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Systematic Review

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Petrous Apex Cerebrospinal Fluid (CSF) Leak: A Review Article

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ABSTRACT

Objective: The objective of this study was to present a review article about petrous apex cerebrospinal fluid (CSF) leak.
Data Sources: Published English-language literatures in PubMed and Google Scholar.
Review Methods: PubMed and Google Scholar were systematically searched using search terms: petrous, apex, cerebrospinal and leak. Temporal, bone, cerebrospinal and leak.
Study Selection: We included studies about petrous apex CSF Leak.
Results: Seventeen studies were included in this study. The results showed that 72% of patients are adult and 28% of patients are children. Meningocele is the most common cause of petrous apex CSF leak in pediatric patients, while iatrogenic trauma is the most common cause in adult patients. Seventy-seven percentage of pediatric patients have active leak, while 96% of adult patients have active leak. Nose is the most common site of CSF leak in both adult and pediatric patients. Sixty-six percentage of pediatric patients have meningitis while only 20% of adults have meningitis. Most cases need surgical procedure. Eleven percentage of pediatric patients have a recurrence, while 20% of adult patients have a recurrence.
Conclusion: Petrous apex is a rare location for CSF leak.

KEYWORDS: Middle fossa approach; Transmastoid approach; Meningocele; Gorham-stout; Spontaneous CSF leak.

ABBREVIATIONS: CSF: Cerebrospinal fluid; MFA: Middle Fossa Approach; TM: Tramsmastoid; TMA: Transmastoid approach; BMI: Body Mass Index; PAC: Cephalocele of petrous apex; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; Anti-IL6: Anti-Interleukin-6; Anti-VEGF: Anti-Vascular Endothelial Growth Factor; ET: Eustachian Tube.

INTRODUCTION

Cerebrospinal fluid leak (CSF) from an intracranial source is rare, as it is a life-threatening condition that can have difficulties in localization, diagnosis, and management. CSF leaks from the petrous apex are extremely rare, as only few cases are reported in the world literature. Surgery of petrous apex area has potentially high morbidity rate due to complex anatomy. Multiple surgical approaches have been developed for reaching petrous apex region (subtemporal, transtemporal, endoscopic transnasal), all of them aiming to increase the anatomic exposure, reduce the complication rates, and result in high successful treatment. Each approach has its advantages and disadvantages. We in this review article discuss about the English literatures of petrous apex CSF leak.[1]

MATERIAL AND METHODS

Literature review was conducted using PubMed (MEDLINE) and Google Scholar for English articles. The following keywords were used: petrous; apex; cerebrospinal and leak temporal, bone, cerebrospinal and leak.

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Inclusion Criteria

All petrous apex CSF leak articles published after 1990 were included in the study.

RESULTS

Sixteen studies about petrous apex CSF leak were available in PubMed (MEDLINE) and Google Scholar in English literature (Table 1).

Demographs

There were 33 patients of age ranged from 5 to 71. There were 9 pediatric patients, 6 patients of them were male 66%, while the other 3 patients were female 33%. There were 24 adult patients, 12 patients of them were male 50% and 12 patients were female 50% (Chart 1).

	Age Sex	Symptoms	Etiology	Treatment	Recurrence	leakage
Kou et al[1]	61 F	Rhinorrhea B/l hearing loss recurrent meningitis	Left cephalocele spontaneous CSF leak	First approach MFA sealed with bone wax and covered with fascia second operation MFA The meningocele was reduced and the defect was plugged with an abdominal fat graft and fibrin glue.	Yes	Nose
Warade et al[2]	26 M	CSF Rhinorrhea	Right Meninogcele	Extradural MFA the defect packed with fat, covered with fascia lata graft and fibrin glue.	No	Nose
Morimoto et al[3]	11 F	Vertigo, Headache, Pulsatile tinnitus. Hearing loss	Right Gorham-stout	Extradural MFA packed with superficial temporal fascia, periosteum flap, and sealed with fibrin glue. Medical treatment; interferon-alpha 2b	No	Cervical Pharyngeal area
Grant et al[4]	53 F	Recurrent meningitis	Left Iatrogenic Acoustic neuroma	First operation: an excision of the mastoid-cutaneous fistula tract, and the wound was closed with a temporoparietal fascia flap. Second operation: modified transcochlear petrous apex. The distal eustachian tube was obstructed with Proplast and abdominal fat placed in the cavity.	Yes	Nose Postauricular CSF fistula
	56 M	Profuse right-sided rhinorrhea, Meningitis	Right iatrogenic	Conservative therapy. First:translabyrinthine obliteration of the mastoid with an abdominal fat graft. Head of the malleus was packed into the Eustachian tube. Second; transcochlear obliteration of the petrous apex, Proplast was packed into the tube and fat used to obliterate the petrous apex.	Yes	Nose
	28 M	CSf otorrhea Heaing loss profound	Right Trauma Acoustic neuroma	Lumbar drainage rest Ventriculoperitoneal shunt. First oberation: This was managed with a radical mastoidectomy and eustachian tube obliteration, Second: Transcochlear approach obliteration was done with fat. The eustachian tube was occluded with Proplast.	Yes	Middle ear
	57 F	CSF rhinorrhea	Right iatrogenic Acoustic neuroma	The CSF leak did not resolve with bed rest and lumbar drainage. She underwent a right-sided transcochlear packed with abdominal fat. Proplast was packed into the medial end of the eustachian tube and abdominal fat packed into the cavity.	No	Nose
Motojima et al[5]	6 F	Recurrent Meningitis	Right meningocele	MFA stuffed soft tissue and fascia in air cells with fibrin glue for repair	No	Nose
Dzaman et al[6]	60 M	Otorhinorrhea Profound hearing.	Right choleasteoma	Combined MFA and Trans-mastoid. Temporal fascia graft, fibrin glue, and collagen patch tachoSil treated the fistula and CSF leak, obliteration of the eustachian tubal orifice, closure of the external auditory canal, and obliteration of the middle ear and mastoid clefts were essential in this procedure. Bony defects were repaired through the use of an acrylic mass.	No	Nose
Cushing et al[7]	12 M	Headache Nausea Vomiting Hearing loss Facial palsy	Right Gorham-stout	Tympanomastoidectomy, eustachian tube plugging, middle ear and mastoid obliteration with fat	No	surgical site zygmotic root, TMJ area

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Isaacson et al[8]	55 F	Otalgia Meningitis Hearing loss	Right cephalocele	Middle fossa approach packing wax, fascia and muscle	No	Not active
Danner et al[9]	49 F	Otorhinorrhea	Latrogenic right Meningioma	Lumbar drain rest Transient	No	Nose
Sekhar et al[10]	37M	CSF Leak	Latrogenic Mhordoma	Lumbar drain	No	One throw wound
	42 F	CSF Leak	Latrogenic Meningioma	Lumbar drain, rest reoperation packing multilayer, fascia, obliteration with fat, ET plugging, bone graft for defect, fibrin glue for sealing	No	Nine throw middle ear
	53 M	CSF Leak Meningitis	Latrogenic Chordoma	Lumbar drain, rest peritoneal shunt (palliative)	No	One
	46 F	CSF Leak	Latrogenic Meningioma	Lumbar drain, rest reoperation packing: multilayer, fascia, obliteration with fat, ET plugging, bone graft for defect, fibrin glue for sealing	No	Through external ear one throw
	33 F	CSF Leak	Latrogenic Chordoma	Lumbar drain, rest nose repacking foreman flap for sphenoid	No	Sphenoid
	58 F	CSF Leak	Latrogenic Meningioma	Lumbar drain	No	
	64 F	CSF Leak	Latrogenic Meningioma	Lumbar drain, rest reoperation packing multilayer, fascia, obliteration with fat, ET plugging, bone graft for defect, fibrin glue for sealing	No	
	35 M	CSF Leak	Latrogenic Chondrosarcoma	Lumbar drain wound	No	
	43 M	CSF Leak	Latrogenic Meningioma	Lumbar drain, rest reoperation packing multilayer, fascia, obliteration with fat, ET plugging, bone graft for defect, fibrin glue for sealing	No	
	46 F	CSF Leak	Latrogenic Aneurysm	Lumbar drain, rest reoperation packing multilayer, fascia, obliteration with fat, ET plugging, bone graft for defect, fibrin glue for sealing	No	
	40 F	CSF Leak meningitis	Latrogenic Meningioma	Lumbar drain packing peritoneal shunt	No	
	38 F	CSF Leak	Latrogenic Meningioma	Lumbar drain	No	
Ota et al[11]	34 M	Rhinorrhea	Right iatrogenic	Lumbar drain trans-petrosal multilayer, HAC Hydroxiappetiate for packing then fiber glue then piece of dura then fat then fiber glue	No	Nose
	59 F	Rhinorrhea	Right iatrogenic	Lumbar drain trans-petrosal multilayer, HAC Hydroxiappetiate for packing then fiber glue then piece of dura then fat then fiber glue	No	Nose
	32 M	Rhinorrhea	Left iatrogenic	Lumbar drain Trans=petrosal multilayer, HAC hydroxiappetiate for packing then fiber glue then piece of dura then fat then fiber glue	No	Nose middle ear
Hervey-Jumper et al[12]	14 M	Recurrent meningitis Headache	Bilateral meningoceles (larger on the left)	MFA Pericranium patch and fat graft, dural repair, and, fibrin glue. Second operation endoscopic trans nasal approach	Yes	Retro pharyngeal
Pross et al[13]	5 F	Recurrent meningitis Facial and abduces palsy Sudden hearing loss rhinorrhea Chiari	Left meningocele	Extradural MFA, Multilayer defect coverage the herniated brain and dura were resected and the dura was closed primarily. The petrous apex was packed with gelfoam as support for temporalis fascia graft underlay. The defect was covered with another piece of temporalis fascia, calvarial bone graft, and synthetic dural substitute	No	Nose
Oyama et al[14]	71 M	Rhinorrhea	Right Iatrogenic cholesteatoma	Lumbar drainage, rest MFA muscle free flap	No	Nose

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Moore et al[15]	5 M	RIGHT CSF leak	Right meningocele	MFA the dura was closed primarily. The petrous apex was packed with gelfoam as support for temporalis fascia graft underlay. The defect was covered with another piece of temporalis fascia, calvarial bone graft, and synthetic dural substitute	No	Nose
Schick et al[16]	12 M	CSF LEAK Meningitis	Right meningocele	Endoscopic transnasal approach perichondrium obtained from the left ear. As a second layer, the prepared mucosal flap was used to cover the site of repair	No	Nose
Mulcahy et al[17]	6 M	Meningitis	Right meningocele	MFA, TM The dura was closed primarily. The petrous apex was packed with gelfoam as support for temporalis fascia graft underlay. The defect was covered with another piece of temporalis fascia, calvarial bone graft, and synthetic dural substitute	No	Not active
	9 M	Meningitis	Right meningocele	MFA, TM The dura was closed primarily. The petrous apex was packed with gelfoam as support for temporalis fascia graft underlay. The defect was covered with another piece of temporalis fascia, calvarial bone graft, and synthetic dural substitute	No	Not active

Table 1: Article in our study.

