/M SCCHN and has since been included in medical insurance coverage. Considering the effectiveness and cost-efficiency of treatment plan and given the local recurrence of carcinoma in this patient, anti-EGFR monoclonal antibody combined with chemotherapy as the first-line treatment was deemed appropriate.

Secondly, in the case of this patient, who has multiple underlying cardiac conditions, selecting a chemotherapy regimen that is both high safety and has manageable side effects was critical. According to current guidelines, the choice lies between the EXTREME or TPEx regimens. How do we decide between these two options?

A multicenter, open-label, randomized, phase 2 trial suggested that the TPEx regimen could offer an alternative to the standard EXTREME regimen in the first-line treatment of patients with R/M SCCHN. This is particularly relevant for patients who may not be ideal candidates for upfront Pembrolizumab treatment[8]. Considering this patient's comorbidities included coronary heart disease, hypertension, and atrial fibrillation, opting for the TPEx regimen, known for its high tolerability in chemotherapy, was a judicious decision.

Thirdly, a key aspect of this case was the innovative use of growth factor in topical application. The patient had developed a large, troublesome ulcer behind the ear due to tumor erosion, characterized by constant pus discharge and bleeding. As cancer ulcers are relatively rare in clinical practice, we drew inspiration from treatments used for radiation-induced oral mucositis[1].A prospective, randomized, double-blind, controlled study by Saarilahti et al showed that for patients with head and neck cancer treated with conventional fractionated radiotherapy, sucralfate (0.04 g/mL, 4 times a day) or GM-CSF (1.5 μg/mL, 4 times a day) were randomly assigned to Gargle during radiotherapy. At the end of radiotherapy, the use of morphine in GM-CSF group was significantly reduced (p = 0.042) . The mucosal healing rate was 24% (5/21) in the GM-CSF group, but not in the sucralfate group[9].

Furthermore, research published in the Cochrane Database indicates that the total dose, frequency of use, and application duration of GM-CSF may positively correlate with its effectiveness in treating mucosal inflammation[10].

Considering this, we decided to apply GM-CSF to the patient's large ulcer, ensuring consistent high concentrations and frequency of use during treatment. Initially, due to substantial local exudation, we applied 400 μg of GM-CSF dry powder directly to the affected area. Remarkably, within a week, we noticed a significant reduction in the size of the ulcer and a substantial decrease in exudation. We then transitioned to a more conventional treatment method: dissolving GM-CSF in 30-50 mL of saline, soaking it into gauze, and applying it to the ulcer at least four times daily for 15-30 minutes each session. Additionally, we used GM-CSF-soaked gauze to pack the purulent cavity.

This approach not only significantly improved infection control but also enhanced the patient's quality of life. Moreover, it increased the sensitivity and local control rate of subsequent radiotherapy.

Fourthly, anti-EGFR monoclonal antibody maintenance therapy was implemented. This therapy plays a crucial role in inhibiting tumor growth and delaying tumor progression. It is noteworthy for its tolerability during maintenance, with 80% of patients maintaining a relative dose intensity of ≥ 80%[8, 11–13]. For this patient, continuing with anti-EGFR monoclonal antibody maintenance therapy after completing chemotherapy and radiotherapy was a prudent decision, aligning with best practice guidelines and supporting optimal patient outcomes.

Finally, when devising treatment plans, employing a multidisciplinary diagnosis and treatment model (MDT) is highly recommended. This approach considers the patient's unique circumstances, including personal preferences, overall health condition, economic status, etc. By doing so, it facilitates for selecting a treatment plan that is safe, effective, and highly compliant with the patient's needs and capabilities. The goal of this strategy is to maximize patients benefits and outcomes[14].

Abbreviations

EGFR, epidermal growth factor receptor; EXTEXTREME (platinum-fluorouracil-cetuximab); R/M SCCHN, Recurrent and metastatic head and neck squamous cell carcinoma; rhGM-CSF, recombinant human granulocyte/macrophage stimulating factor; TPEx (docetaxel-platinum-cetuximab).

Ethical approval and consent to participate

The participant in this study has provided informed written consent before enrollment.

Authors' contributions

HXY, FG and HM fomulated and implemented treatment for this patient. HM prepared figures and wrote the manuscript.

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