PERIFERNA PARALIZA FACIJALNOG NERVA KAO MANIFESTACIJA NEUROENDOKRINOG TUMORA SREDNJEG UVA – PRIKAZ SLUČAJA

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CASE REPORT

PERIPHERAL PARALYSIS OF THE FACIAL NERVE AS A MANIFESTATION OF NEUROENDOCRINE TUMOR OF THE MIDDLE EAR – CASE REPORT

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SAŽETAK

Uvod: Periferna paraliza facijalnog nerva je akutna idiopatska paraliza često povezana sa virusnim infekcijama kao što je reaktivacija virusa *Herpes simplex* tipa 1. Neuroendokrini tumori (NET) srednjeg uva (MEANT) su retki i prisutni su sa nespecifičnim simptomima, uključujući gubitak sluha, otalgiju i neuropatiju, što otežava ranu dijagnozu.

Prikaz slučaja: Prikazan je slučaj 47-godišnje pacijentkinje lečene od hroničnog otitisa od 2020. Godine 2024., početak paralize perifernog facijalnog nerva podstakao je naprednu dijagnostiku, uključujući MRI, CT, biopsiju i imunohistohemijske analize, potvrđujući MEANT. Lečenje je uključivalo hiruršku eksciziju, terapiju gama nožem i redovno praćenje tumorskih markera. Odložena dijagnoza tumora istakla je potrebu za povećanom kliničkom sumnjom u slučajevima hronične patologije uha sa atipičnom progresijom.

Zaključak: Neuroendokrini tumori srednjeg uva predstavljaju dijagnostički i terapijski izazov zbog svoje retkosti i nespecifične prezentacije. Rano prepoznavanje periferne paralize facijalnog nerva kao potencijalnog pokazatelja osnovnog maligniteta je ključno. Multidisciplinarno upravljanje, integrišući napredno snimanje, histopatološke potvrde, hirurške intervencije i pomoćne terapije, poboljšavaju ishode i minimiziraju rizik od recidiva. Lekari opšte medicine igraju ključnu ulogu u identifikaciji ranih simptoma kako bi se smanjila dijagnostička kašnjenja.

Ključne reči: paraliza perifernog facijalnog nerva, hronični otitis srednjeg uha, retki tumori, rano prepoznavanje bolesti, opšta medicina

ABSTRACT

Introduction: Acute idiopathic peripheral facial nerve paralysis is often linked to viral infections such as *Herpes simplex* virus type 1 reactivation. Neuroendocrine tumors (NETs) of the middle ear (MEANT) are rare and present with non-specific symptoms, including hearing loss, otalgia, and neuropathy, complicating early diagnosis.

Case report: Report the case of a 47-year-old patient treated for chronic otitis since 2020. In 2024, the onset of peripheral facial nerve paralysis prompted advanced diagnostics, including MRI, CT, biopsy, and immunohistochemical analyses, confirming MEANT. Treatment included surgical excision, gamma knife therapy, and regular tumor marker monitoring. A delayed diagnosis of the tumor highlighted the need for heightened clinical suspicion in cases of chronic ear pathology with atypical progression.

Conclusion: Neuroendocrine tumors of the middle ear are diagnostic and therapeutic challenges due to their rarity and non-specific presentation. Early recognition of peripheral facial nerve paralysis as a potential indicator of an underlying malignancy is critical. Multidisciplinary management, integrating advanced imaging, histopathological confirmation, surgical intervention, and adjuvant therapies, improves outcomes and minimizes relapse risks. General practitioners play a pivotal role in identifying early symptoms to reduce diagnostic delays.

Keywords: peripheral facial nerve paralysis, chronic otitis media, rare tumors, early recognition of the disease, general medicine

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UVOD

Periferna paraliza facijalnog nerva je često nepoznatog uzroka. Smatra se idiopatskim stanjem iako se sve više dokaza povezuje s virusnim infekcijama, poput reaktivacije *Herpes simplex* virusa tipa 1 [1]. Karakteristična klinička slika uključuje iznenadnu slabost ili paralizu mišića jedne strane lica, što može biti praćeno bolom iza uha, oslabljenim čulom ukusa i povećanom osjetljivošću na zvukove.