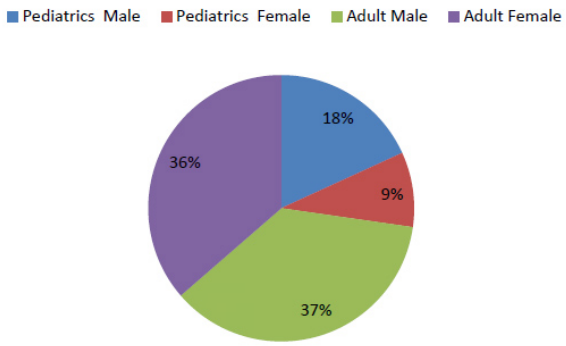

Chart 1: Petrous apex CSF leak demographs.

Side of CSF leak: Seven pediatrics patients had CSF leak from right side 77%, one from left side 11%, and one had B/L CSF leak 11%. Nine adult patients had CSF leak from right side 75%, while the other 3 patients had CSF leak from left 25%.

CSF Leak Site

Pediatrics patients: Four patients had CSF leak from nose, 3 patients had CSF leak in petrous apex surrounding areas (neck, retropharyngeal, and zygomatic area), while the other 2 patients had no active CSF leak (Chart 2).

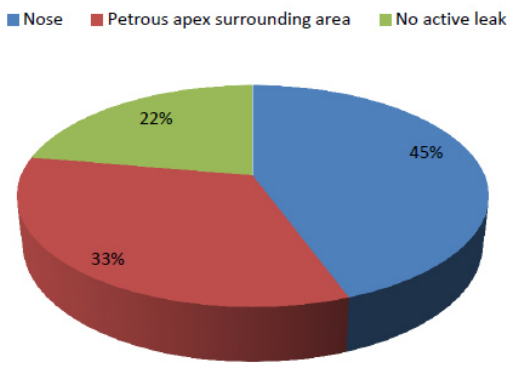

Chart 2: Petrous apex CSL leak sit in pediatrics.

Adult patients: Twelve patients had CSF leak from nose, 10 patients had CSF leak from middle ear, 2 patients had CSF leak from the surgical wound, one from external auditory canal, and one had no active CSF leak (Chart 3).

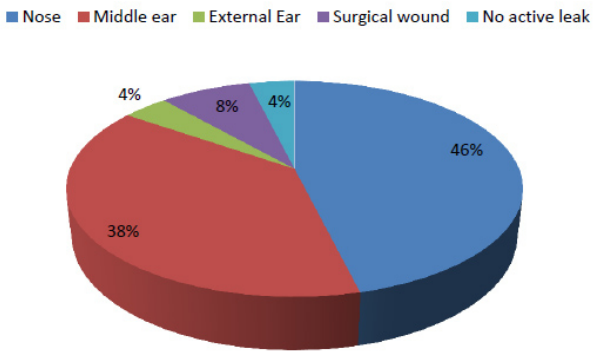

Chart 3: Petrous apex CSF leak site in adult patients.

Etiology

Pediatric patients: Seventy-seven percentage of patients had meningocele (the most common cause in pediatric patient), while the 22% patient had Gorham-stout syndrome which is lympho-vascular proliferation malformation of bones (Chart 4).

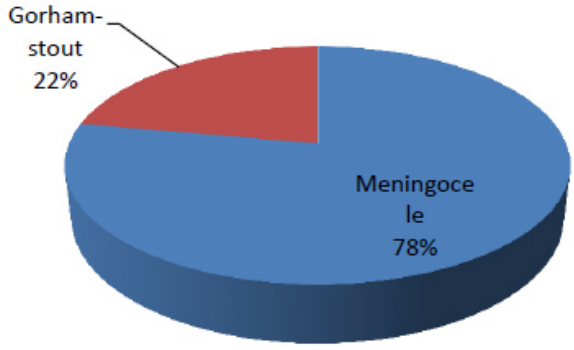

Chart 4: Etiology in pediatric patients.

Adult patients: Eighty-three percentage of patients had iatro-

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genic trauma (the most common cause in adult patients), 8% of patients had cephalcele, 4% of patients had external trauma, and 4% had spontaneous CSF leak (Chart 5).

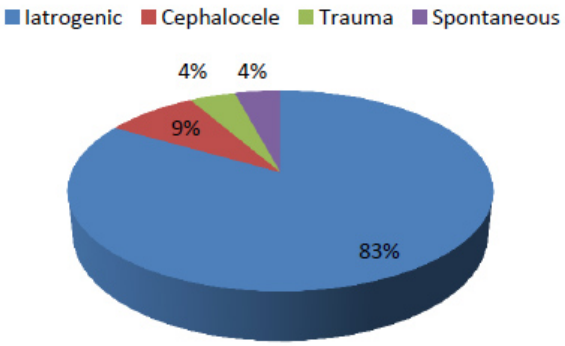

Chart 5: Etiology in adult patient.

Associated Symptoms

Pediatrics: Seventy-seven percentage of patients had active CSF leak, 66% of patients had history of meningitis, 33% of patients had headache, and 33% of patients had hearing loss (cranial 8 nerve involvement) (Chart 6).

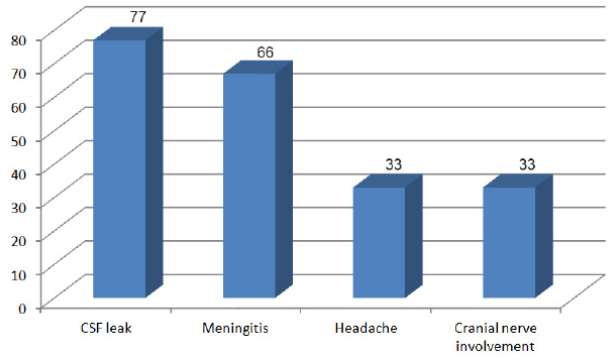

Chart 6: Associated symptoms percentage in pediatric patients.

Adults: Ninety-six percentage of patients had active CSF leak, 20% of patients had history of meningitis, 8% of patients had headache, and 16% of patients had cranial nerve palsy (CN VI, CN VII and CN VIII) (Chart 7).

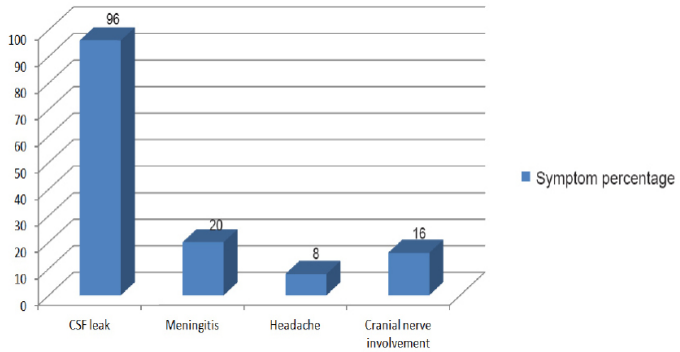

Chart 7: Associated symptoms percentage in adult patient.

Treatment

Pediatrics: Five patients had middle fossa approach (MFA), one of them had a recurrence and had another endoscopic trans-nasal approach to repair the CSF leak. Two patients had a combined MFA and trams-mastoid (TM), one had transmastoid approach (TMA) and one patient had trans-nasal approach (Chart 8).

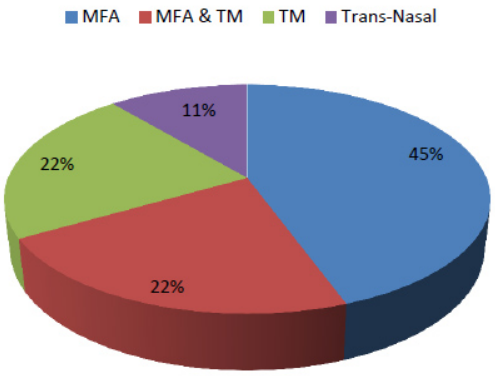

Chart 8: Treatment approaches in pediatric patients.

Adult: Twenty-one patients had conservative management and CSF leak continued in 17 patients of them, 2 patients had lumboperitoneal shunt, 6 patients had re-exploration of surgical site with repacking, 4 patients had MFA and one of them had recurrence and treated with MFA approach, and 6 patients had trans-petrosal approach and 3 patients of them had recurrence and treated with tras-petrosal approach (Chart 9).

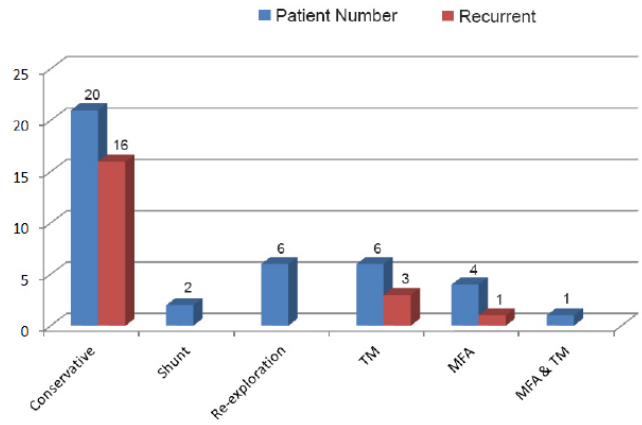

Chart 9: Treatment approaches in adult patients.

