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Favorable treatment for rare case tumor in oral cavity: A whartin's tumor review article

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Abstract
Introduction: Warthin's tumor is a benign tumor of the salivary glands, especially in the parotid gland, usually cystic, 10% of all tumors are usually bilateral. Meanwhile, based on the histological image, the tumor is formed by a wide acinus with a papillary-cystic appearance. The epithelium is similar to the salivary ducts which are attached by dense lymphoid tissue that is visible in the lymphoid follicles. According to the Hamburg Salivary Gland Registry, the overall incidence of salivary gland tumors is 5 per 100,000 with an estimated 65% of these tumors being benign. Warthin's tumor ranks second after pleomorphic adenoma of the parotid gland, 90% of cases occur in the superficial lobe of the parotid gland and rarely in the deeper lobe (10%). And Warthin's tumors account for about 15% of all epithelial tumors of the parotid gland.
Discussion: Definitive diagnosis requires a tissue sample. Fine needle aspiration (FNA) has played a larger role in recent years. In general, FNA has good overall accuracy for diagnosing salivary gland tumors (87% to 97%), and has been widely used for the diagnosis of Warthin's tumor. The main treatment for salivary gland tumors is surgery. Radiotherapy as postoperative adjuvant therapy is given only as indicated, or given to inoperable salivary gland carcinoma. Chemotherapy is only given as an adjuvant, although it is still under study, and the results are not satisfactory.
Conclusion: The prognosis for salivary gland cancer depends on staging, histology, type of cancer, patient age, and adequacy of evidence from surgical removal. The most important prognostic factor is cancer staging. Furthermore, the most important factor is the histologic grade of the cancer.

Keywords: whartin's tumor, salivary gland, rare, treatment, surgery

Introduction

Warthin's tumor, also known as papillary cystadenoma, is a relatively rare and generally benign growth of new tissue that grows slowly and has controversial etiology. Among the salivary tumors, Warthin's tumor is the second most prevalent for pleomorphic adenoma and usually in people in their fifties and sixties. The parotid glands are one of the most commonly affected by this type of tumor (84%). Warthin's tumor accounts for 14% to 30% of parotid tumors. Warthin's tumor constitutes 5-14% of parotid tumors and 2-5% of sub maxillary tumors. These tumors were mainly found in men with a ratio of 6:1 in incidence compared to women, increasing incidence experience with smoking habit. Warthin's tumor almost always occurs in older adults. In men, the peak incidence is in the 7th decade, whereas in women it is in the 6th decade. Patient's age, smoking history, symptoms, and might be factor predisposition of Warthin's tumor [1].

Smokers have 8 times the risk of developing Warthin's tumor. This is thought to be due to the retrograde flow of substances in tobacco smoke into the saliva channels or the excretion of substances from the smoke into the saliva ducts. A fact that has caught the attention of pathologists is that the incidence is in men and the incidence is increased in women. These changes may be due to a decrease in smoking habits in men and trends in women[2]. Definite diagnosis requires a tissue sample. In the past, most specimens were excised and the diagnosis was established after excision. Fine needle aspiration (FNA) has played a larger role in recent years. In general, FNA has good accuracy in total for diagnosing salivary tumors (87% to 97%), and has been widely used for the diagnosis of Warthin's tumor. Based on the histological image, the tumor is formed by a wide acinus with a papillary-cystic appearance. The epithelium is similar to the salivary ducts which are attached by dense lymphoid tissue that is visible in the lymphoid follicles. According to the Hamburg Salivary Gland Registry, the overall incidence of salivary gland tumors is 5 per 100,000 with an estimated 65% of these tumors being benign. Warthin's tumor ranks second after pleomorphic adenoma of the parotid gland, 90% of cases occur in the superficial lobe of the parotid gland and rarely in the deeper lobe (10%). And Warthin's tumors account for about 15% of all epithelial tumors of the parotid gland [1, 2, 3].

Favorable treatment of these tumors is by surgery, which can be easily performed, because the location of the tumor is generally on the surface. Some surgeons prefer local resection of the surrounding tissue, while other surgeons prefer superficial parotidectomy. This condition avoids rupturing the capsule of the tumor, also combination with pharmacology might be needed. Warthin's tumor has a low recurrence rate (2-5%) [3].

Discussion

Definition

Barthin's tumor is a benign tumor of the salivary gland which was first introduced by Dr. Hildrebrand in 1896. Then further developed by Dr. Warthin in 1929[4]. As a benign salivary gland neoplasm and named by pathologist Aldred Scott Warthin, Warthin's tumor has synonyms adenolymphoma, cystadenolymphoma, and papillary cystadenoma lymphomatosum. