

A case of otoliquorrhoea secondary to immunotherapy response in head and neck cutaneous squamous cell carcinoma. When abrupt response may worry the physician

Key words: cutaneous squamous cell carcinoma, head and neck, cerebrospinal fluid leak, immunotherapy

Dear Editor,

Extension of cutaneous squamous cell carcinoma (cSCC) to the temporal bone represents a challenging scenario associated with poor outcomes¹. Scarce literature data are available to guide clinicians towards the optimal management of this disease. A dedicated TNM staging is lacking, and the modified Pittsburgh classification is typically adopted². Up to 80% of cSCC arises in the head and neck (HN) area, and the ear is part of the so called “H-zone”, an area at high-risk for tumour. Invasion of temporal bone is a condition to be considered in auricular cSCC, representing the consequence of a direct invasion of mastoid cortex or through external auditory canal (EAC) and middle ear³. Herein, we report the clinical case of a life-threatening cerebrospinal fluid (CSF) leak secondary to abrupt tumour response to immune checkpoint inhibitor (ICI) administered for the treatment of an unresectable recurrent cSCC infiltrating the temporal bone with intracranial invasion.

In March 2022, an 82-year-old man presented to the Department of Otolaryngology of the University of Brescia, complaining of a bleeding lesion in the left mastoid region. Medical history revealed that in 2008 the patient had undergone total auricectomy (with preservation of the tragal cartilage) and parotidectomy followed by adjuvant radiotherapy for a pT4aN0 cSCC of the left auricle. In addition to the sequelae of previous total auricectomy, clinical evaluation revealed a bleeding, ulcerated lesion extended between the posterior aspect of the EAC and the mastoid region, ipsilateral complete facial palsy, anacusis and suppressed but compensated vestibular function. ECOG performance status (PS) was 0. HN magnetic resonance (MR) showed a local advanced lesion, extending through the mastoid, middle ear and otic capsule to infiltrate the dura of middle and posterior cranial fossae, compressing the sigmoid sinus and invading the temporal lobe. Perineural spread along the facial nerve to the geniculate ganglion and through the petrosal nerves to the oval window with mandibular nerve enlargement was detected. The lesion was confirmed to be a recurrent cSCC at incisional biopsy. PET scan excluded regional and distant metastasis. The patient was discussed within the multidisciplinary head and neck group. Because deemed unresectable (yrT4bN0M0) and with intracranial invasion, surgery and radiotherapy were not proposed. Considering the performance score, absence of comorbidity, and extension of disease, the patient started systemic treatment with

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cemiplimab 350 mg flat dose every 3 weeks to address the most relevant symptoms, including pain and bleeding. After two cycles (6 weeks since the start of treatment), at physical examination the lesion was greatly reduced with

only a residual skin fistula with mastoid air cells and complete symptomatic resolution.

Before starting the third cycle, the patient was admitted to the emergency room because of abundant clear discharge