Fistula Repair

Five patients had multilayer repair using fascia, fibrin glue, fat packing to obliterate middle ear, Eustachian tube (ET) plugging and bone graft to support defect. Five patients had multilayer repair using primary dura closure, fascia, gelfom packing, and ET pulgging and synthetic dura. Five patients had a fascia for duraplasty, ET plugging, fat obliteration and fibrin glue. Three patients had multilayer repair using hydroxyapatite packing, fiber glue, fascia and fat. Three cases had fascia for durplasty, patched

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with fascia and fibrin glue for sealing. One patient had only fascia and bon wax, 2 had free flab. One patient had perichondrium graft and nasal mucosal flap. One had fascia and packing with muscle and bone wax sealed by fibrin glue. One patient had fistula removal and packed with fascia (Table 2).

Prognosis

There was one recurrent case in pediatrics group 11%, and 4 recurrent cases in adult group 16% (Chart 10).

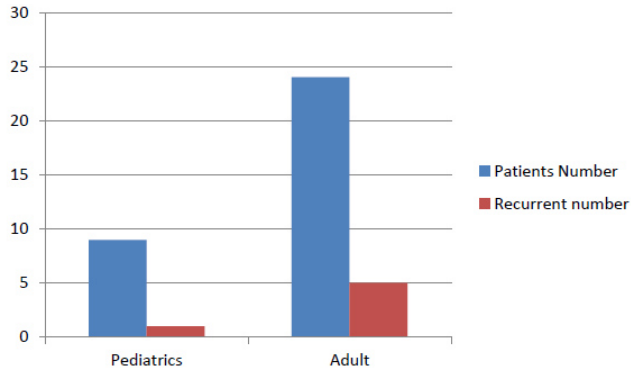

Chart 10: Recurrent cases.

DISCUSSION

Cerebrospinal fluid (CSF) leak develops when there is a fistula between the subarachnoid space and the aerated areas of the temporal bone. Spontaneous leaks are commonly misdiagnosed as chronic serous otitis media. Generally, the diagnosis is done by the presence of β2-transferrin in the middle ear and nasal fluid. Meningitis is the most significant complication of persistent CSF otorrhea or rhinorrhea. Common causes of petrous apex CSF leaks include iatrogenic injury, congenital malformation, meningocele, trauma, and choleasteoma and spontaneous CSF leak 1.

Pelosi et al[18] reported 14 cases of temporal bone CSF leak, one of them was from petrous apex area. Patients with spontaneous CSF leaks are usually females aged 40-60 with body mass index (BMI) greater than 30. They should also be evaluated for other problems associated with idiopathic intracranial hypertension (IIH) (ophthalmologic, neurologic, and empty sella). We should suspect this disease in patients with multiple meningitis and we review their imaging even if they have a negative β2 transferrin.

Cephalocele of petrous apex (PAC) is a rare lesion, it extends into the petrous apex from Meckel's cave. It is usually asymptomatic in adults. CSF leak of PAC has only been seen in children. PAC might make up of either one or all 3 layers of the meninges. It could be congenital or acquired. The symptoms of PAC are CSF rhinorrhea, otorrhea, trigeminal neuralgia, headache and recurrent episodes of meningitis in children. Chronic pulsations against the thin anterior wall of a pneumatized petrous apex and raised intracranial pressure leading to dehiscence, herniation of meninges and CSF leak through weak points in the petrous apex. These lesions may be either unilateral or bilateral. Magnetic resonance imaging (MRI) has a key role in diagnosing these lesions as they follow CSF signal on all sequences and that these directly communicate with Meckel's cave. Treatment is surgical removal for symptomatic cases and surgical approach whether MFA or tranpetrosal is determined by patients hearing ability (Figures 1 and 2).[2]

Gorham-Stout syndrome is a lymphovascular proliferation of unknown etiology, lymph vessels usually do not penetrate the temporal bone. Computed tomography (CT) findings are helpful to assess the extent of bone destruction, while T2-weighted MRI can show the extent of abnormal lymphovascular proliferation. Contrast lymphangiography can be used to find exactly the site of leakage. Meningitis secondary to CSF leakage is a life-threatening complication of Gorham-Stout syndrome. Surgical treatment does not prevent progression of the disease, but it is effective. Gorham-Stout osteolytic lesions should be removed minimally and carefully since the leakage increases in some cases after biopsy. Anti-interleukin-6 (Anti-IL6) receptor antibody and anti-vascular endothelial growth factor (anti-VEGF), antibodies (bivacizumab) that decrease angiogenesis, bisphosphonates that decrease osteoclast activity and bone resorption, interferon propranolol can be used to treat this disease (Figure 3).[3]

Iatrogenic trauma is the most common cause of petrous apex CSF leak in our study, it is usually seen in pneumatized petrous apex that have anatomic pathway between the petrous apex and the medial ET. It is recommended to close ET and obliterate middle ear and mastoid cavity when the patient has pneumatized

	Multilayer fascia oblitartion with fat, ET plugging, bone graft, fibrin glue for sealing	Multilayer Fascia HAT and fat for packing, ET plugging, sealing with fibrin glue	Multilayer, primary dura closure, fascia, gelfom packing, ET bulging, synthetic dura	Fascia for durplasty, patched fascia and fibrin glue for sealing	One patient had only fascia and bon wax	Free flab	Perichondrium graft and nasal mucosal flap	Fascia for duraplasty, packing with muscle and bone wax, sealed by fibrin glue	Fascia for duraplasty ET plugging, fat obliteration, fibrin glue sealing	Fistula removal, and packing with fascia
Patients	5	3	4	3	1	2	1	1	5	1
Recurrence	0	0	0	1	1	0	0	0	2	1

Table 2: Fistula repair.

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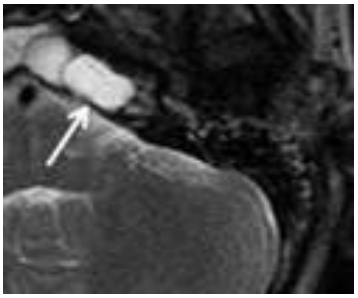

Figure 1: Meningocele axial T2-weighted note that the lesions demonstrate a signal identical to that of CSF, and are located in the petrous apex.

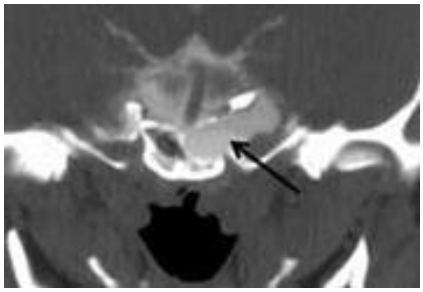

Figure 2: Coronal CT scans performed after intrathecal administration of contrast material, illustrating left petrous apex meningocel with leakage of contrast into the sphenoid sinus.

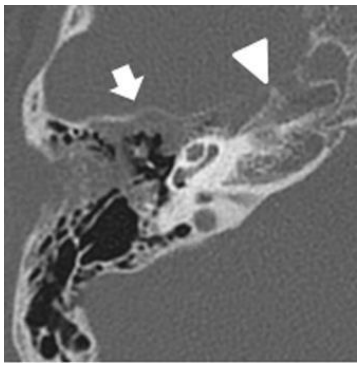

Figure 3: Non-contrast axial CT of the temporal bone, showing partially lytic lesion in the right mastoid air cell (arrow) and petrous apex (arrow head). Note fluid in the mastoid air cells and at the apex of the petrous temporal bone.

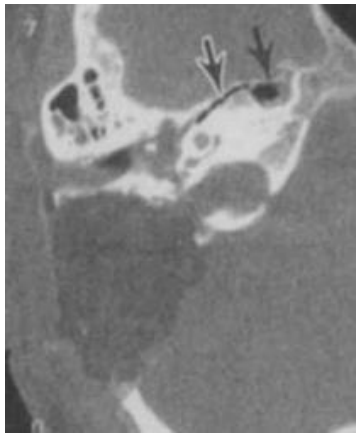

Figure 4: Axial CT scan showing air and defect in the petrous apex.

petrous apex with that abnormal pathway. Surgical repacking using multilayered obliteration technique is recommended for the cases that do not respond to conservative treatments (Figure 4).[4]

Petrosal cholesteatoma is rare entity, it may be primary or acquired in the origin. Primary congenital cholesteatoma arise from embryonary ectodermal inclusions but the pathogenesis is not clear. Congenital cholesteatoma may be asymptomatic or manifest as a conductive hearing loss, otalgia, vertigo and facial palsy. CSF rhinorrhea is extremely rare manifestation of cholesteatoma. Treatment is surgery *via* MFA or transpetrosal depending on hearing abilities in symptomatic cases, a multilayered obliteration technique in which artificial and autologous materials are combined is the best modality of treatment with the highest rate of success.[6]

CONCLUSION

Petrous apex CSF leak is more common in adults, iatrogenic trauma is the most common cause in adult patients while meningocele is the most common cause in pediatrics, CSF leak is more from right side. Meningitis, cranial nerves involvement and headache can also be associated with CSF leak. Multilayer fistula repair is least likely to recurre (Table 3).

	Pediatrics	Adults
Percentage	27%	73%
The most common cause	Meningocele	Iatrogenic
Sex	M<F	M=F
Side	Right<Left	Right<Left
Active leak	77%	96%
Meningitis	66%	20%
Treatment	Surgery	Conservative management then Surgery
Recurrence	11%	16%

Table 3: Petrous apex CSF leak conclusion.

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CONFLICTS OF INTEREST

The author declared that he has no conflicts of interest.

