Case Report

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Extrapulmonary small cell carcinoma of the external auditory canal: a case report and review of the literature

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Abstract

Extrapulmonary small cell carcinoma (EPSCC) affecting the external auditory canal (EAC) is uncommon. We herein report a case involving a 56-year-old man with EPSCC of the EAC who had a 48-year history of recurrent purulent discharge in both ears and a 20-day history of right ear pain and hemorrhage followed by incomplete right eyelid closure and an askew mouth. He underwent surgical removal of middle ear granulation tissue, residual ossicles, and a right EAC mass. Postoperatively, pathomorphological examination combined with immunohistochemical staining supported a diagnosis of small cell carcinoma. Radiation therapy at a dose of 60.06 Gy in 33 daily fractions was completed 1 month after surgery, and synchronous etoposide–cisplatin regimen chemotherapy was performed for two cycles and four sequential cycles. One year postoperatively, magnetic resonance imaging showed no tumor in the ear; however, computed tomography showed multiple liver space-occupying lesions that were considered to indicate liver metastasis. Further chemotherapy was performed, but the patient died 15 months postoperatively. This case indicates that timely and accurate chemoradiotherapy is likely the most reasonable approach to EPSCC of the EAC given the aggressiveness of this tumor.

Keywords

Extrapulmonary small cell carcinoma, external auditory canal, thyroid transcription factor 1, chemoradiation, prognosis, liver metastasis

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Introduction

Although most small cell carcinomas are of lung origin, they can also originate outside of the lung. Extrapulmonary small cell carcinomas (EPSCCs) are defined as histologically identical neoplasms in extrapulmonary sites with no evidence of pulmonary involvement.[1] EPSCCs are uncommon, accounting for only 2.5% to 5.0% of all small cell cancers.[2,3] Only 10% to 15% of EPSCCs are found in the head and neck region. The fauces is the most frequently affected area, followed by the salivary glands and the nasal cavity and sinuses.[3–5] EPSCC involving the external auditory canal (EAC) is a rarely reported carcinoma. To the best of our knowledge, only three cases of EPSCC of the EAC have been described worldwide to date. One case was an EPSCC metastasis from a tonsil carcinoma to the EAC,[2] one was an EPSCC of the middle ear that had extended to the EAC,[6] and one originated from the EAC itself.[7] We herein report a case of hepatic metastasis following treatment of EPSCC of the EAC along with a literature review.

Case presentation

A 56-year-old man was admitted to the Second Hospital of Jilin University. He had a 48-year history of recurrent purulent discharge in both ears and a 20-day history of right ear pain and hemorrhage followed by incomplete right eyelid closure and an askew mouth. The patient had no history of alcohol abuse or hepatitis. On admission, physical examination showed no yellow discoloration of the skin or mucosa and no swelling of any superficial lymph nodes. However, his right forehead wrinkles had disappeared, his right eyelid was incompletely closed, and his right labial sulcus was shallow. A polypoid mass with a small amount of purulent secretion was covering the eardrum in both EACs, and the condition was more severe in the right EAC (Figure 1). Computed tomography (CT) showed soft tissue densities in the bilateral tympanic cavities and right EAC, bone destruction in the wall of the EAC, visible exposure of the vertical part of the right facial nerve, inability to see the right tympanic membrane, and unclear local bone of the right root of the anvil (Figure 2a and b). Magnetic resonance imaging (MRI) showed

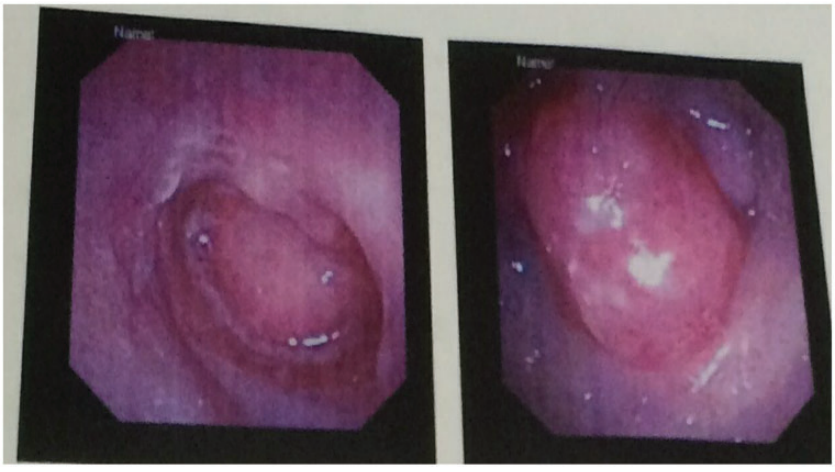

Figure 1. Electronic otoscopic examination revealed granulation tissue in the bilateral external auditory canals (more severe on the right side), with purulent secretion and no visible tympanic membrane.

