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Squamous Cell Carcinoma of the Temporal Bone Arising from Cholesteatoma: A Case Report and Review of the Literature

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Abstract

Objective Present a case of squamous cell carcinoma of the temporal bone (SCCTB) arising in a 61-year-old female with a prior history of cholesteatoma and persistent otologic symptoms and review the current literature regarding this disease presentation.

Setting Tertiary academic center.

Patient A 61-year-old female with a history of left ear cholesteatoma for which she had undergone surgery 54 years prior. The patient presented with a persistent history of otorrhea since first surgery and developed exacerbation of symptoms just prior to presentation at our department. The clinical picture was highly suspicious of cholesteatoma recurrence. However, the biopsy was consistent with squamous cell carcinoma.

Intervention Surgical debulking of the lesion was followed by a brief course of radiation therapy later halted by the patient due to side effect intolerance.

Conclusion SCCTB may arise from cholesteatoma. A high index of suspicion for SCCTB should be maintained in patients with a prior history of cholesteatoma and evidence of a temporal bone mass with persistent otologic symptoms.

Keywords
- squamous cell carcinoma of temporal bone
- cholesteatoma
- skull base
- chronic otorrhea

Introduction

Cholesteatoma is a relatively common benign disease of the middle ear. By contrast, squamous cell carcinoma of the temporal bone (SCCTB) is a rare diagnosis and has a relatively poor prognosis, particularly in advanced stages.[1] A few reports have implicated cholesteatoma as an etiologic factor for SCCTB.[2–5] However, a direct association between both entities (i.e., progression from cholesteatoma to squamous cell carcinoma [SCC]) remains unproven.

Case Report

We present a case of SCCTB in a 61-year-old female who had undergone surgery for a left ear cholesteatoma 54 years prior. The patient presented to our institution with a long history of left-side hearing loss, persistent ipsilateral otorrhea, and vertigo. All symptoms had reportedly been present since just after her first ear surgery but had intensified a few months before the latest encounter. She had no personal or significant family history of malignancy. Physical

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examination revealed tympanic membrane perforation, purulent otorrhea, and mild canal edema with granulation tissue. No mastoid tenderness or fluctuance was present.

A computed tomography scan was significant for an expansile left temporal bone (TB) lesion and tegmen erosion. A subsequent magnetic resonance imaging (MRI) scan lesion extension into the dura overlying the left cerebellar hemisphere. No evidence of lymphadenopathy was present on imaging or physical examination. While the clinical picture was highly suspicious of cholesteatoma recurrence, imaging was concerning for malignancy. Thus, the decision was made to proceed to the operating room jointly with neurosurgery for a combined left middle cranial fossa (MCF) approach and mastoidectomy for biopsy with possible total resection.

Neurosurgery performed a MCF approach. During osteoplastic flap elevation, the lesion was noted to involve the bony flap and the lateral skull base. The lesion was probed and was noted to extend into the left jugular bulb, sigmoid sinus, and posterior fossa dura, as well as to be continuous with the skin of the external acoustic canal (EAC). The facial nerve and vestibule were both uninvolved. A small portion was sent for intraoperative pathology consultation. Diff-Quikstained squash preparation demonstrated numerous dispersed and cohesive squamous cells with marked nuclear atypia and the hematoxylin and eosin stained histology slide confirmed SCC. Given the extent of the disease and the low likelihood of improving the patient's prognosis with aggressive TB resection, only conservative lesion debulking, with preservation of the EAC, was performed. The remainder of the excised tissue was submitted for permanent pathologic evaluation. Microscopic examination revealed invasive keratinizing well-differentiated SCC that invades the stroma and bone, with adjacent areas of dysplastic squamous epithelium (see ►**Fig. 1A–D**). Additionally, there were focal areas with "flaky" keratin debris, fibrosis, and chronic inflammation, suggestive of a cholesteatoma (see ►**Fig. 1E–F**). For research purposes, human papillomavirus (HPV) testing was performed on the tissue sample. There was no staining with p16 immunostain, and HPV DNA in situ hybridization for family 6 (types 6 and 11) and family 16 (types 16, 18, 31, 33, and 51) was negative.

