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Late onset middle ear neuroendocrine tumor presenting with distant metastasis

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ABSTRACT

Tumors of the ear with neuroendocrine features are a very rare group of neoplasms, with neuroendocrine adenoma representing the more frequent entity found; the prevalence of middle ear neuroendocrine tumors is so low that it has never been determined exactly.

Herein we describe the case of a 74 years old woman who presented a pure moderately differentiated middle ear neuroendocrine tumor after a long history of adhesive otitis media. Patient abruptly developed otalgia and a sense of plugged ear. Otomicroscopy revealed a polypoid mass of the external auditory canal. On histopathologic exam a neoplastic proliferation of monomorphous epithelioid cells arranged in small nests and clusters was present, being positive to cytokeratins, chromogranin, synaptophysin and CD56, and negative to S100. Ki-67 proliferation index was 20%. The lesion was diagnosed as a moderately differentiated neuroendocrine tumor (NET grade 2). CT and PET scans highlighted the concurrent presence of locoregional lymph nodes involvement but also at distance liver metastases.

The patient underwent chemotherapy and liver repetitions were treated locally. At the time of the writing the patient is in good general condition.

We describe an exceeding rare case of a moderately differentiated neuroendocrine tumor with primitivity in the middle ear and concurrent distant metastasis at the time of the diagnosis.

This case represents a clinical and histological challenge, for the rarity of the lesion and the aspecific symptoms of the patient.

1. Introduction

Neuroendocrine neoplasms (NENs) of head and neck region represent a rare group of epithelial lesions [1], with heterogeneous clinical, pathological and prognostic features. Moreover, the complexity of this district, with different subsites, leads to difficulties in uniforming classification and management of the majority of these neoplasms.

The 4th edition of World Health Organisation (WHO) classifies neuroendocrine neoplasms into three grades of differentiation - well differentiated (carcinoid, neuroendocrine tumors - NET - grade 1), moderately differentiated (atypical carcinoid, neuroendocrine tumors - NET - grade 2) and poorly differentiated (neuroendocrine carcinomas - NEC) neoplasms, with the latter further subclassified into small cell carcinoma (SCNEC) and large cell carcinoma (LCNEC) [2].

Neuroendocrine neoplasms are discussed in the larynx section as the 4th WHO edition reports the different neoplasms according to the subsite where they are more frequently found. Indeed, in the chapter dedicated to middle and inner ear neoplasms only one lesion with neuroendocrine features is described, which is middle ear adenoma, as it is a site specific tumor. Middle ear adenoma is a benign lesion, with low grade potential of recurrences and local metastasis, composed of a dual cell population of epithelial exocrine cells and neuroendocrine elements [2]. Nomenclature is still controversial, as this lesion is often called "neuroendocrine adenoma", "adenomatous tumor", "middle ear adenoma with neuroendocrine differentiation" and "carcinoid of the middle ear". The latter terminology is confusing, as "carcinoid" refers to a

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malignant, well differentiated pure neuroendocrine neoplasm. Although some authors [3] suggest that neuroendocrine adenoma and carcinoid must be considered as the same entity, others [4] prompt that they are two different neoplasms. The latter theory is supported by the risk of distant metastatic disease occasionally found in literature in cases of middle ear carcinoid (NET grade 1) which is never reported in neuroendocrine adenoma [5,6]. Moreover, it is possible that primary middle ear tumors with neuroendocrine features which develop distant metastasis could be more aggressive lesions than neuroendocrine adenomas and could behave as atypical carcinoids, being classified as carcinoids for the localization of the primary tumor.

Herein we present an exceedingly rare case of a late onset pure primitive middle ear moderately differentiated NET of the middle ear occurring over a long lasting chronic fibro-adhesive middle ear otitis, with local lymph nodes and, overall, distant metastasis at the time of the diagnosis.