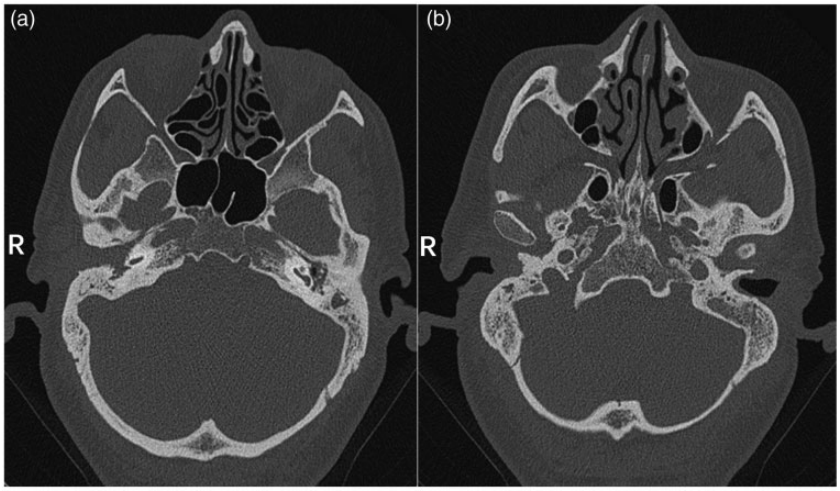

Figure 2. (a, b) Preoperative axial computed tomography scan of the temporal bone. Bone destruction was found in the wall of the right external auditory canal. Soft tissue shadows were seen in the bilateral mastoid processes, bilateral tympanic membranes, and right external auditory canal. Local bone was not clear in the right anvil, and the vertical part of the right facial nerve was exposed.

that the right middle ear was filled with long T1 and slightly longer T2 signals, and diffusion-weighted imaging showed high-intensity signals; slightly longer T2 signals were seen in the bilateral mastoids.

The initial diagnosis was right-sided chronic suppurative otitis media and peripheral facial paralysis (House–Brackmann grade IV). No abnormalities were found in routine preoperative examinations. A modified mastoidectomy was performed on the right ear. During the operation, a granuloma of about 0.8×1.0 cm was found to be blocking the EAC; it was not protruding into the tympanic cavity. The fallopian canal was destroyed, and the facial nerve was exposed in a horizontal section of about 3 mm. The middle ear granulation, residual ossicles, and right EAC mass were removed. Microscopic examination showed that the neoplastic cells were round, oval, or fusiform; had abnormal nuclei with fine granular staining; and exhibited more nuclear karyokinesis and less cytoplasm than normal cells (Figure 3a). The tumor was positive for cytokeratin (CK) (AE1/AE3), CD56, thyroid transcription factor 1 (TTF-1), CK7, and epithelial membrane antigen (Figure 3b and c) and negative for CK20, CK5/6, P40, P63, chromogranin A, synaptophysin, vimentin, S-100, and carcinoembryonic antigen. The proliferation activity (positivity for Ki-67) was 95% (Figure 3a and c). Postoperatively, routine pathomorphological examination combined with immunohistochemical staining supported a diagnosis of small cell carcinoma. No cancer cells were found in the left ear canal tissue. At admission, lung CT showed a streaky high-density shadow in the upper lobe of the left lung, and repeated sputum cytology examination after surgery showed no malignant cells. The patient declined positron emission tomography (PET)–CT examination and a second extended surgical resection. Radiation therapy at a dose of 60.06 Gy in 33 daily fractions was completed 1 month after surgery, and synchronous etoposide–cisplatin regimen chemotherapy was performed for 2 cycles and 4 sequential cycles. One year postoperatively (2 months after the end of