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Systematic Review

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Radiation-Induced Parotid Mucoepidermoid Carcinoma: A Systematic Review

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ABSTRACT

Background: Mucoepidermoid Carcinoma (MEC) of the parotid gland has been reported in patients who have been previously exposed to radiation. The purpose of this article is to review the literature examining radiation-induced parotid gland MEC.
Procedure: A PubMed search of related articles in English was performed using a combination of the following keywords: "radiation induced parotid tumors," "radiation induced salivary gland tumors," "radiation induced parotid MEC," "radiation induced salivary gland MEC,".
Results: The search results indicated 18 related articles describing the condition of 40 patients who have been previously exposed to radiation and subsequently developed parotid MEC. According to pre-existing studies, acute lymphoblastic leukemia (ALL) was a common observation among the patients following the initial diagnosis. The patients were divided into two groups on the basis of the treatment they received which included patients subjected to radiotherapy (RT) alone (n=13) and patients subjected to both radiotherapy and chemotherapy (n=27). The recorded latent time for secondary MEC development was significantly reduced in the chemoradiotherapy group of patients relative to the group undergoing radiotherapy alone. The overall survival rate for patients recorded over a period of 2 and 5 years was recorded as 97.4% and 95.4% respectively. The overall locoregional control rates recorded over a period of 2 years and 5 years were 97.4% and 93.1% respectively. There was no Significant difference in the recorded survival or locoregional control rates between the groups of patients exposed to radiation alone or a combination of chemotherapy and radiotherapy.
Conclusion: Radiation-induced parotid MEC has an excellent prognosis supporting the survival of over 90% diagnosed patients.

KEY WORDS: Radiation induced parotid tumors; Radiation induced salivary gland tumors; Radiation induced parotid MEC; Radiation induced salivary gland MEC.

ABBREVIATIONS: MEC: Mucoepidermoid Carcinoma; ALL: Acute Lymphoblastic Leukemia; RT: Radiotherapy; LT: Latent time.

INTRODUCTION

Salivary gland tumors are uncommon tumors that represent about 1% of head and neck tumors, only 5% of which occur among children. Among epithelial tumors of the salivary glands, mucoepidermoid carcinoma (MEC) is the most frequently observed histological type of cancer occurring in both adults and children. It is also the most common type of parotid gland malignancies. Parotid gland MEC may be characterized by symptoms such as the formation of a painless mass, facial weakness, referred otalgia, trismus and parenthesis. MEC can occur either as a primary or secondary malignancy. Exposure to radiation has been associated with an increased risk of developing secondary parotid MEC. Multiple cases have been reported about the incidence of secondary MEC in patients exposed to radiotherapy. Long-term evaluation and a high index of suspicion for second cancers are mandatory for all patients had radiotherapy previously. The secondary salivary MEC usually develop years or even decades after treatment of the first neoplasm has been completed. Since the survival of patients with cancer is improving, particularly amongst children, awareness of the spectrum of possible second tumors like parotid gland MEC is of increasing importance. The purpose of our article is to review

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the literature investigating the cases of parotid MEC induced by radiation.[1-3]

MATERIALS AND METHODS

Search Strategy

A systematic review was conducted for all cases of radiation induced Parotid MEC from 1967 to 2016 using the PubMed database.

Search criteria were input as "radiation induced parotid tumors", "radiation induced salivary gland tumors," "radiation induced parotid MEC," and "radiation induced salivary gland MEC,".

Six hundred seventeen initial articles were obtained. Articles were then filtered to exclude non-human and non-English language research.

Abstracts were first reviewed to search for articles that discussed cases of MEC induced by radiation occurring in the parotid gland and full-text articles were subsequently selected and reviewed for extraction of data. References of the included studies were examined for additional cases.

Selection Criteria and Data Extraction

All English, human studies that reported individual data for radiation induced parotid mucoepidermoid carcinoma were included if they reported diagnosis, treatment, follow-up, and outcome.

Non-human, radiologic, cadaveric, anatomical, and histological studies were excluded, as were sources with insufficient or unextractable data. Articles with unobtainable full text were also excluded.

Outcome measures extracted included: demographic data, radiation dose for primary desease, latent time, primary treatment modality, secondary parotid MEC treatment, follow-up, recurrence, metastasis.

Two-year overall survival and locoregional control were calculated using the Kaplan-Meier method. Differences in the survival rates were assessed by the log-rank test. All p values were two sided, and a p value <0.05 was adopted as the threshold for significance (Figure 1).

RESULTS

The final PubMed searches using the keywords yielded 18 studies comprising a total of 40 patients which were left for analysis. All 18 studies included individual patient data that was extractable and fit the minimum criteria for inclusion (Table 1).

Patients Characteristics

Our study yielded 40 patients with RT related MEC of parotid gland. The median age during primary diagnosis was 11.9 years (range 0.3-28 years); the male to female ratio was 17/23 (Table 2).

Initial Diagnosis conditions

The most commonly observed results of diagnosis were ALL (n=14), acne and skin disorders (n=6), and Hodgkins lymphoma (n=5). The other results following diagnosis included thyroid papillary tumor (n=3), AML (n=2), NPC (n=2), rhabdomyosarcoma (n=2) and astrocytoma (n=2). There was one recorded case each of CML, medulloblastoma, neuroblastoma, retinoplastomaand recurrent sore throat.

The treatment for initial tumor or similar condition in-

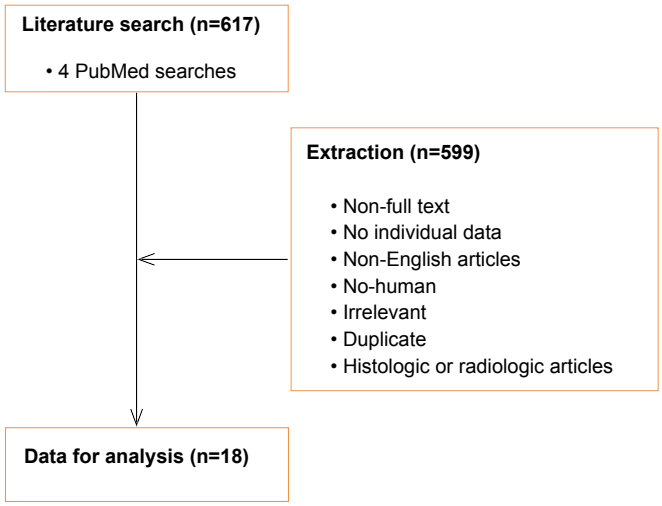

Figure 1: Flowchart of the study selection process.

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		Age at RT Exposure	Age At diagnosis	LT	Primary condition	Treatment for Initial condition	Treatment for Secondary MEC	Outcomes	Follow Up	Grade
Beal et al[1]	M	12	28	16	Hodgkin	RT+C 44 Gy	Surgery	NED	86 mo 7 yr	I
	M	17	32	15	Hodgkin	RT+C 30 Gy	Surgery RT	NED	22 mo 2 yr	II
	F	28	34	8	Hodgkin	RT+C 36 Gy	Surgery	NED	22 mo 2 yr	I
	M	15	58	43	Acne	RT Low dose	Surgery	NED	6 mo 1 yr	I
	F	15	79	64	Acne	RT Low dose	Surgery RT	NED	8 mo 1 yr	II
	M	15	21	6	NPC	RT 70 Gy	Surgery	NED	100 mo 8 yr	I
	F	5	50	45	Ringworm	RT Low dose	Surgery RT	NED	28 mo 2 yr	II
Prasannan et al[2]	M	22	10	9	ALL	RT+C 18 Gy	Surgery	NED	24 mo 2 yr	I
	F	3	12	9	ALL	RT+C 18 Gy	Surgery	NED	7 yr	I
Whatley et al[4]	5 M 3 F			29	NPC	RT+C 41	Surgery ND	NED	3 yr alive with distant	III
				11	Rhabdomyosarcoma	RT+C 37	Surgery ND RT	NED	6 yr	III
				13	Astrocytoma	RT 54	Surgery	NED	6 yr	II
				8	ALL	RT+C 24	Surgery RT	NED	6 yr	II
				3	Hodgkins	RT+C 24	Surgery	NED Local recurrence after 3 year reoperated	3 yr	II
				5	CML	RT+C 14	Surgery ND RT	NED	3 yr	II
				9	ALL	RT+C 24	Surgery RT	NED	9 yr	I
				5	ALL	RT+C 18	Surgery	NED	5 yr	I
Rodriguez-cuevas et al[5]	F	15,5	19	3.5	Thyroid papillary tumor	RT 100 mci radioiodine	Surgery	NED	1 yr	I
Henze et al[6]	F	20	39	19	Thyroid papillary tumor	RT 322 mci radioiodine	Surgery ND RT	NED	4 yr	N/V
Tugcu et al[7]	F	3	8	5	ALL	RT+C 12 Gy	Surgery	Recurrence 3 month Reoperated After 2 month Surgery ND RT	2 yr	I
Pierre Olivier Vedrine et al[8]	M	5	9	4	Astrocytoma	RT+C 50 Gy	Surgery	NED	16 yr	I
	M	5	18	13	ALL	RT+C 12 Gy	Surgery	NED	4,5	II
	F	11,5	17	6,5	ALL	RT+C 12 Gy	Surgery	NED	2	I

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	F	0.3	9	8	Retioplastoma	RT 52 Gy	Surgery	NED	9 yr	I
	M	11	14	3	Medulloblastma	RT+C 54 Gy	None	Dead		I
	F	5	12	7	Hodgkins	RT+C 20 Gy	Surgery	NED	2	I
	F	4	19,5	15	ALL	RT+C 18 Gy	Surgery RT	NED	2	I
Myer et al[9]	M	2	10	8	ALL	RT+C 18 Gy	Surgery	NED	2	II
Loy et al[10]	F	9	15	6	ALL	RT+C 18 Gy	Surgery	NED	3	i
	M	1	10	9	AML	RT+C 24 Gy	Surgery	NED	4	I
Sevelli et al[11]	F	2	15	13	ALL	RT+C /RT 12 Gy	Surgery	NED	7 yr	I
Arnold et al[12]	M	20,3	30,9	10,6	Rhabdomyasrcoma	RT+C 50 Gy RT field not Head and neck	Surgery	NED	13 yr	I
Zidar et al[13]	F	1	22	21	ALL	RT+C N/V	Surgery	NED	3	I
Piccinelli et al[14]	M	15	24	9	AML	RT+C 12 Gy	RT	NED	3 yr	N/V
Althan et al[15]	F	6	13	7	ALL	RT+C 18 Gy	Surgery ND RT Chemotherapy	NED	2 yr	III
Brito et al[16]	F	48	56	8	Thyroid papillary tumor	RT 150 mic	Surgery	NED	3 yr	I
welstad et al[17]	F	35	67	32	Recurrent sore throat	RT Low dose	Surgery	NED	2	I
	F	15	48	33	Acne	RT Low dose	Surgery RT	NED	2	I
Rice et al[18]	F	16	37	21	Acne	RT 6 Gy	Surgery	NED	2 yr	N/V
Smith et al[19]	F	10	42	32	scar	RT Low dose	Surgery RT	NED	10 mo 1 yr	N/V

LT: Latent time; RT: Radiotherapy.