Postavljanje dijagnoze periferne paralize facijalnog nerva je kliničko ali podrazumeva da se izuzmu u obzir drugi mogući uzroci [2]. Diferencijalna dijagnoza može da ukaže na niz različitih bolesti i stanja. Moždani udar na primer za razliku od periferne paralize facijalnog nerva, često zahvata samo donji deo lica i povezan je s drugim neurološkim deficitima [3]. Lajmska bolest može imitirati perifernu paralizu facijalnog nerva, ali se obično javlja u endemskim područjima i prati je borelijski eritem [4]. Tumori baze lobanje su takođe uzrok, ali retko i mogu uzrokovati slične simptome, što naglašava važnost snimanja magnetnom rezonancom [5,6]. Infekcije poput otitis media i *Herpes zoster oticus* (Ramsay Hunt sindrom) mogu uzrokovati slične simptome, ali su obično praćeni bolom ili osipom pa nas tu drugi klinički simptomi navode na pravi uzrok. Autoimuna stanja poput Guillain-Barré sindroma i sarkoidoza takođe mogu biti razmatrane diferencijalno dijagnostički [5].

Neuroendokrini tumori (NET) predstavljaju raznoliku grupu tumora koje nastaju iz neuroendokrinih ćelija. Ove ćelije, koje dele karakteristike neuološkog i endokrinog sistema, mogu se pronaći u različitim organima i tkivima tela. NET su relativno retki ali mogu biti lokalizovani u plućima, digestivnom traktu, pankreasu pa čak i u srednjem uvu, što predstavlja posebnu i nedovoljno istraženu podgrupu. Neuroendokrini tumori srednjeg uva, poznati i kao neuroendokrini adenomatni tumori srednjeg uva (MEANT), izuzetno su retki i čine manje od 2% svih tumora srednjeg i unutrašnjeg uva. Do danas je u literaturi na engleskom jeziku prijavljeno manje od 150 slučajeva, pod različitim nazivima, uključujući karcinoidne tumore, adenome srednjeg uva, adenomatne tumore srednjeg uva, adenokarcinoidne tumore i amfikrine tumore. Prvi dokumentovani primarni adenomatni tumor ograničen na šupljinu srednjeg uva opisan je 1976. godine. NET se dele na dobro diferentovane (tipično benigni ili niskog malignog potencijala) i loše diferentovane (visokog malignog potencijala). Histološki, ovi tumori izlučuju specifične markere poput sinaptofizina i hromogranina, što olakšava dijagnostiku putem imunohistohemije [7-9]. Klinička slika zavisi od lokalizacije i sekretorne aktivnosti tumora [8]. Ovi tumori se često nazivaju *adenomatous neuroendocrine tumors* (NAME) ili timpanalni adenom. Oni se najčešće manife-

INTRODUCTION

Peripheral facial nerve paralysis is often of unknown origin. It is considered an idiopathic condition, although increasing evidence links it to viral infections, such as the reactivation of Herpes simplex virus type 1 [1]. The characteristic clinical presentation includes sudden weakness or paralysis of the muscles on one side of the face, which may be accompanied by pain behind the ear, diminished sense of taste, and increased sensitivity to sound.

Diagnosing peripheral facial nerve paralysis is clinical but requires ruling out other possible causes [2]. The differential diagnosis may suggest a range of different diseases and conditions. Stroke, for instance, unlike peripheral facial nerve paralysis, often affects only the lower part of the face and is associated with other neurological deficits [3]. Lyme disease can mimic peripheral facial nerve paralysis but usually occurs in endemic areas and is accompanied by a Borrelia-related erythema [4]. Skull base tumors are also a rare cause but can produce similar symptoms, highlighting the importance of magnetic resonance imaging [5,6]. Infections such as otitis media and *Herpes zoster oticus* (Ramsay Hunt syndrome) may cause similar symptoms but are usually accompanied by pain or rash, which helps guide us to the correct cause. The differential diagnosis should also consider autoimmune conditions like Guillain-Barré syndrome and sarcoidosis [5].