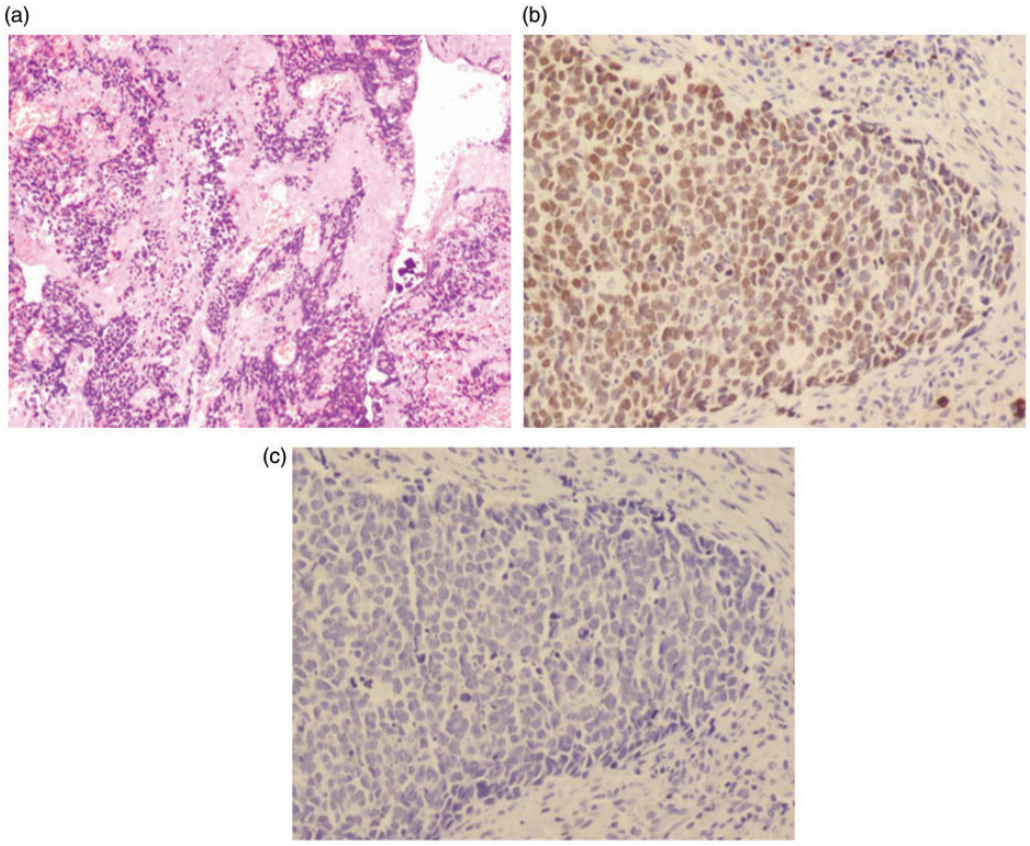

Figure 3. (a) On microscopic examination, the neoplastic cells in the subepidermal dermis were round, oval, or fusiform; nuclear subnormal, stained fine and granular, with more nuclear schizotaxis and less cytoplasm (hematoxylin and eosin (HE), ×100). (b) Thyroid transcription factor 1 was positive (HE, ×200). (c) Cytokeratin 20 was negative (HE, ×200).

the last chemotherapy), MRI showed no tumor in the right ear (Figure 4); however, upper abdominal CT showed multiple liver space-occupying lesions that were considered to indicate liver metastasis (Figure 5). PET–CT showed no pulmonary neoplasm. Further chemotherapy was performed in another hospital, and the patient died 15 months postoperatively.

Discussion

To the best of our knowledge, small cell carcinoma is the most invasive form of neuroendocrine carcinoma as indicated by the World Health Organization.[8] Small cell carcinoma is synonymous with small cell neuroendocrine tumor, oat cell cancer, anaplastic small cell tumor, and small cell neuroendocrine cancer of intermediate type.[4] Although most small cell cancers originate from the lung, they can also originate in extrapulmonary locations.[9] EPSCC can occur in any tissue or organ outside the central nervous system.[9] The esophagus is the most common organ in which EPSCC occurs, comprising 53.0% to 71.0% of all EPSCCs.[9] Whether any lifestyle-related elements increase the risk of EPSCC remains unclear.[9] Small cell lung cancer (SCLC) is

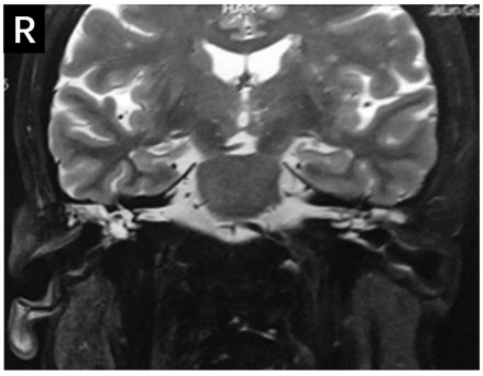

Figure 4. One year after surgery (2 months after the end of chemotherapy), magnetic resonance imaging of the middle ear showed no local tumor recurrence in the right ear.

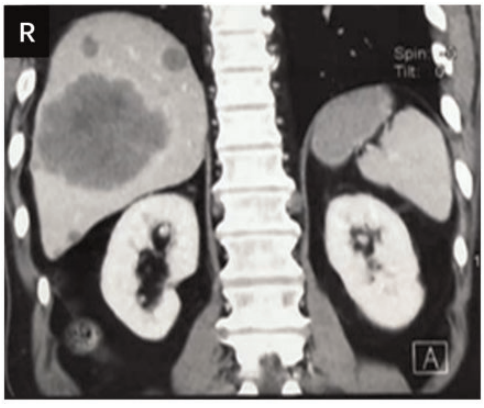

Figure 5. One year after surgery (2 months after the end of chemotherapy), upper abdominal computed tomography showed multiple space-occupying lesions in the liver.

consistently associated with smoking, and approximately 30% of patients with EPSCC are nonsmokers.[10] Our patient denied a smoking history. Some clinical features of EPSCC are similar to SCLC; however, the biological behavior, etiology, rate of brain metastasis, and prognosis of EPSCC are different from those of SCLC.[9] According to the three cases ESCC of the EAC reported to date, the most common clinical signs of EPSCC occurring in the EAC are otorrhea, facial paralysis, otalgia, and hearing loss. Examination of the EAC can reveal abnormal granulation tissue. These symptoms are similar to those of otitis media.

Diagnosis of small cell carcinoma depends on histopathologic and immunohistochemical examinations. Microscopic examination of these tumors reveals a large number of small- to intermediate-sized cells, necrosis, a high mitotic rate, and lack of neurofibrillary stroma.[8] Electron microscopy generally displays tightly packed nuclear secretory granules and abnormal cellular processes. These tumors also consistently stain positively for at least one neuroendocrine indicator, such as synaptophysin, CD56, neuron-specific enolase, or chromogranin A.[7,8,11,12] CD56 is found at a high level in both small cell carcinoma and its metastatic lymph nodes without organ specificity, and it can serve as a useful diagnostic marker of small cell cancer.[13] In one study, the monoclonal antibody 123C3 to CD56 diffusely stained a majority of small cell cancers with a strong membranous pattern (sensitivity of 0.99), and the specificity of neuroendocrine markers in the diagnosis of small cell cancer was 0.95 while that of 123C3 was 0.94.[14] The histologic morphology of EPSCC occurring in the EAC resembles that of SCLC.[7] Our patient's tumor was positive for CD56, which is consistent with the above conclusion. Another study indicated that CK20 can serve as the preferred alternative in an antibody panel to confirm or eliminate a gastrointestinal tract source.[15] Cutaneous small cell cancer must be distinguished from Merkel cell carcinoma (MCC).[16] CK20 positivity is a significant diagnostic indicator for MCC, which is also negative for TTF-1.[17,18] The immunohistochemical pathologic examination in our case showed TTF-1 positivity and CK20 negativity, allowing us to exclude cancer

metastasis from a gastrointestinal tract origin and MCC. Despite the TTF-1 positivity, there was no imaging evidence to support a primary tumor in the lung; therefore, we believe that our patient had a primary small cell carcinoma of the EAC.