2. Case report

M.A., a 74 years old woman, had been followed for 30 years at the Audiology Unit of Careggi University Hospital in Florence for recurrent otitis since her childhood. At the age of 38 the patient started being regularly studied for a left moderate conductive hearing loss not worsening over time except for the presbycusis component. Since the first evaluation, the otomicroscopic examination showed a very mild retraction of the whole right eardrum and a subtotal atelectasis of the left tympanic cavity as a consequence of a chronic fibro-adhesive otitis. ENT examination was otherwise negative. The patient remained stable until she was 68, when she abruptly started complaining of pain and a sense of plugging in the left ear, without fluid leaking. An otomicroscopy was performed, revealing the presence of a soft, not bleeding, hyalinoid, polypous-like lesion located in the postero-superior area of the external auditory canal. Pure tone audiometry showed a left mixed hearing loss, with the air conduction hearing threshold slightly worsened compared to the one detected in the previous exams and with a stable bone conduction hearing threshold. Tympanogram showed a C-type pattern in the right ear and a B-type pattern in the left ear. The patient started local and general antibiotic and corticosteroid therapy without clinical improvement thus a cranial CT scan was performed, showing the presence of an isodense material occupying the epitympanum and the mastoid, encasing the ossicles, without clear bone erosion and extending into the outer ear canal, occupying it almost completely (Fig. 1).

In the clinical suspect of a chronic hyperplastic otitis media, a canal wall-up mastoidectomy was programmed. At surgery, the mastoid and the tympanic cavity were diffusely occupied by a soft, grey-pink redundant tissue that was not surely ascribable to a hyperplastic flogosis. This material actually encased the ossicles, with partial resorption of the stapes crura. After a complete toilette of the middle ear cavities, an ossiculoplasty was also performed in order to preserve the hearing function. The material was sent for histological examination.

Microscopic exam showed middle ear epithelium composed of a normal single layer of ciliated cells and a deep neoplastic proliferation of monomorphous epithelioid cells arranged in small nests and clusters. Neoplastic elements showed cuboidal shapes and mild pleomorphism, with uniform round to oval nuclei and finely dispersed chromatin. Mitotic figures were rare and necrosis was absent. Immunohistochemistry showed uniform positive stain to pan-cytokeratin cocktail (clone AE1/AE3/PCK2 and CAM5.2, Ventana, Roche) chromogranin (clone LK2H10, Ventana, Roche) synaptophysin (clone MRQ40, Ventana, Roche) and CD56 (MRQ-42, Ventana Roche), and negative stain for S100 (clone 4C4.19, Ventana Roche). Ki-67 (clone 30-9, Ventana Roche) was 20%. The tumor was diagnosed as a moderately differentiated neuroendocrine carcinoma. Immunohistochemistry for TTF1(clone SP141, Ventana Roche), CDX2 (clone EPR2764Y, Ventana, Roche) and CK20 (SP33, Ventana, Roche) were performed, with negative results, in order to exclude lung and gastrointestinal primitivity (Fig. 2).

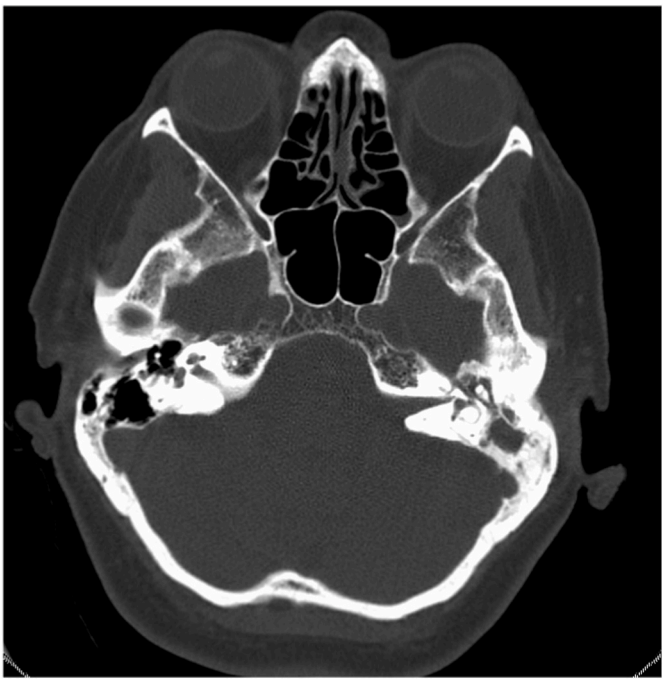

Fig. 1. On the left side, axial CT scan shows a total opacification of mastoid cells and the presence of isodense tissue in the middle ear cavity without signs of ossicular chain erosion. Labyrinthine structures do not show any involvement.