Table 1: 18 studies included individual patient data that was extractable and fit the minimum criteria for inclusion.

	RT=13	Chemo/RT=27
Gender		
Male	3	14
female	10	13
Initial diagnosis		
malignant	6	27
Benign	7	0
Latent time		
median	27.9	9.78
range	3.5-64	1.3-29
Grade of MEC		
low	7	17
intermediate	3	6
High	0	3
Unknown	3	1

Table 2: Patients characteristics.

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cluded radiotherapy for 13 patients and a combination of chemotherapy radiotherapy in 27 patients. The median RT dose delivered was 28, 25 Gy (ranged 6-70 Gy).

Latent time (LT) from Initial Treatment to Development of Muccoepidermoid Carcinoma

The median LT recorded from completion of initial treatment to diagnosis of MEC was 11.9 years. LT in RT alone and combination of chemotherapy and RT were 23.7 years and 9.45 years respectively. LT in Chemotherapy-RT group was significantly lesser than LT in patients who were in the Radiotherapy group (p<0.01). LT was 38.7 years (21-64 years) in patients treated for benign conditions relative to 9.7 years (range 3-21 years) in patients treated for malignant conditions (significant at p<0. 01). There was no statistically significant difference in LT due to the influence ofgenderand grade of secondary MEC.

Secondary MEC Carcinoma Properties

Tumor grade was reported in 36 cases. 25 cases (66%) were that of low grade MEC, 6 cases (15%) were that of intermediate MEC, and 3 cases (7.5%) were that of high grade MEC. There was no difference in the grade of secondary MEC with respect to the use of radiotherapy alone or both chemotherapy and radiotherapy (p<0.05).

The secondary MEC was inside or at the edge of the RT field in all the patients who were treated initially with RT alone. For patients who were treated with both RT and chemotherapy, all except one case of secondary MEC developed inside or at the edge of RT field.

Treatment and Outcomes

A majority of patients were treated with surgery alone (n=27) 67% or in combination with radiation (n=10) 25%. The remaining patients received surgery, combination of chemotherapy and RT (n=1), and RT alone (n=1).

The median follow-up after diagnosis of secondary MEC was 4.16 years. The overall survival rates over a period of 2 years and 5 years were recorded as 97.5% and 95,4% respectively. One patient was dead of medulloblastoma. There was no statistically significant difference in survival rates with respect to the treatment for the initially diagnosed condition by chemoradiotherapy or by radiotherapy alone.

The overall locoregional control rates recorded over a period of 2 years and 5 years were 97.4% and 93.1% respectively. Local recurrence was seen in 2 patients treated with surgery alone. One patient had intermediate MEC, and the other one had a low grade MEC. There were no regional failures. There was no statistically significant difference in locoregional control with respect to the treatment of initially diagnosed condition i.e., by chemoradiotherapy or by radiotherapy alone.

There was one recorded case of a patient with high grade MEC who developed distant metastasis. One patient with low grade MEC had positive regional lymph node at presentation and was treated with surgery alone. There were no recorded cases of regional failures.

DISCUSSION

The carcinogenic properties of radiation were reported in the early 20th century. Radiation can damage DNA and lead to clinical conditions due to cross-linking between nucleotide bases, and single-stranded and double-stranded breaks in the DNA. The double-stranded DNA breaks and their inappropriate repair may result in mutations. Radiation may also induce mutations of tumor suppressor genes, genomic instability and transmissible instability that maximize the initiationof carcinogenesis. Irradiation may induce development of multiple tumors such as leukemia, carcinoma of mucous membranes, sarcomas, and head and neck carcinoma.[4]

The relationship between irradiation and the head and neck carcinoma has been extensively studied. Saenger reported 11 cases of development of thyroid tumors, 1 case of carcinoma of the parotid and submandibular glands respectively among 1,644 patients who were treated with radiation.[20] Epidemiological studies also, have established a linked between radiation therapy and the development of salivary gland neoplasms. This relationship has been observed particularly among atomic bomb survivors and patients who underwent radiation therapy for treating benign or neoplastic conditions. There are numerous instances in the literature indicating second malignancies among patients who underwent treatment for childhood neoplasia. However, the number of reportedcases for salivary gland tumors was low.[4] Garwicz et al reviewed the study of 30,000 children undergoing treatment for cancer and identified 247 cases of secondary malignancy, however, only 2 cases of these secondary tumors originated in salivary glands.[21] Though most studies report salivary gland tumors to be benign, radiation-induced salivary gland tumors are more often associated with malignancies.[4]

Irradiation may induce the formation of benign and malignant tumors of the salivary gland. Benign tumors more commonly occur in the form of pleomorphic adenoma or benign mixed tumor. Malignant tumors are generally identified with MEC, myoepithelial, malignant mixed tumor, adenocarcinoma, adenocytic carcinoma and acinic cell carcinoma. Modan et al[22] reported that the latent time until the development of salivary gland tumor was 11 years in case of malignancies and 21.5 years for the benign condition. The data collected following the study of atomic bomb survivors revealed that the incidence of parotid MEC increased with radiation dose and that MEC was the most common histopathological type observed in salivary gland tumor MEC induced by radiation. A similar observation has also been reported in both the series by Modan et al[22] and Beal et al[1]

Verma et al[3] reported 58 cases of salivary gland MEC

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induced by radiation and chemotherapy, most of which were low grade MECS and localized in the parotid gland. He observed that the latency time was shorter in case of the patients treated with chemotherapy +/- radiotherapy versus radiotherapy alone. The overall survival rates recorded over a period of 2 years and 5 years were 98% and 93.4% respectively and the locoregional control rates recorded for over 2 years and 5 years were 97.7% and 92.4% respectively.[3]

All the patients underwent surgical excision of the primary lesion as indicated by the size and location of the tumor. Neck dissection was performed in selected patients with intermediate and high grade pathology, and post-operative radiation was given to any patient with high grade malignancy, positive margins, or local recurrence. When treated aggressively, the prognosis of these patients appears relatively favorable.[4] The majority of cases reported for parotid MEC were low grade mucoepidermoid carcinoma, with an excellent prognosis following the complete removal of the tumor.[3]

This meta-analysis is limited due to small number of cases and the incomplete data found in the studies included that may prevent reaching statistically significant results. Although data heterogeneity might better reflect overall global population trends and enable generalization of the findings, many of the included studies have relatively small populations, which subject the analysis to publication bias. This may result in an over- or underestimation of treatment effect.

CONCLUSION

Radiation induced parotid MEC was most commonly diagnosed among females. In most of the reported cases, the initial diagnosis indicated the occurrence of ALL, acne and Hodgkins lymphoma. The latent time for secondary MEC development was significantly shorter in chemotherapy and radiotherapy groups. A majority of patients were treated with surgery alone (n =27) (67%) or in combination with radiation therapy (n=10)(25%). The overall survival rates recorded over a period of 2 years and 5 years were 97.5% respectively and the locoregional control rates recorded over a period of 2 years and 5 years were 97.4% and 93.1% respectively. There was no statistically significant difference in the survival or locoregional control rates between the groups exposed to radiation or a combination of chemotherapy and radiation. There was one recorded case of a patient with high grade MEC who developed distant metastasis. Also, the study indicated one patient with low grade MEC with positive regional lymph node at presentation who was treated with surgery alone. Only 1 case of patient death has been reported on account of medulloblastoma. There has been no evidence of regional failures.

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Research

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Relationship Between Serum Vitamin D Levels and Childhood Recurrent Tonsillitis

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ABSTRACT

Background: Many factors are associated with the development of recurrent tonsillitis. These include patient incompliance, premature cessation of antibiotherapy, inadequate antibiotic absorbance, bacterial tolerance, bacterial load, bacterial biofilms, and immune system deficiencies.
Objective: To compare between recurrent tonsillitis patients undergoing three to seven tonsillitis episodes per year within less than two years with controls having less than three tonsillitis episodes per year on the basis of vitamin D levels.
Study design: A retrospective review of clinical charts.
Methods: A total of 426 patients were enrolled in this study. The patients were divided into two groups according to the number of acute tonsillitis episodes: Those who had less than three episodes per year (Group A) and those with three to seven episodes per year (Group B). The patients in Group A were assigned to the control group. Each patient in Group B was considered as a potential candidate for recurrent tonsillitis. The total number of episodes of acute tonsillitis within one year, demographic characteristics of the patients and the mean serum 25-hydroxyvitamin D levels of both groups were compared.
Results: Group A consisted of 277 patients (132 women, 145 men; mean age 4.40±2.46 years; range 2 to 10 years), while Group B consisted of 149 patients (66 women, 83 men; mean age 5.22±2.26 years; range 2 to 10 years). The mean serum vitamin D levels of Group A and Group B were 57.83±23.10 nmol/L and 48.03±31.36 nmol/L, respectively. Serum vitamin D level of Group B was lower than the Vitamin D levels of Group A which was statistically significant (p=0.001, p<0.01, respectively).
Conclusion: This is the first study investigating vitamin D levels among patients for the diagnosis of recurrent tonsillitis during the follow-up. However, further prospective randomized-controlled studies are conducted to gain a better understanding as to whether vitamin D supplementation would reduce the tonsillectomy rates in the diagnosis of recurrent tonsillitis.

KEYWORDS: Vitamin D level; Children; Tonsillectomy; Recurrent tonsillitis.