Neuroendocrine tumors (NETs) represent a diverse group of tumors arising from neuroendocrine cells. These cells, which share characteristics of the nervous and endocrine systems, can be found in various organs and tissues throughout the body. NETs are relatively rare but can be localized in the lungs, gastrointestinal tract, pancreas, and even the middle ear, representing a distinct and under-researched subgroup. Neuroendocrine tumors of the middle ear, also known as middle ear adenomatous neuroendocrine tumors (MEANTs), are sporadic and account for less than 2% of all middle and inner ear tumors. To date, fewer than 150 cases have been reported in the English literature, under various names, including carcinoid tumors, middle ear adenomas, middle ear adenomatous tumors, adenocarcinoid tumors, and amphicrine tumors. The first documented primary adenomatous tumor confined to the middle ear cavity was described in 1976. NETs are classified as well-differentiated (typically benign or of low malignant potential) and poorly differentiated (highly malignant). Histologically, these tumors secrete specific markers such as synaptophysin and chromogranin, which aid diagnosis via immunohistochemistry [7–9]. The clinical presentation depends on the tumor's location and secretory activity [8]. These tumors are often

stuju simptomima poput gubitka sluha, tinitusa ili osećaja punoće u uhu [9]. Histopatološki, NET srednjeg uha mogu pokazivati mešovitu neuroendokrinu i ne-neuroendokrinu komponentu [7]. Smatra se da MEANT tumori potiču iz epitela koji oblaže sluznicu srednjeg uva, što predstavlja produžetak i modifikaciju respiratornog epitela [8]. Dijagnostika uključuje dijagnostičke metode poput kompjuterizovana tomografija temporalne kosti (CT) i magnetna rezonanca (MRI), dok je konačna potvrda moguća samo putem biopsije i imunohistohemijskog pregleda. Iako su NET srednjeg uva izuzetno retki, prevalencija je nešto veća kod muškaraca srednje životne dobi [8,10]. Klinički simptomi zavise od veličine i lokalnog širenja tumora. Većina pacijenata prezentira se s jednostranim gubitkom sluha, dok manji deo može razviti otoreju ili bol [11].

PRIKAZ SLUČAJA

Pacijentkinja, stara 47 godina, lečena je konzervativno i paracentezom zbog hroničnog nesupurativnog otitisa i uočenog sadržaja u mastoidnoj šupljini na MRI pregledu. U avgustu 2024. javila se kao hitan slučaj zbog periferne paralize facijalnog nerva, što je iniciralo dodatna ispitivanja.

Izveden je operativni zahvat timpanoplastike sa mastoidektomijom i rekonstrukcijom slušnih koščica na levoj strani, a patohistološki nalaz ukazao je na adenoidno-cistični karcinom. Revizija nalaza kasnije je potvrdila neuroendokrini tumor srednjeg uha (MEANT), klasifikovan kao G1 neuroendokrini adenom sa niskim proliferativnim potencijalom (Ki-67 < 1%). Imunohistohemijski profil uključuje pozitivne markere (INSM1, sinaptofizin, p63) i negativne markere (hromogranin A, CD117, CK7, SOX-10).

Radiološki nalazi, uključujući MR i CT pregled, ukazali su na postoperativne promene i prisustvo tumorskog resta sa infiltracijom u nivou baze kranijuma, sa ekstrakranijalnom i temporobazalnom ekstenzijom, ali bez znakova moždanog edema i intrakranijalnog krvarenja. CT vrata i gornjeg abdomena nije pokazao značajne limfadenopatske promene, dok je cistična lezija jetre (9 mm) klasifikovana kao benigna. Predložen je multidisciplinarni terapijski pristup koji obuhvata hiruršku eksciziju postoperativnu gama nož (*gamma knife*) terapiju i praćenje neuroendokrinih tumorskih markera (CgA i NSE). Preporučena je konsultacija sa ORL hirurgom, neurohirurgom i onkologom radi dalje procene i praćenja.