For staging purposes, an enhanced total body CT scan and a total body FDG PET were performed; these exams showed multiple laterocervical and abdominal metastatic lymph nodes as well as several liver localizations. Moreover, a 68Ga-DOTANOC PET showed a high, diffuse expression of somatostatin receptors in all the lesions evidenced (Figs. 3 and 4).

After this diagnosis, the patient started chemotherapy with Temodal and Capecitabine. The CT scan, performed after 4 cycles of chemotherapy, revealed a stable disease. The patient therefore started maintenance therapy with Everolimus and Somatostatin analogue in a clinical trial that continued until December 2017. A liver biopsy confirmed the same histological and immunohistochemical features of the primary middle ear tumor, with Ki-67 = 15% that corroborated the conviction of the metastatic nature of the disease. Liver metastases were treated with a transarterial chemoembolization with Doxorubicin.

Regular follow up exams were conducted over time and, one year after the surgical removal of the primary tumor, two new lymph nodes localizations were found, appearing hard and fixed on the deep soft tissues, being one in the preauricular region and the other behind the mandibular angle.

In a 5-year follow-up period, the left outer ear canal was free of disease and the appearance of the tympanic membrane and middle ear cavity remained of the atelectasis type. Audiometric and impedance findings did not change overtime. Cranial, petrous bone and maxillofacial direct and enhanced CT scans, performed during follow up, evidenced stable lesions as concerned to middle ear pathology and locoregional repetitions, the latter sometimes increasing in number and localization sometimes reducing, especially with regard to the intraparotid nodularities.

The patient remained stable until 2018, when abdominal CT scan demonstrated the progression of the disease in the liver and in the abdominal lymph nodes, requiring a new line of chemotherapy and radiometabolic treatment.

In January 2020 a CT scan revealed a further progression of the liver metastasis and the patient was submitted to a new hepatic needle biopsy which confirmed the metastatic nature of the disease. The patient thus