INTRODUCTION

Acute tonsillopharyngitis is a clinical presentation which is usually characterized by clinical acute inflammatory manifestations such as hyperemic tonsils and pharynx, exudation, and ulceration.[1,2] Although this condition shows a viral etiological origin, approximately 5% to 17% of the cases are bacteriological which is mostly Group A β-hemolytic streptococci.[3] As previously described by Paradise et al, recurrent tonsillitis is defined as seven episodes of the condition within one year or five episodes in the preceding two years and more or three episodes in the preceding three years and more.[4,5] Many factors are related with the development of recurrent tonsillitis. These include patient incompliance, premature cessation of antibiotherapy, inadequate antibiotic absorbance, bacterial tolerance, bacterial load, bacterial biofilms, and immune system deficiencies.[3]

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It is well-established that vitamin D plays an important role in bone mineralization of the skeletal system. Serum levels of vitamin D may differ according to racial differences and seasonal changes. Afro-Americans and Hispanics have been reported to have lower vitamin D levels than Caucasians.[6] In the winter season, lower amounts of vitamin D synthesis occurs in the skin.[3,7] Solar ultraviolet B radiation (wavelength: 290-315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is rapidly converted to vitamin D3. Vitamin D from the skin and diet is metabolized by the liver to form 25-hydroxyvitamin D (25(OH) D). Then, 25 (OH) D is metabolized by the enzyme 25-hydroxyvitamin D-1α- hydroxylase (CYP27B1) to its active form, 1.25-dihydroxyvitamin D. Inadequate circulation may lead to the development of cancer, diabetes mellitus, cardiovascular diseases, and immune deficiencies.[8-10] In addition, vitamin D has a critical role in the production of surface anti-microbial peptides (AMPs), which plays an important role in innate immunity.[11] These peptides have a wide spectrum antimicrobial activity and directly prevent proliferation of microorganisms in a tissue.[12] Anti-microbial peptides are not only produced from neutrophils, but also produced from macrophages and natural killer (NK) cells. Also, they have been shown to play a critical role in the respiratory defense system.[12,13] Many recent studies have confirmed the positive correlation between low levels of vitamin D and increased incidence of upper respiratory tract infections (URTIs).[14-16]

In the present study, we aimed to compare recurrent tonsillitis patients undergoing three to seven tonsillitis episodes per year within less than two years with controls having less than three tonsillitis episodes per year with respect to the vitamin D levels.

METHODS

This retrospective study was conducted among a total of 426 children who were diagnosed with acute tonsillitis between June 2013 and June 2014 at our hospital, Otolaryngology-Head and Neck Surgery Department. The age of the patients ranged between 2 and 10 years. The inclusion criteria were as follows: The absence of complications due to acute URTIs or a condition requiring hospitalization, not receiving vitamin D in the depot or on daily basis within the past three months. The patients affected by chronic disease, who were unwilling to give a written informed consent or those with inaccessible medical data, were excluded from the study. All the patients were followed-up for at least one year and the total number of acute tonsillitis episodes was recorded. Serum 25 (OH) D levels, serum C-reactive protein (CRP), creatinine, serum calcium, total protein, albumin, and complete blood count was analyzed within the first three days of the first episode of acute tonsillitis. Serum 25 (OH) D level was determined using enzyme linked immunosorbent assay (ELISA) method. 25 (OH) D levels below 50 nmol/L was defined as a deficiency, between 50 to 80 nmol/L as inadequacy, between 80 to 250 nmol/L as normal, between 250 to 325 nmol/L as excessiveness, and greater than 325 mol/L as toxicity.[17,18] Normal values were between 0 to 0.50 mg/dL for CRP, 0.4 to 0.60 mg/dL for creatinine, 8.6 to 10.0 mg/dL for calcium, 6.4 to 8.3 g/dL for total protein, 3.5 to 5.2 g/dL for albumin, and 4000 to 11.000 cells/mm^3 for white blood cell counts (WBCs). According to the number of acute tonsillitis episodes they underwent, the patients were divided into two groups: Those who had less than three episodes per year (Group A) and those with three to seven episodes per year (Group B) in the last two years. The patients in Group A were assigned to the control group. Seven or more episodes within one year were defined as recurrent tonsillitis according to the Paradise criteria.[5] Recurrent tonsillitis was considered indicative of tonsillectomy and these patients were recommended for tonsillectomy. Each patient in Group B was considered as a potential candidate for recurrent tonsillitis. Age, sex, chronic diseases, total number of acute tonsillitis episodes per year, serum 25 (OH) D levels, body mass index (BMI), tonsil size, serum CRP levels, creatinine, serum calcium levels, total protein, albumin, and complete blood counts were recorded. The total number of acute tonsillitis episodes within one year, demographic characteristics and the mean serum 25 (OH) D levels of both groups were compared.

All patients were informed about the study and a written consent was obtained from each patient or parents of the patients. The study protocol was approved by the Institutional Ethics Committee (ethical committee number: 2014/64). The study was conducted in accordance with the principles of Helsinki Declaration.

STATISTICAL ANALYSIS

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 software (Utah, USA). Other than the descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum), the Mann-Whitney U test was performed to analyze the abnormally distributed quantitative data between the groups. The Yates continuity correction (Yates chi-square) test was performed to compare the qualitative data between the groups. p-values of <0.01 and <0.05 were considered as statistically significant.

RESULTS

A total of 426 patients were enrolled in this study. Group A consisted of 277 patients (132 women, 145 men; mean age 4.40±2.46 years; range 2 to 10 years), while Group B consisted of 149 patients (66 women, 83 men; mean age 5.22±2.26 years; range 2 to 10 years). The demographic characteristics of the groups have been summarized in Table 1.

The mean serum vitamin D levels of Group A and Group B were 57.83±23.10 nmol/L and 48.03±31.36 nmol/L, respectively. None of the patients had a serum 25 (OH) D level at toxic levels. The mean 25 (OH) D levels of Group B were found to be at the deficiency level, whereas Group A was at the

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Table 1: Patient Demographics.

	Group A (n=277) Mean±SD	Group B (n=149) Mean±SD	*p**
Age (year, mean±SD)	4.40±2.46	5.22±2.26	**0.012***
Serum CRP (ng/dl)	0.675±0.123	1.4±0.8	**0.079***
Creatinine (mg/dl)	0.82±0.4	0.78±0.2	**0.186***
Calsiyum (mg/dl)	9.3±1.1	9.4±1.4	**0.376***
Total protein (g/dl)	6.84±3.7	7.0±2.9	**0.028***
Albumin (g/dl)	4.3±3.3	4.8±2.2	**0.662***
WBC (10^3/mm^3)	11.9±4.7	13.3±4.4	**0.018***
BMI	14.7±3.8	16.4±4.4	**0.628***

*Man-Whitney U test

inadequacy level. Serum 25 (OH) D levels of Group B were lower than the levels of Group A and this difference was statistically significant (p=0.001, p<0.01, respectively) (Table 2). Of the patients in Group A and Group B, 145 and 83 were males, respectively. However, there was no statistically significant difference in the number of acute tonsillitis episodes between the groups on the basis of sex (p>0.05) (Table 3).

No statistically significant difference was observed either in terms of the mean CRP (ng/dL), creatinine (mg/dL), calcium (mg/dL), total protein (g/dL), albumin levels (g/dL), and WBCs (cells/mm^3) between groups.

The tonsil size according to the Brodsky Scale[19] and the mean 25 (OH) D levels have been shown in Table 4. Based on our results, lower 25 (OH) D levels were significantly associated with larger tonsil sizes (p=0.023).

DISCUSSION

The adaptive immune system is a complex system associated with the contribution of many cells.[20] Vitamin D plays a critical role in the adaptive immune system.[11] Effects of vitamin D on the immune system have been the subject of many researches, particularly focusing on its effects on the production of AMPs. Gombart et al[21] showed that 1, 25 (OH) D increased the production of cathelicidin peptides. These peptides have been demonstrated to have a protective role against URTIs in the previous studies.[22-24] In another study, Ball et al[13] compared tonsillectomies for recurrent tonsillitis and obstructive sleep apnea syndrome and concluded that AMPs of the tonsil surface epithelium, beta-defensin 1, 3 - and cathelicidin decreased in the recurrent tonsillitis group.

Table 2: Vitamin D Levels of the Study and Control Groups.

	Group A (227) mean±SD	Group B (149) mean±SD	*p**
Serum vitamin D levels (nmol/L)	57.83±23.10	48.03±31.36	**0.001***

**Man-Whitney U test
SD: standart deviation.

Table 3: Comparison of Sex of the Study and Control Groups According to the Yates Continuity Correction Test.

		Group A (277) (%)	Group B (149) (%)	*p**
Gender	Male	145 (63.6)	83 (36.4)	0.122*
	Female	132 (66.7)	66 (33.3)	

*Yates Continuity Correction Test

Table 4: Correlation between the Tonsil Size and Mean 25 (OH) Vitamin D Levels.

Groups/tonsil size	Grade 1(No)	Grade 2	Grade 3	Grade 4	
A (227)	65.8 (44)	61.5 (76)	53,0 (80)	49.7 (27)	p=0.023*
B (149)	53.4 (23)	50.2 (42)	43,5 (64)	40.4 (20)	
	p:0.622*	p:0.42*	p:0,882*	p:0.346*	

*p: Man-Whitney U test

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Lack of vitamin D receptors (VDR) were also shown to develop hypertrophy of subcutaneous lymph nodes due to the accumulation of mature dendritic cells in mice.[25] In addition, low levels of 1, 25 (OH) D were considered to decrease the inhibition of differentiation of dendritic cells, thereby, resulting in adenotonsillar hypertrophy.[11] Moreover, vitamin D-induced antiviral peptides were shown to be effective against the herpes simplex type 1, adenovirus, human immunodeficiency virus, and chickenpox virus as has been implicated in the previous studies.[26]