A postoperative positron emission tomography scan revealed no evidence of distant metastasis or another source of primary focus. Following the University of Pittsburgh Staging System, the final pathologic stage was pT4 pN0 $_{PM}$0, given the TB and dural involvement. Adjuvant radiotherapy was then pursued; however, it was halted early due to side effect intolerance by the patient. The patient opted to undergo palliation treatment instead. The patient was still alive at the time of submission.

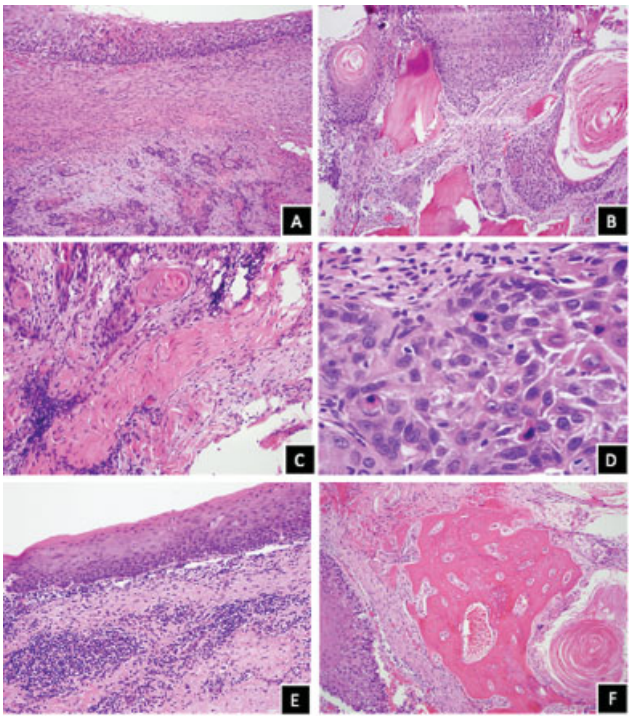

Fig. 1 Invasive keratinizing squamous cell carcinoma (**A–D**) with background cholesteatoma (**E–F**). Microscopic examination showing keratinizing squamous cell carcinoma with invasive nests of neoplastic cells surrounded by desmoplastic stromal reaction (**A**, hematoxylin and eosin [H&E] at 10x), temporal bone invasion (**B**, H&E at 10x), and perineural invasion (**C**, H&E at 20x). The carcinoma was moderately differentiated with pleomorphic nuclei and numerous dyskeratinocytes (**D**, H&E at 60x). Adjacent to the invasive component there is a background of squamous epithelium, fibrosis, chronic inflammation, and flakey keratin with foci of dysplasia and bone destruction (**E**, H&E at 10x).

Discussion

Primary SCCTB is a rare condition, with an estimated one to six cases per 1 million population per year worldwide and comprising less than 0.2% of all head and neck tumors.[6,7] However, of the different types of tumors to involve the TB, the most common is SCC, comprising 80% of all malignancies in this location.[8]

Patients with SCCTB often present between 55 and 65 years of age.[9] There is a reported female predominance in cancers of the external auditory canal, in contrast to those of the external ear pinna, which shows a male predominance.[3,9] Symptoms of SSCTB are relatively nonspecific, with chronic otorrhea, otalgia, hearing loss, and bleeding dominating the clinical picture.[2,3,6] The overlapping differential diagnosis for these nonspecific symptoms contributes to the difficulty and a delay in diagnosis often encountered in SCCTB.

Diagnostic imaging is paramount in the evaluation of chronic otorrhea or other chronic ear symptoms because it cannot only help clarify diagnosis; if malignant, it can lead to earlier diagnosis and guide staging.[8] The extent of the disease is determined by the Pittsburgh staging system, which is based on location and degree of bone invasion at time of presentation.[10] However, other mass-like lesions in the ear, including cholesteatomas, may cause bone destruction and mimic malignancy. Imaging can be useful to differentiate this benign process from a more malicious one. Cholesteatomas do not enhance with gadolinium on T1, whereas most tumors