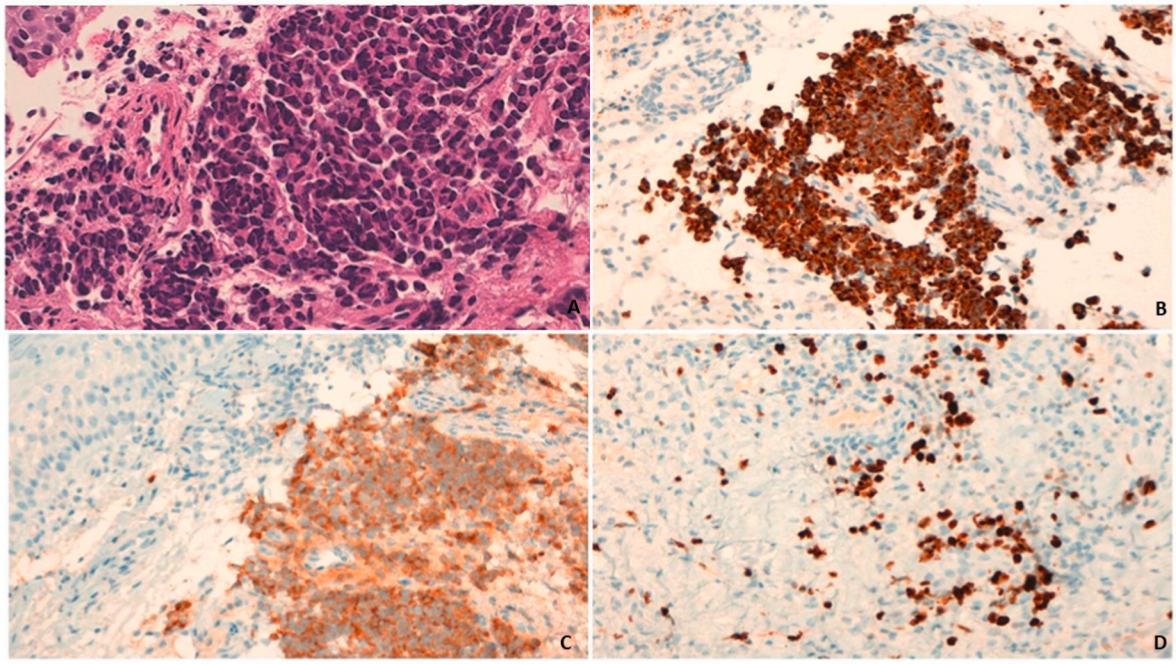

Fig. 2. A, neoplastic cells with nested and solid pattern of growth; monotonous cell elements with high nuclear/cytoplasmic ratio; B–C, cells show positivity to chromogranin and synaptophysin markers, confirming neuroendocrine nature of the lesion; D, Ki-67 is 20%.

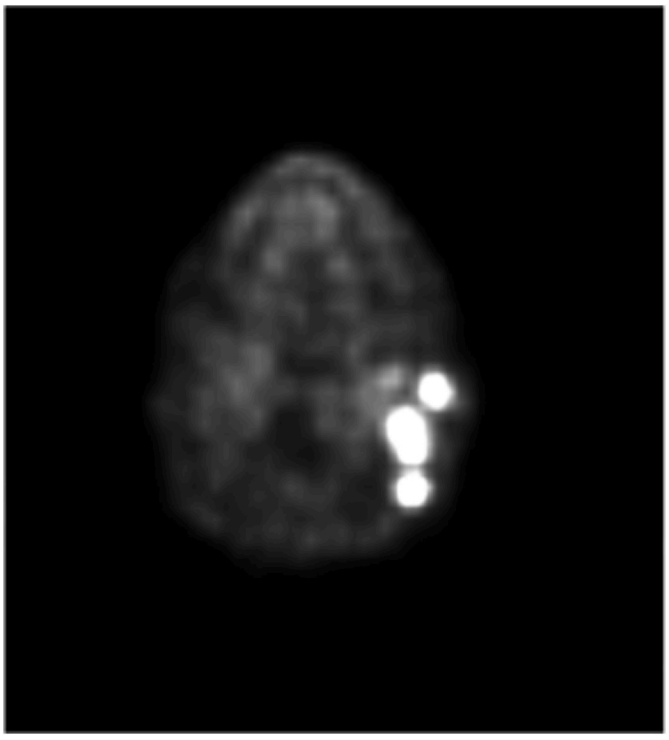

Fig. 3. Head and neck PET scan highlights left laterocervical and preauricular lymph nodes.

started a new line of chemotherapy with Oxaliplatin and 5-Fluorouracil, that is still in progress.

At the last follow up in November 2020, six years after the diagnosis, the otological, clinical and radiological examinations did not highlight any disease recurrence or progression and the patient was in good general conditions.

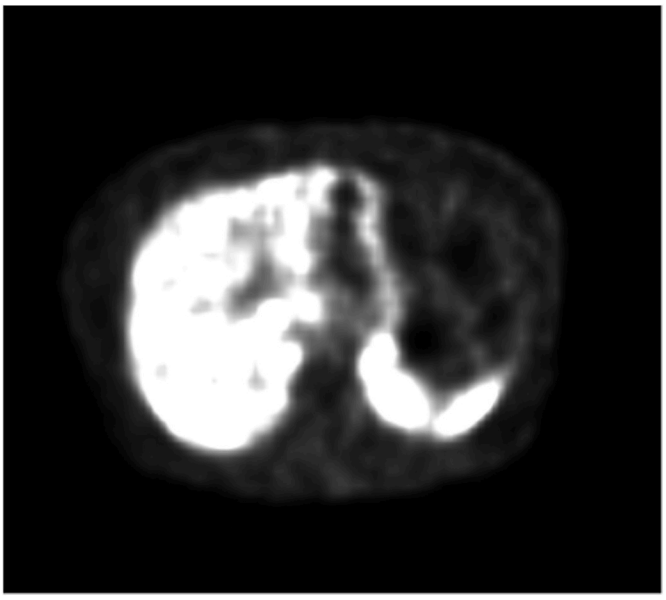

Fig. 4. Abdominal PET scan shows early liver involvement.