Furthermore, Science et al[27] demonstrated that a higher risk for viral URTIs which was confirmed by polymerase chain reaction (PCR) was associated with low vitamin D levels. The authors revealed that the risk for URTIs increased by 50%, when vitamin D levels were below 70 nmol/L, whereas the risk increased by 70%, when vitamin D levels were below 50 nmol/L. The authors concluded that young age and low levels of vitamin D increased the incidence of URTIs. Similarly, in our study, recurrent tonsillitis candidate group (Group B) was younger. In a study, Ginde et al[28] reported that adults with vitamin D levels of ≥75 nmol/L had fewer URTI episodes and children undergoing tonsillectomy due to recurrent tonsillitis had a mean serum vitamin D level of <75 nmol/L. In another study, Nseir et al[3] found a positive correlation between recurrent Group A streptococci (GAS) tonsillitis and vitamin D deficiency. In their study, the mean vitamin D level was 26±7 ng/mL (64.7±17.4 nmol/L) in the control group and 11.5±4.7 ng/mL (28.6±11.7 nmol/L) in the recurrent GAS group. Reid et al[11] found that low vitamin D levels were associated with dark skin, high body mass index, and large tonsil sizes. However, there was no significant relationship between BMI values and vitamin D levels. 25 (OH) D levels were significantly associated with the operating surgeon's classification technique of the tonsil size; however, multiple linear regression analysis showed that this association was not a major predictor of 25 (OH) D status. In the present study, we found a negative correlation between the tonsil size and 25 (OH) D status, consistent with the results of study of Reid et al.[11] Although, this may be a potential explanation, further studies are required to assess the association of larger tonsil sizes with lower 25 (OH) vitamin D status. In another study, Esteitie et al[6] measured the mean vitamin D levels as 28.4±7.7 ng/mL (70.7±19.2 nmol/L) in children undergoing adenotonsillectomy and 27.1±7.1 ng/mL (67.5±17.7 nmol/L) in the control group, suggesting no significant Vitamin D deficiency between the two groups. In addition, Yıldız et al[29] measured serum vitamin D levels as 142.7±68.1 nmol/L in patients with recurrent tonsillitis and 192.3±56.1 nmol/L in healthy controls. The authors suggested that the recurrent tonsillitis group had significantly lower vitamin D levels, compared to healthy children. In the same study, VDR polymorphisms were investigated; however, no significant difference was found between the groups. In their study, Aydın et al[7] showed that there was no significant difference between vitamin D levels and VDR polymorphism among children with recurrent tonsillitis and healthy subjects. They measured serum vitamin D levels as 176±79 nmol/L in the recurrent tonsillitis group and 193±56 nmol/L in the control group. Varying results of the studies may be explained by the several factors such as working groups, seasonal, personal or racial factors, vitamin D measurement methods, studied endpoints or VDR polymorphisms. Our study can be distinguished from previous studies, as it aims to demonstrate the relationship between the incidence of acute tonsillitis and vitamin D levels with a control group consisting of the same patient population. In the current study, we addressed patients with frequent acute tonsillitis episodes but not diagnosed with recurrent tonsillitis. The patients with three or more episodes of acute tonsillitis are also followed-up to evaluate whether they would continue to have more than three episodes and be diagnosed with recurrent tonsillitis in the next two or three years. This is the first reported study in the literature, directed towards investigating vitamin D levels among recurrent tonsillitis candidates. Furthermore, we divided the patients into two groups according to the number of episodes they underwent. Higher vitamin D levels in Group A than Group B suggest that vitamin D levels may have an influence on the frequency of episodes. As a result, several studies in the literature have led to the emergence of a new controversy. The question "if low levels of vitamin D increase the incidence of URTIs, can vitamin D supplementation reduce the incidence of upper URTI?" has been the subject of interest of many researchers. Recent studies on this subject produced different results. In randomized-controlled studies, vitamin D supplementation was shown to reduce the incidence of URTI.[30,31] On the contrary, Li-Ng et al[32] was unable to retrieve any data indicating that the supplementation therapy reduces the incidence of URTIs. In another study, Robertson et al[10] reported that there was no relationship between vitamin D levels and URTIs and concluded that vitamin D supplementation did not reduce the incidence of URTIs in the Norwegian population.

On the other hand, there are some limitations to this study. Firstly, the seasonal changes of vitamin D levels were ignored. Secondly, the vitamin D levels were measured only once. An ideal study should encompass vitamin D level measurements at the same seasonal period. Although our laboratory test results are consistent with the studies conducted worldwide, we obtained different results from other studies of Yıldız et al[29] and Aydın et al[7] which were carried out among the Turkish children. This may have been due to our ignoring the seasonal changes, laboratory testing and also not measuring VDR polymorphism. This can be also attributed to the small sample size and variable characteristics of the control groups of two other studies.

CONCLUSIONS

In this study, vitamin D levels of children who are potential candidates for recurrent tonsillitis and tonsillectomy were significantly lower than those with tonsillitis episodes less than three within one year. Evaluation of vitamin D levels in candidates for tonsillectomy may reduce the rates of tonsillectomy operations. However, we were unable to find any study investigating whether the vitamin D supplementation reduced the rates of tonsillectomy operations. Therefore, further studies are required to investigate that how much reduction in the operation rates

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would be obtained from the vitamin D supplementation. In addition, studies which determine optimal levels of vitamin D for adequate immune function in children are needed.

CONFLICTS OF INTEREST

No conflicts of interest was declared by the authors.

FINANCIAL DISCLOSURE

The authors declare that this case has received no financial support.

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Case Report

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Serum Calcitonin Levels may be Used in the Differential Diagnosis of Vagal Glomus

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ABSTRACT

Medullary thyroid carcinoma (MTC) is a neuroendocrine (NE) tumor and is very rarely observed. MTC originates from the parafolliculer C cell and can show various histopathological patterns. Head and neck paragangliomas are seen rarely. Paragangliomas in the head and neck region are usually non-functional. MTC should be considered in the differential diagnosis of paragangliomas in the head and neck region. A high degree of clinical investigation is needed to determine the rare potential etiology underlying this condition. Because patients with MTC can present different clinical manifestations, otolaryngologist must be aware of MTC and its rare medical presentations. This case presented here highlights the importance of serum calcitonin levels in the differential diagnosis of paragangliomas in the head and neck region.

KEY WORDS: Calcitonin; Medullary thyroid cancer; Glomus vagale.

ABBREVIATIONS: MTC: Medullary Thyroid Carcinoma; NE: Neuroendocrine; US: Ultrasonography; CEA: Carcinoembryonic antigen; SEER: Surveillance, Epidemiology, and End Results.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a neuroendocrine (NE) tumor and comprises lesser than 10% of all thyroid malign tumors. So it is a very rarely occuring tumor in all malignancies.[1-3] Due to recent Surveillance, Epidemiology, and End Results (SEER) data in the United States, MTC accounts for 1% to 2% of all thyroid cancers.[4,5] A large part of the medullary carcinomas are sporadic, and familial form constitutes nearly 25%.[4-6] The 10-year survival rate of MTC is approximately about 75% with respect to current literature. The study of Jung et al[7] reported that the 5- and 10-year survival rates for MTC were 92% and 87%, respectively. The MTC spreads early to both paratracheal and lateral cervical lymph nodes, and distant spreading occurs in the liver, lungs, bones, and less frequently in brain and skin. All the patients undergoing a pre-operative diagnosis of MTC should be evaluated with a detailed neck ultrasonography (US) and measurement of serum calcitonin and carcinoembryonic antigen (CEA). Basal serum calcitonin concentrations usually can be linked to tumor burden but also indicates tumor differentiation in MTC.[8-10]

MTC is a neuroendocrine cancer that originates from the parafollicular C cells and can indicate various histopathological patterns. One of these is a paraganglioma-like pattern.[9,11] Another type of NE cancer is an extra-adrenal parasympathetic paraganglioma that is usually found in the head and neck region. These type of paragangliomas are usually non-functional tumors (95%).[8] Paragangliomas constitute nearly 0.6% of all head and neck tumors and they orig-

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inate from the vagus nerve ganglion, carotid body, jugular bulb and tympanic plexus.[12] The differential diagnosis of neuroendocrine tumors appear to be quite difficult in certain unusual clinical presentations. Preoperative fine needle aspiration biopsies provide the results for the early diagnosis of MTC. Biochemical and genetic screening would also help determine patients with early stage sporadic MTC. However, FNAB is never excluded from a malignancy and sometimes proves to be inadequate in the differential diagnosis of MTC. The reported case illustrates a valuable example of what needs to be done in a similar situation. MTC should be considered in the differential diagnosis of paragangliomas in the head and neck region. A high degree of clinical investigation is needed to determine the rare potential etiology underlying this condition. To the best of our knowledge, this is the first case reported in the literature to focus on the differential diagnosis of MTC with serum calcitonin levels.

CASE PRESENTATION

A 25 year old female patient reported to our clinic with a 3 cm mass in level 4 of the left side of her neck. She noticed 3 months ago that the mass showed a tendency to grow. On performing clinical investigation, there was no medical evidence other than a mass in the neck. No pathological findings were observed following the pan endoscopic examination. A mass of About 3 cm size in the left side of the neck was revealed in the ultrasonography (USG) reports. A diffuse echo reduction and, pseudonodular image in the thyroid gland was observed in the USG report. On performing the MRI of the neck, a 40×23 mm sized, well-circumscribed mass was seen that displaced the left common carotid artery and jugular vein to the anterior and the right. This mass showed intense contrast enhancement and vascular structures were observed in the mass. This view was consistent with the observation of the glomus vagale radiologically. No pathological finding was observed in the thyroid gland and other neck structures (Figure 1). Because glomus tumors are generally seen at level 2-3, radiological diagnosis of glomus tumor was viewed with medical suspicion. For this reason, a fine needle aspiration biopsy (FNAB) was performed. FNAB was also found to be compatible with the vagal glomus and the patient was referred to the endocrinology clinic. The 24-hour analysis of adrenaline, noradrenaline, vanilmandelic acid, metanephrine, normetanephrine, dopamine and, 5-hydroxyindolacetic acid levels in the urine were observed to be in the normal range, where upon the patient was operated with the diagnosis of the non-functioning of the glomus vagale tumor to the left. While performing the surgery, the mass in close relation with the vagina carotica was extended into the carotid sheath posterolaterally. When the mass was dissected, it was observed that there was no direct relation with any structure in the carotid sheath and, the mass could be easily stripped from the vagus. Thereupon, the mass was subjected to frozen examination with the consultation of the pathologist. In the opinion of the pathologist, the mass was a neuroendocrine tumor and a glomus tumor and thyroid medullary cancer was observed following differential diagnosis. Palpation of the thyroid gland, and assessment of level 6 and level 4 was performed intraoperatively. Because of the lack of any pathological symptom during the intraoperative assessment, it was decided that before undertaking any further action, a definitive pathological report had to be obtained. In the definitive pathological examination, with chromogranin, synaptophysin and calcitonin by immunohistochemical staining, the reports following diagnosis were indicative of medullary thyroid cancer metastases (Figure 2). After pathological examination, we assessed the level of serum calcitonin and this was recorded as 809 pg/ml (n:0-5). Total thyroidectomy, bilateral functional neck dissection and level six neck dissection were decided to be performed by the endocrine surgery council. The operation was completed without any complications. Once, three of the four parathyroid glands were observed and confirmed by frozen examination, which were replanted to the left sternocleidomastoid muscle 1/3 middle segment. Postoperatively, bilateral vocal cord movements were normal, but to address the cause of hypocalcemia, calcium 2×1500 mg and 1×0.25 mcg calcitriol® had to be administered. In the post-operative pathological report; four focus micromedullary thyroid cancer, four metastasis in the

Figure 1: Neck Contrast Enhanced Magnetic Resonance Imaging.