Table 1 Summary of cholesteatoma-associated SCCTB literature

	Age/sex	Chief complaint	Imaging	Surgery	Pathology	Cholesteatoma history	Adjuvant treatment	Outcome
Yanez-Siller et al, 2021	61 years/female	Chronic persistent otorrhea	CT showed an expansile left TB lesion with erosion and involvement of the dura overlying the left cerebellar hemisphere.	Lesion debulking	Invasive well differentiated SCC with high-grade dysplasia of surrounding squamous epithelium	History of cholesteatoma. History of cholesteatoma treated with surgery (age 7)	Radiotherapy (halted early due to side effect intolerance)	14 months after surgery, alive without disease progression
Ben Gamra et al. 2015[8]	42 years/male	8 months of progressive intractable otorrhea, tinnitus, and progressive hearing loss	MRI showed erosion of the EAC, tympanic bone and facial nerve	MRI showed erosion of the EAC, tympanic bone, and facial nerve Subtotal petrosectomy including a portion of the facial nerve, total parotidectomy, and level II-V neck dissection	Invasive SCC with 1 of 16 positive lymph nodes	Concurrent attic cholesteatoma	Radiotherapy	12 months after surgery, alive without recurrence
Rothschild et al, 2009[3]	71 years/male	Fetid hemorrhagic otorrhea	N/A	Subtotal petrosectomy	Invasive moderately differentiated SCC with adjacent high-grade dysplasia of squamous epithelium	History of cholesteatoma treated with surgery (age 16)	Radiotherapy	12 months after surgery, dead from unrelated cause
Takahashi et al 2005[4]	43 years/male	Sudden onset of unilateral facial palsy	Soft tissue density in right tympanic cavity and antrum with extensive bony erosion of the MCF and petrous bone with erosion into dura	Mastoidectomy	Invasive SCC	Concurrent cholesteatoma	Chemoradiotherapy	20 months after surgery, alive without disease recurrence
Westerman et al, 1981 [15]	25 years/male	Chronic purulent otorrhea	X-ray: sclerotic mastoid with no evidence of cholesteatoma or bony erosion	Atticoantrostomy and wide local excision of tympanic membrane	Invasive SCC	History of cholesteatoma (presumptive)	Radiotherapy	11 years after surgery, alive without disease recurrence
	38 years/male		N/A		Invasive SCC			

(*Continued*)

Table 1 (*Continued*)

	Age/sex	Chief complaint	Imaging	Surgery	Pathology	Cholesteatoma history	Adjuvant treatment	Outcome
Coachman 1951 [16]		Unilateral facial paralysis and associated 1 cm fistulous left mastoid erosion		Radical mastoidectomy		History of cholesteatoma (age 2)	Radiotherapy (total dose of 2000 X-rays)	6 months after surgery, alive without disease recurrence

Abbreviations: CT, computed tomography; EAC, external acoustic canal; MCF, middle cranial fossa; MRI, magnetic resonance imaging; N/A, no data available; SCC, squamous cell carcinoma; SCCTB, squamous cell carcinoma of the temporal bone.

will enhance with gadolinium. Furthermore, cholesteatomas will show high intensity of diffusion weighted images compared with other tumors.[8] Contrast-enhanced MRI can demonstrate perineural disease and/or dural involvement that would be seen in a malignant and not a benign condition.[1,6]

SCC is the most common malignancy to involve the TB, followed by basal cell carcinoma and adenoid cystic carcinoma.[1] SCCTB can be primary or secondary. Primary SCCTB is most common (60–80%), arising from SCC of the EAC and/or the middle ear.[11] Secondary SCCTB is more uncommon, often as an infiltrating tumor from periauricular skin or salivary glands. Histologically, the tumors of the ear are classified according to the 2017 fourth edition of the World Health Organization Classification of Tumors of the Head and Neck.[12] SCC is the most common malignancy of the ear. Those arising from the pinna have a different pathogenesis and prognosis compared with those arising within the EAC, which are most common, and middle ear, which are much less common.[11]