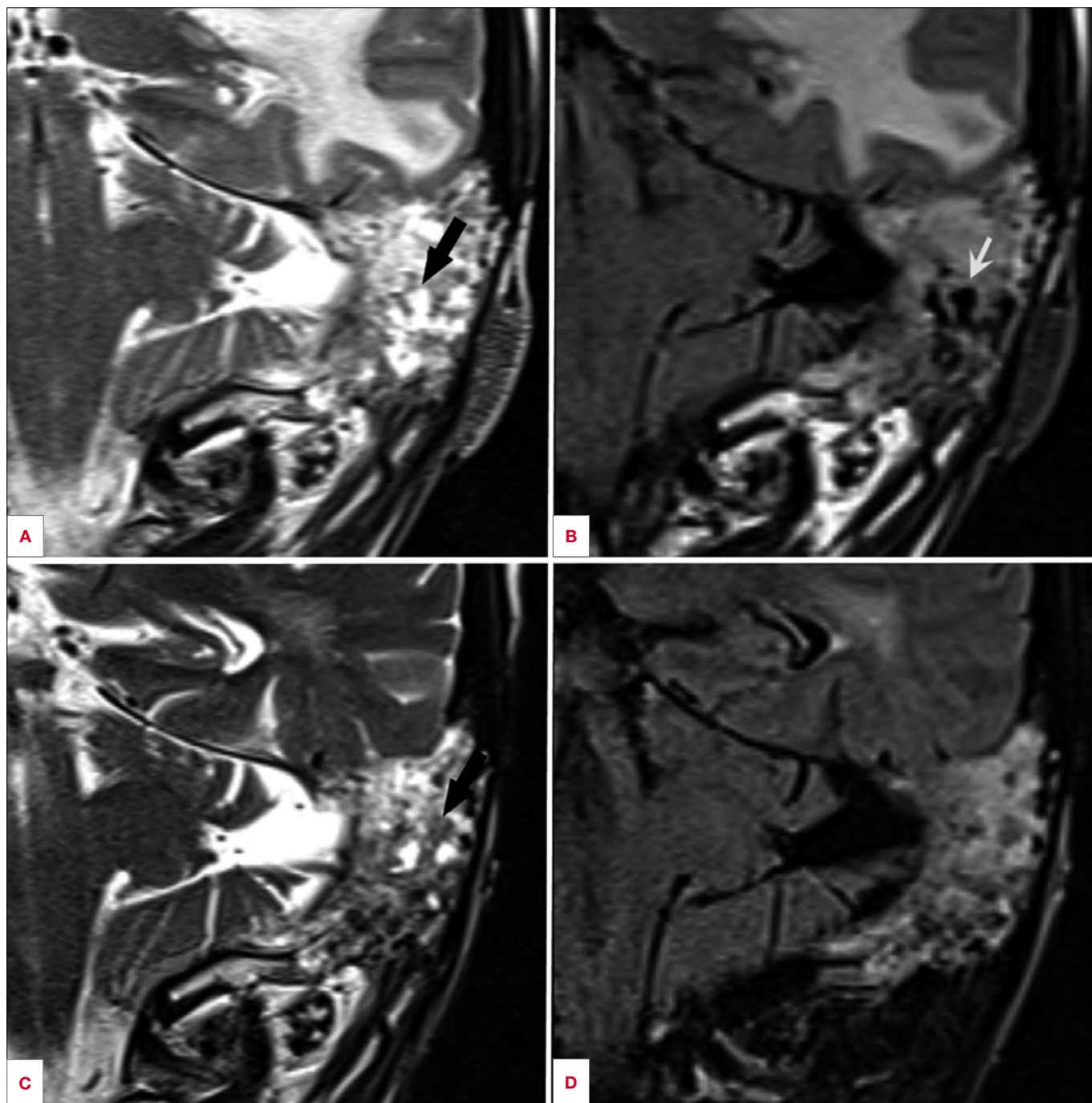


Figure 1. MRI showing mastoid cells with fluid content marked by the black arrow, hyperintense in T2-TSE sequence (A); hypointense in the sequence with saturation for cerebrospinal fluid (T2-FLAIR) (B); demonstration of CSF leak (C); resolution of CSF leak (D).

from the EAC and mastoid fistula, without neurological symptoms or signs. At otolaryngological evaluation, the suspect of CSF leak was posed, and MRI and biochemical analysis of the ear discharge were performed.

Brain MRI showed more than 90% reduction of the initial lesion, and the appearance of white matter temporal lobe oedema with ventricular system shift, extensive erosion of the left petrous part of the temporal bone with multiple bone continuity solutions, including tegmen timpani and tegmen antri, and presence within the petro-mastoid cells of areas of CSF signal intensity compatible with otoliquorrhoea (Fig. 1A,B).