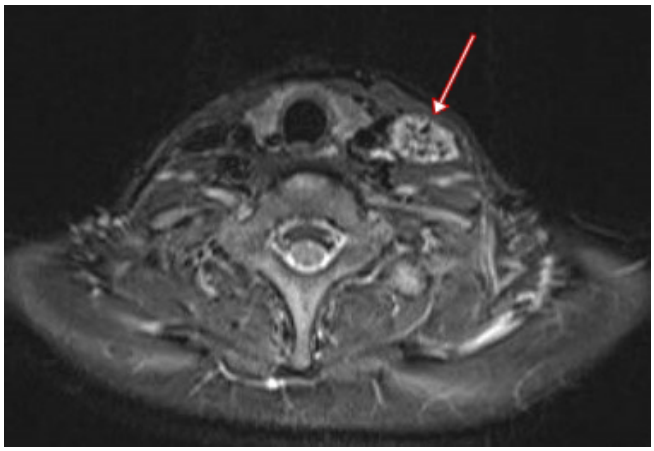

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Figure 2: Medullary Thyroid Carcinoma Metastasis, Including Amyloid Deposits that Infiltrate the Lymph Node in the Environment with Follicular Hyperplasia (4x).

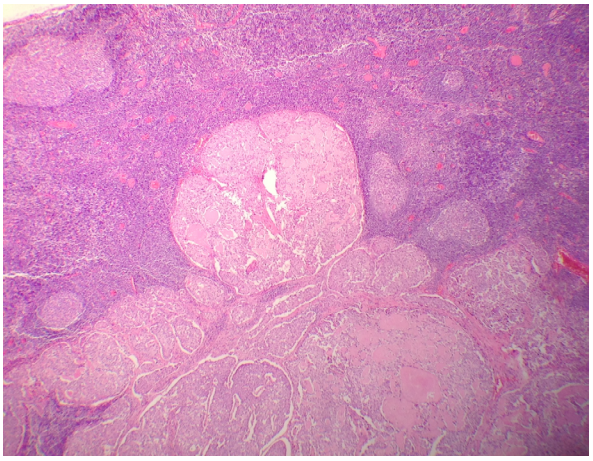
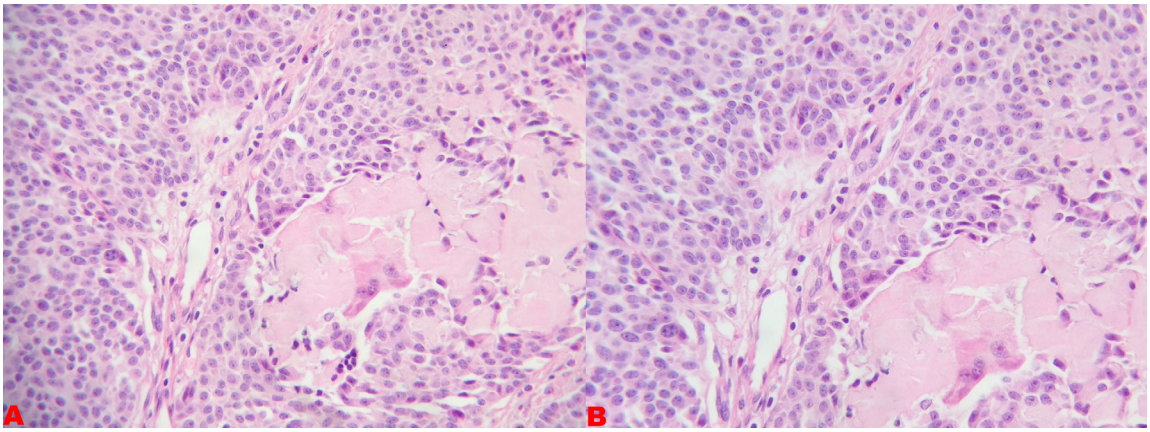


Figure 3: A) The Tumor, Composed of Cells with Uniform Mononucleolide with Salt Pepper Chromate and Amyloid Accumulation is Observed in the Lower Right Corner (40x). B) Tumor Tissue, Composed of Cells with Large Single Nucleolus and, Salt Pepper Chromatin Structure and, Large Eosinophilic Material Accumulation (40x).



central neck dissection specimen and, pericapsular invasion in one of these four metastasis and, one metastasis with pericapsular invasion in the right neck dissection specimen was revealed (Figure 3A-3B). When the calcium and rocaltrol® treatment was terminated in the first month following the surgery, the serum calcium level remained stable at 8.25 mg/dL. In the early follow-up period, pregnancy occurred. Thus, adjuvant therapy was not administered. The patient is still followed up regularly without any sign of distant metastasis and local recurrence as has been observed in the imaging findings but the serum calcitonin level has been recorded at 66.20 pg/mL (n:0-5)

DISCUSSION

An elevated serum calcitonin level is a highly sensitive and specific tumor marker for postsurgical follow-up of patients with MTC following total thyroidectomy. However, relative to more advanced tumors, which may be dedifferentiated by decreased calcitonin production, CEA may be a more worthy tumor marker.[13] Other important prognostic factors for adverse outcome include advanced age at diagnosis, extent of primary tumor, and nodal metastasis and distant metastases.[14] Standard treatment for patients with MTC is total thyroidectomy and dissection of cervical lymph node (LN) compartments, depending on serum calcitonin levels and neck US findings. Usually in sporadic MTC, the tumor is unifocal and defined in the fifth or sixth decade of life. In the hereditary MTC, a vast majority of patients are asymptomatic initially and diagnosed by genetic or biochemical screening tests during the early stages of the disease. The clinical symptoms of sporadic MTC contain a thyroid nodule or mass, cervical lymphadenopathy or other cervical symptoms, metastatic disease, and seldom diarrhea, flushing, or Cushing's syndrome due to chronic ectopic adrenocorticotropic hormone production.[15-18]

Histopathological differential diagnosis of MTC in-

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cludes paraganglioma and other NE tumors.[10] To distinguish NE tumors on the basis of cytomorphology is difficult. Owing to this reason, clinicians must keep the pathologist informed and immunohistochemistry must be performed.[11] In the diagnosis of MTC, calcitonin, chromogranin A, or CEA immunostaining can be used.[8] Calcitonin is an important molecule because it has a very significant role in the diagnosis and clinical follow-up of patients with MTC.[6] If immunohistochemistry cannot be performed and there is a confusion regarding the diagnosis, the serum calcitonin level can help clarify the diagnostic reports.[7] In particular, the glomus vagale has an origin in the neuroendocrine tumor and can be located anywhere in the vagus ganglia. Other neuroendocrine tumors and metastases of these tumors are observed by differential diagnosis. Especially in the evaluation of the head and neck region glomus tumors, medullary thyroid cancer metastasis is clinical relevant. As has been indicated in this case, such that FNAB and imaging cannot provide relevant information based on the differential diagnosis. Therefore, monitoring the role of calcitonin in preoperative evaluation will be very helpful in the planning of operations, thus preventing from possible secondary operations and eliminating additional risks of morbidity and mortality.

The main causes of death of patients with MTC are distant metastases. Survival after the discovery of distant metastases is 51% in 1 year, 26% in 5 years, and 10% in 10 years according to the existing research literature.[19-21] Long-term survival of the two types of MTC patients was not significantly different. Various factors have been proposed as prognostic factors for the outcome for patients with MTC. Age at diagnosis, TNM stage and completeness of initial surgery are significant factors affecting the outcome.[22,23] Therefore, patients with MTC should be closely followed-up and recommended about related endocrine pathologies and the risk of the disease for other family members.

CONCLUSION

MTC should be considered for the differential diagnosis of paragangliomas in the head and neck region. A high degree of clinical suspicion needs to be observed to determine this rare potential etiology. Because patients with MTC can present with different clinical manifestations, the otolaryngologist must be aware of MTC and its rare presentations.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

INFORMED CONSENT

Written informed consent was obtained from the patient who participated in this case.

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Letter to the Editor

NIFTP: A Critical Pathologist View

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In the last two years, there has been an interesting discussion on NIFTP (Non-invasive folicular Thyroid neoplasm papillary-like nuclear features), the previous encapsulated folicular variant of papillary thyroid carcinoma (EFVPTC). The study of Nikiforov et al,[1] laid the foundations of this new discovery, which are:

a. The morphological features, i.e., the follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC);

b. Lack of invasion, which separates this tumor from invasive FVPTC;

c. Clonal origin determined by finding a driver mutation, which indicates that the lesion is biologically a neoplasm; and

d. A very low risk of adverse outcome when the tumor is non-invasive.

However, some practical pathological problems arose in relation to this new pathological entity:

1. During freezing procedure of thyroidectomy, it would be necessary to freeze the entire capsule to discard microscopic foci of invasion, that would change the classification of the lesion to FVPTC;
2. The NIFTP cannot be diagnosed only by fine needle aspiration cytology (FNAC).[2] In this case, it is necessary to correlate the observations with the imaging findings (Thyroid US with encapsulated lesion);
3. During histological processing, it is interesting to note that the lesion is fully represented, because exclusion criteria for NIFTP such as necrosis and vascular invasion may appear focally;
4. In some developing countries, it is very difficult to perform molecular testing to confirm the mutation that is leading to this lesion.

Due to the aforementioned facts, I believe that NIFTP is a diagnosis of exclusion in patients with encapsulated lesions showing papillary nuclear characteristics and follicular architecture. I also believe that further studies should be done with an attempt to characterize this new entity, definitively separating it from the follicular variant of papillary carcinoma.

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