The etiology of primary SCCTB from the ear canal is likely multimodal. Ionizing radiation, often secondary to radiotherapy for nasopharyngeal tumors, is an extremely rare but widely accepted risk factor, with a rate 1000x greater than the general population.[9] However, risk factors related to chronic inflammation, for instance associated with trauma, infection, or surgery to the EAC or middle ear, are more common but controversial.[13] Importantly, cholesteatoma, a relatively common form of chronic otitis, has also been implicated in the development of primary SCCTB.[14] A total of six cases (five from the literature in addition to the current case report) of SCCTB associated with cholesteatomas are reported in the literature (►**Table 1**).[3,4,8,15,16]

Several mechanisms of how cholesteatoma may progress to SCCTB have been proposed, with most believed to result from localized chronic inflammation.[2] Chronic inflammation is an accepted and well-known risk factor for SCC in many parts of the body. Infection is commonly implicated as the cause of inflammation. This can be caused by certain bacteria, such as antibiotic-resistant and/or biofilm-forming pathogens, particularly *Pseudomonas aeruginosa,* which can induce squamous cell proliferation.[17] Additionally in addition to bacteria, a few reports have considered HPV infection as a possible cause of cholesteatoma.[18–20] HPV has also been reported in middle ear carcinomas.[21,22] At the molecular level, common to other malignancies, alterations in the cell cycle, namely, uninhibited telomerase activity, inactivation of tumor suppressors, and upregulation of growth factor receptors, are thought to govern the progression toward SCCTB.[2,23] Despite a variety of theories, a direct etiologic and pathophysiologic association between these two TB disease entities remains elusive.

Traditionally, the standard treatment includes surgical excision with or without TB resection, followed by adjuvant radiotherapy, with a recommended total dose of 50 to 70 Gy.[8] Chemotherapy is not a part of standard treatment as the occurrence of metastases is uncommon.[13] By contrast, a few publications have reported primary radiation as an adequate alternative, reporting recurrence and survival rates similar to

a combined (i.e., surgery plus radiation) approach.[2] Multidisciplinary approaches employing extensive surgical excision and adjuvant chemoradiotherapy have been proposed with varying results.[4,6] Others suggest reserving chemoradiotherapy for settings where surgery cannot be performed.[13] Given the scarcity of studies, which have been primarily limited to small case series without control subjects, a general consensus on the optimal strategy remains to be reached and management approaches vary widely between institutions and authors.[2]

Overall, long-term survival for SCCTB is rare and directly related to the age at presentation.[12] The prognosis for SCCTB using the University of Pittsburgh staging system has a 2-year survival of 95 to 100% in T1 and T2 patients; unfortunately, tumors are often aggressive, destructive, and diagnosed at later stages, which have a much more dismal prognosis, with a 2-year survival of 50% in T3 and 15% in T4 patients.[14] This results not only from its aggressive nature but also from frequent delayed diagnosis resulting in late-stage disease at presentation. Additionally, the proximity to critical neurovascular structures complicates surgical management.[2]

Our patient had undergone surgery for the removal of cholesteatoma, more than 50 years prior to presenting for evaluation at our department, with associated decade-long nonspecific symptoms resembling a chronic inflammatory ear condition, and a TB lesion suspicious of recurrent cholesteatoma. Despite being a benign condition, the propensity for cholesteatomas to recur and to invade bone often mimics a malignancy. Ironically for this reason, true malignancy may go under- or misdiagnosed in this particular area, as presented here, were biopsy of the lesion was consistent with SCC.

Our findings suggest an etiologic association between cholesteatoma and SCCTB, something strongly previously speculated in several prior published reports.[3–5] Although firm conclusions remain to be drawn, given the overlap in clinical presentation, consideration of the etiologic relationship is warranted in patients with recurrent, persistent, or worsening otologic symptoms, associated with long past history of cholesteatoma with or without prior surgical management.

Conclusion

The present case report supports the theory that SCCTB may arise from cholesteatoma.[2] Only a few similar cases have been reported in the literature.[3–5,8,15,16] A high index of suspicion should be employed in patients with a prior history of cholesteatoma and evidence of a TB mass and persistent otologic symptoms. Further research is warranted to elucidate an etiologic relationship among both disease entities.

Note
Portions of this work were presented as a poster presentation at the 30th Annual North American Skull Base Society Meeting, San Antonio, Texas, February 7–9, 2020.

Disclosure
The authors have no personal, financial, or institutional interest to declare.

Conflict of Interest
None declared.

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