DISKUSIJA

Prikaz ovog slučaja neuroendokrinog tumora srednjeg uha (MEANT) ističe ključnu ulogu ranog prepoznavanja simptoma od strane lekara opšte medicine, naro-

referred to as **adenomatous neuroendocrine tumors (NAME)** or tympanic adenomas. They commonly present with symptoms such as hearing loss, tinnitus, or a sensation of fullness in the ear [9]. Histopathologically, middle ear NETs may exhibit a mixed neuroendocrine and non-neuroendocrine component [7]. It is believed that MEANTs originate from the epithelium lining the middle ear mucosa, which is a continuation and modification of respiratory epithelium [8]. Diagnostic methods include imaging such as computed tomography (CT) of the temporal bone and magnetic resonance imaging (MRI), while definitive confirmation is only possible through biopsy and immunohistochemical examination. Although middle ear NETs are extremely rare, their prevalence is slightly higher in middle-aged men [8,10]. Clinical symptoms depend on the size and local spread of the tumor. Most patients present with unilateral hearing loss, while a smaller portion may develop otorrhea or pain [11].

CASE REPORT

A 47-year-old female patient was initially treated conservatively and with paracentesis for chronic nonsuppurative otitis and a noted mass in the mastoid cavity observed on MRI. In August 2024, she presented as an emergency case due to peripheral facial nerve paralysis, which prompted further investigation.

A surgical procedure was performed, including tympanoplasty with mastoidectomy and ossicular chain reconstruction on the left side. The initial histopathological finding suggested adenoid cystic carcinoma. However, a subsequent review of the pathology confirmed a middle ear neuroendocrine tumor (MEANT), classified as a G1 neuroendocrine adenoma with low proliferative potential (Ki-67 < 1%). The immunohistochemical profile showed positive markers (INSM1, synaptophysin, p63) and negative markers (chromogranin A, CD117, CK7, SOX-10).

Radiological findings, including MRI and CT scans, indicated postoperative changes and the presence of residual tumor with infiltration at the skull base, exhibiting both extracranial and temporobasal extension, but without signs of cerebral edema or intracranial hemorrhage. CT scans of the neck and upper abdomen showed no significant lymphadenopathy, while a 9 mm cystic liver lesion was classified as benign.

A multidisciplinary therapeutic approach was proposed, including surgical excision, postoperative gamma knife therapy, and monitoring neuroendocrine tumor markers (CgA and NSE). Consultations with an ENT surgeon, neurosurgeon, and oncologist were recommended for further evaluation and follow-up.

čito kod pacijenata sa dugotrajnim ili ponavljajućim simptomima. Pacijentkinja je od 2020. godine lečena zbog hroničnog otitisa sa evidentnim zastojnim sadržajem u mastoidnom nastavku, što je već tada ukazivalo na potrebu za detaljnijim ispitivanjem i multidisciplinarnim pristupom. U ovom slučaju, tek razvoj periferne facijalnog nerva 2024. godine podstakao je dalje dijagnostičke korake, što ukazuje na potencijalni vremenski jaz između pojave simptoma i postavljanja tačne dijagnoze. Neuroendokrini tumori srednjeg uha su retki i često izazivaju nespecifične simptome poput hronične otalgije, otoreje ili gubitka sluha, što otežava njihovo rano prepoznavanje [1-3,5]. Klinička sumnja lekara opšte medicine može igrati ključnu ulogu u ubrzavanju dijagnostičkog procesa. Rano prepoznavanje simptoma poput trajne otalgije, gubitka sluha i periferne neuropatije od strane lekara opšte medicine moglo bi poboljšati ishod, jer omogućava ranije uvođenje dijagnostičkih procedura, poput MR i CT [12]. Dijagnostički izazovi uključuju i specifičnost patohistoloških nalaza, gde je imunohistohemijski profil tumora ključan za diferencijaciju MEANT od drugih karcinoma. Na primer, pozitivni markeri poput INSM1 i sinaptofizina, zajedno sa niskim Ki-67 indeksom (< 1%), ukazuju na nizak proliferativni potencijal ovog tumora [7,13,14]. Ki67 je antigen vezan za proliferaciju ćelija koji igra ključnu ulogu u deobi ćelija i proliferaciji tumorskih ćelija. Visok indeks Ki67 ukazuje na aktivnu proliferaciju ćelija, potencijalno signalizirajući rizik od malignog tumora [8,9].