3. Discussion

We report a rare case of moderately differentiated neuroendocrine tumor with primitivity in the middle ear and simultaneous regional but, overall, distant metastasis.

This case is particularly challenging both for clinical and for pathological features.

Clinically, acute ear pain and a sense of plugged ear abruptly complained by the patient were not ascribable to any specific inflammatory or neoplastic condition. Moreover, the otoscopic exam only revealed a polypoid mass protruding in the external auditory canal, apparently involving the middle ear structures. All these elements suggested a reactivation of the underlying chronic phlogistic process, and local and

systemic pharmacological therapy were considered the first treatment for the patient.

Moreover, imaging did not help in clarifying the specific nature of the lesion, as petrous bone CT scan performed after the lack of clinical improvement indicated the presence of an unspecified pathological tissue involving the epitympanum, the antrum and the mastoid, encasing the ossicles without signs of clear erosion.

The diagnosis of moderately differentiated neuroendocrine tumor was made after microscopic and immunohistochemical histological examination on the surgical sampling.

Compared to the similar cases described in literature, classified both as middle ear "adenoma" and "carcinoid", some clinical differences emerge: the age of the subjects described in literature is generally lower, at the time of the diagnosis, than that of our patient, as they were all younger than 50 years old except in one case [7]; the starting symptoms complained by literature framed patients were mainly hearing loss, tinnitus and otorrhea [8–16], just three of them complaining only ear pain, accompanied in two cases with a sense of plugged ear [17–19]. Middle ear adenomas and carcinoids are usually treated only with surgery (tympanomastoidectomy) [8–20]; chemotherapy and radiotherapy have been sometimes added in some difficult cases reported by literature, essentially because of the relapsing behaviour of the disease [11, 12]. Conversely, as soon as surgical therapy was performed, our patient started to receive the suitable chemotherapeutic treatment for neuroendocrine tumors.

Even though various non neoplastic and benign conditions can resemble it [13,18,21] macroscopically the lesion that we found was immediately suspicious for an uncommon neoplastic process. Indeed, paraganglioma presents like a reddish pulsatile vascular mass that can protrude through the tympanic membrane into the external auditory canal, while cholesteatoma is usually associated to an epithelial matrix: such features were not present in our case.

Also the clinical behaviour of the lesion suggested a malignant neoplasm, as neck lymph nodes and liver metastases were found during staging exams. Compared to other middle ear tumors with neuroendocrine features described in literature, our case showed a more aggressive behaviour; actually our patient developed liver metastasis almost simultaneously with the primitive lesion, while the sporadic metastatic tumors reported by others manifested repetitions only very late [6,7,12, 22].

On histopathologic examination, the lesion showed morphological and immunohistochemical features coherent with a pure neuroendocrine neoplasm, with a moderate grade of differentiation both in the middle ear and in the liver metastasis. The final diagnosis was "middle ear neuroendocrine tumor, grade 2", according to the 4th edition of the WHO.

The spectrum of differential diagnosis is very wide and comprise lesions of different nature.

Among benign lesions, the main differential diagnosis is with middle ear neuroendocrine adenoma, which is a site specific lesion, with neuroendocrine differentiation. Nevertheless, our lesion lacked the typical amphicrine cell growth seen in neuroendocrine adenomas, that show both endocrine cells containing neurosecretory granules and exocrine elements often containing mucous granules arranged in nests or glandular structures [23].

Jugulotympanic paraganglioma, which is the most frequent middle ear tumor, has to be considered in the differential diagnosis. In our case no vascular-rich stroma was seen and cells were positive to cytokeratins, thus paraganglioma was excluded [2]. Another nerve sheet tumor that can mimic the case herein described is vestibular schwannoma, especially in small biopsies and fragmented specimens [24]. However, schwannoma is composed of spindle cells arranged in typical cellular (Antoni A) areas and hypocellular (Antoni B) areas and Verocay bodies, and shows positivity to S100 with negative epithelial markers. Meningioma can involve the middle ear, but it has peculiar histological features that are not seen in neuroendocrine tumors, as whorled patterns of growth, intranuclear inclusions and psammomatous bodies [25].