The high level of beta2-transferrin found in the ear discharge confirmed the clinical and radiological diagnosis of otoliquorrhoea. The case was evaluated by a multidisciplinary team composed by otolaryngologists, oncologists, neurosurgeons, radiation oncologists, and infectious disease specialists. Considering both tumour persistence and the patient's age, surgical symptomatic repair of CSF leak was excluded given the unacceptable treatment-related morbidity and mortality risks.

A best-supportive-care strategy was started, consisting of regular medications and prophylactic amoxicillin-clavulanate antibiotic therapy. Throughout the following 2 months the patient maintained prophylactic antibiotic treatment and always remained asymptomatic, except for a few episodes of fever that were well managed with paracetamol. Medications consisted of EAC packing and sterile dressing of mastoid fistula every two days in the attempt to reduce the amount of CSF leak and were progressively discontinued when otoliquorrhoea gradually diminished until it ceased one month later. At this time, MRI showed a reduction of white matter temporal oedema, complete resolution of CSF leak, and further reduction in tumour size of the neoplastic lesion (Fig. 1C, D). On January 2023, MRI showed a progression of the disease at the temporal lobe, without signs of CSF leak, while the patient was still asymptomatic. Due to disease progression, cemiplimab 350 mg every three weeks (q3w) was restarted. Treatment has been well tolerated, without any treatment related toxicities. However, the subsequent MRI on March 2023 showed further disease progression. A second line treatment was therefore started based on carboplatin (Area Under the Curve 5, q3w) combined with cetuximab (400 mg/m² as loading dose, followed by 250 mg/m² weekly). Up to May 2023, the patient was in good clinical conditions, did not show treatment related toxicities, and the last MRI performed on 19 May 2023 showed reduction in the size of the neoplastic lesion at the temporal lobe level.

Patients with temporal bone involvement from cSCC usually present symptoms impacting the quality of life (QoL) such as painful, bleeding skin lesions, hearing and vestibular function impairment and facial palsy⁴. Surgery with or without adjuvant radiotherapy represents the mainstay of cSCC treatment^{5,6}. When the temporal bone is involved, surgery is tailored to remove the lesion with wide negative margins, preserving hearing and facial nerve function as much as possible¹. In very selected locally advanced cases, total temporal bone resection may be proposed, although the high surgical morbidity, risk of mortality and lack of a proven survival benefit make its application questionable⁷. However, intradural extension of cSCC of the auricle and mastoid area, especially when extensive as in the present case, contraindicates any surgical procedure with curative intent.

Cemiplimab showed activity and safety in locally advanced or metastatic cSCC; intriguingly, primary cSCC located at the HN level were more likely to have a good response to treatment⁸. To our knowledge, no data exist regarding the activity of ICIs in treating auricular cSCC with temporal and intradural involvement and the consequent risk of abrupt tumour responses. This rapid tumour reduction may create a CSF leak, which in the literature shows a risk of life-threatening meningitis in 4-50% of cases⁹. Management of CSF leak may include both conservative and surgical approaches. In the present case, we chose a conservative approach due to the high risk of surgical intervention.

The efficacy and tolerability of immunotherapy in the elderly will presumably increase the number of treated patients affected by cSCC located at the HN level. Therefore, physicians will face more frequent life-threatening complications such as CSF leak or damage to structures like vessels or nerves due to rapid or abrupt treatment response. Thus, we suggest close monitoring of these possible complications during treatment with an ICI in order to prevent and/or offer a prompt diagnosis of such events.

Conflict of interest statement

PB: participated in advisory boards or received conference honoraria from Merck, Sanofi-Regeneron, Merck Sharp & Dohme, Sun Pharma, Angelini, Molteni, Bristol-Myers Squibb, GSK.

All other authors declare no conflict of interest.

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Author contributions

PB; LL: conception and design or analysis and interpretation of data; PB; LL; AE; PR; MR; MT: drafting of the manuscript or revising it for important intellectual content. Final approval of the version to be published: all authors.

Ethical consideration

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee (NP4262).

Written informed consent was obtained from each participant/patient for study participation and data publication.

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