Treatment of small cell carcinoma is ordinarily based on a combination of radiotherapy and chemotherapy. The treatment of EPSCC is generally similar to that of SCLC. The combination of chemotherapy and radiotherapy with surgical resection may improve the efficacy of EPSCC.[11] However, Pointer et al.[19] demonstrated that adding surgery to chemoradiotherapy failed to prolong the survival time of patients with small cell carcinoma of the head and neck. Systemic chemoradiotherapy mostly influences survival.[5] The incidence of brain metastasis of EPSCC is significantly lower than that of SCLC; hence, prophylactic cranial irradiation is not recommended.[5] However, an exception is that EPSCC originating from the neck and head region is associated with a higher incidence of brain metastasis, making it necessary to add prophylactic cranial irradiation.[5] The 56-year-old man in the present case had undergone surgery, but the benefit was minimal.

Small cell carcinoma of the head and neck has a poor treatment outcome because it tends to be partly invasive and associated with systemic metastasis.[2] The benefits of thorough clinical inspection are enormous for patients with small cell carcinoma of the head and neck, and such inspection should include CT/MRI of the head and neck, MRI of the brain, a PET scan, bronchoscopy for sputum examination, and possible bone marrow biopsy.[4]

Because primary or metastatic EAC often resembles chronic suppurative otitis media, the diagnosis of EAC carcinoma is often not verified until $\geq$6 months after the emergence of symptoms and physical signs.[9] Research has shown that small cell tumors of the head and neck are rare, aggressive and usually appear in the terminal stages; 61% of patients present with stage III, IVA, or IVB carcinomas, and 22% of patients appear with metastatic disease.[19] Metastasis of ESPCC from the EAC to other sites is infrequent; most common primary tumors arise from the breast, lung, prostate, and kidney.[7,20] In our patient, no primary tumors were found in these areas; therefore, we believe that our patient had an EPSCC originating from the EAC. The 5-year survival rates of patients with small cell carcinoma of the head and neck and other EPSCCs are reportedly $<$15%.[21,22] In one study, the overall survival of patients with small cell cancer of the head and neck was 20.3 months.[19] Small cell cancer of the head and neck appears to have a prognosis similar to that of SCLC.[19] Pointer et al.[19] showed that among patients with small cell carcinoma of the head and neck, those with early-stage tumors (stages I and II), those with locally advanced tumors (stages III, IVA, and IVB), and those with metastatic disease had a median survival of 49.0, 22.3, and 10.0 months, respectively and a 2-year overall survival rate of 69.1%, 48.3%, and 15.7%, respectively. Our patient underwent surgical resection, chemotherapy, and radiotherapy and died of his disease 15 months later. This is consistent with the survival rate reported in the literature.[19]

Small cell cancer of the EAC is peculiar, and many otolaryngologists have little understanding of it; thus, misdiagnosis easily occurs. The present report has highlighted the nonspecific symptoms of EAC, such as pain, bleeding, otorrhea and facial paralysis. Because of the patient's 48-year history of purulent ear discharge, a preoperative misdiagnosis of EAC inflammatory granulation was made. Even with surgery, radiation, and chemotherapy, the patient still developed liver metastasis 1 year after surgery and died 3 months later. Therefore, otolaryngologists should be

more vigilant of the fact that (1) elderly patients may develop rapid growth of the EAC neoplasm within a short period of time along with radiographic bone destruction, and a preoperative biopsy should be performed to guide the scope of the operation; and (2) once a pathological diagnosis of small cell carcinoma has been obtained, whole-body PET–CT examination is strongly recommended to identify any metastases.

Conclusions

EPSCCs infrequently occur in the EAC and have an unfavorable prognosis. Therefore, timely and accurate chemoradiotherapy seems to be vitally important. Nevertheless, rapid liver metastasis occurred in this 56-year-old patient despite comprehensive treatment, indicating that this tumor is considerably aggressive. Further research is needed to establish more effective treatments.

Authors' contributions

MZ and JYW were responsible for the study conception and design. JYW and DQL drafted the initial manuscript and revised it critically for important intellectual content. YDM and YYG analyzed and interpreted the data. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics and consent

This case report was approved and supervised by the ethics committee of The Second Hospital of Jilin University. The patient provided written informed consent for publication of his clinical details and clinical images.

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