Međutim, bez ranijeg prepoznavanja, ovi nalazi često dolaze kasno u kliničkom toku bolesti, kada su potrebne agresivne terapijske mere. Multidisciplinarni pristup lečenju, koji uključuje hiruršku eksciziju i postoperativnu gama nož terapiju, pokazao se kao efikasan u upravljanju ovakvim slučajevima [13]. Takođe, praćenje markera kao što su hromogranin A (CgA) i neuron-specifična enolaza (NSE) ključno je za procenu odgovora na terapiju i otkrivanje recidiva [10,13,14]. Ovaj slučaj naglašava potrebu za kontinuiranom edukacijom lekara opšte medicine o važnosti prepoznavanja ranih simptoma malignih bolesti srednjeg uha. Uvođenje dijagnostičkih algoritama i bliska saradnja sa specijalistima mogu unaprediti kvalitet nege i značajno poboljšati prognozu kod pacijenata sa sličnim stanjima.

ZAKLJUČAK

Neuroendokrini tumori srednjeg uha iako retki, mogu izazvati značajne dijagnostičke i terapijske izazove. Manifestacija periferne paralize facijalnog nerva kao prvog simptoma kod ovih tumora zahteva brzu i preciznu dijagnozu kako bi se obezbedilo pravovremeno lečenje i smanjio rizik od trajnih posledica. Uloga leka-

DISCUSSION

This case report of a middle ear neuroendocrine tumor (MEANT) highlights the crucial role of early symptom recognition by general practitioners, particularly in patients with persistent or recurrent symptoms. Since 2020, the patient had been treated for chronic otitis with evident effusion in the mastoid process, which already indicated the need for more thorough evaluation and a multidisciplinary approach. In this case, it was not until the development of peripheral facial nerve palsy in 2024 that further diagnostic steps were initiated, pointing to a potential time gap between symptom onset and accurate diagnosis. Middle ear neuroendocrine tumors are rare and often present with non-specific symptoms such as chronic otalgia, otorrhea, or hearing loss, which complicates early recognition [1-3,5]. Clinical suspicion from the general practitioner can expedite the diagnostic process. Primary care physicians could improve outcomes by early recognition of symptoms such as persistent otalgia, hearing loss, and peripheral neuropathy by enabling earlier diagnostic procedures like MRI and CT scans [12].

Diagnostic challenges also include the specificity of histopathological findings, where the immunohistochemical profile of the tumor is essential for differentiating MEANT from other carcinomas. For instance, positive markers such as INSM1 and synaptophysin, combined with a low Ki-67 index (<1%), indicate a low proliferative potential of this tumor [7,13,14]. Ki-67 is a proliferation-associated antigen that plays a key role in cell division and tumor cell proliferation. A high Ki-67 index indicates active cell proliferation, potentially signaling the risk of malignancy [8,9]. However, without earlier recognition, these findings often appear late in the clinical course of the disease, when aggressive therapeutic interventions are already necessary. A multidisciplinary treatment approach, including surgical excision and postoperative gamma knife therapy, has proven effective in managing such cases [13]. Additionally, monitoring markers such as chromogranin A (CgA) and neuron-specific enolase (NSE) is essential for evaluating treatment response and detecting recurrence [10,13,14].

This case emphasizes the need for continuous education of general practitioners regarding the importance of recognizing early symptoms of malignant middle ear diseases. Implementing diagnostic algorithms and close collaboration with specialists can improve the quality of care and significantly enhance the prognosis for patients with similar conditions.

CONCLUSION

Although rare, middle ear neuroendocrine tumors can pose significant diagnostic and therapeutic challeng-

ra opšte medicine kao prvog koji se sreće sa pacijentom i multidisciplinarni pristup koji uključuje kliničku evaluaciju, radiološke metode i patohistološku analizu ključan je za postavljanje dijagnoze i određivanje optimalnog tretmana. Iako tumori sa niskim proliferativnim potencijalom imaju povoljniju prognozu, praćenje zbog mogućih recidiva i metastaza ostaje od kritične važnosti.

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es. The manifestation of peripheral facial nerve paralysis as an initial symptom in such tumors necessitates prompt and accurate diagnosis to ensure timely treatment and reduce the risk of permanent consequences. The role of the general practitioner as the first point of contact, along with a multidisciplinary approach involving clinical evaluation, radiological methods, and histopathological analysis, is essential for establishing a diagnosis and determining the optimal treatment. While tumors with low proliferative potential tend to have a more favorable prognosis, continuous monitoring for possible recurrences and metastases remains critically important.

Conflict of interest: None declared.

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