A number of malignant lesions of the middle ear can resemble NET, as adenocarcinoma, malignant glomus tumor and rhabdomyosarcoma, even if all of them show histological peculiar features that can help in the differential diagnosis. Indeed, adenocarcinoma shows more pleomorphism, necrosis and a high mitotic activity, while malignant glomus tumor has a typical vascular and capillary network surrounding the lesion [26,27]. Moreover, both lesions lack the expression of neuroendocrine markers. Rhabdomyosarcoma, especially the alveolar variant, can be similar to NET for the presence of plasmacytoid elements and it can be aberrantly positive for cytokeratins and neuroendocrine markers. However, the peculiar expression of desmin and myogenin helps to recognize this entity [28].

For the involvement of the external auditory canal and the neuroendocrine features, Merkel cell carcinoma has also to be excluded. While histological features are similar, as Merkel cell carcinoma is considered a primary cutaneous neuroendocrine tumor, CK20 is a very useful immunohistochemical marker, that is positive in this lesion, with a classical dot-like paranuclear stain [29]. In our case CK20 was performed with a negative result.

Hepatic lesions of our patient displayed the same histological and immunohistochemical features of the middle ear NET, so they were diagnosed as metastatic. A primitive NET of the liver is a very rare lesion, usually found in young adults, while the liver is one of the most common sites of metastasis of other district NET [12,22].

4. Conclusions

Considering all the above, we think it is very important to carefully follow over time chronic phlogistic pathologies of the middle ear, not only those of paediatric or of the young age but even those who present in advanced age subjects, even if long standing, being aware that, although in extremely rare cases, it is possible that they will turn into neoplastic forms of a neuroendocrine nature, capable of metastasizing at a distance, also very soon.

It must always be taken in account that symptoms of a newly developed NEN lesion into the middle ear couldn't differ too much from those of a sudden riacutization of a chronic otitis and that the objective clinical picture could continue to give evidence of a phlogistic pathological process despite its malignant nature.

Therefore, regardless of the patient's age, a new acute lesion into the external and/or middle ear, resistant to general and local therapy, although with the appearance of a lesion of an inflammatory nature, should induce to consider, among the other more frequent diagnostic hypotheses, also the possibility of a pure NET of the middle ear with a minor or major malignant potential.

Histologically, the correlation with clinical information and imaging, with the help of immunohistochemistry, can differentiate primary middle ear neuroendocrine lesions from metastases and from neuroendocrine neoplasms of lung or gastrointestinal tract. Moreover, all neuroendocrine tumors have to be carefully classified according to the 4th WHO classification, in order to have a uniform terminology and avoid confusion.

Early diagnosis of these extremely rare forms would allow the best therapeutic approach, surgical, medical or both, in order to limit their evolution and repetitions.

Author contributions

FP: study conception and design, data collection and interpretation, drafting the manuscript, discussion of results, critical reading of the manuscript, intellectual editing and comments, and approval of the manuscript.

RP: study conception and design, data collection and interpretation, critical reading of the manuscript, intellectual editing and comments, and approval of the manuscript.

EP: data collection and interpretation.
PV: data collection and surgical performance.
CT: data collection and interpretation, drafting the manuscript, discussion of results, critical reading of the manuscript, intellectual editing and comments, and approval of the manuscript.
BG: study conception and design, data collection and interpretation, drafting the manuscript, discussion of results, critical reading of the manuscript, intellectual editing and comments, and approval of the manuscript.

Ethical Statement

Hereby, I, Federica Pollastri, consciously assure that for the manuscript "Late onset middle ear neuroendocrine tumor presenting with distant metastasis" the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

I agree with the above statements and declare that this submission follows the policies of Solid State Ionics as outlined in the Guide for Authors and in the Ethical Statement.

Declaration of competing interest

The authors state that they have no conflicts of interest. No funding was received.

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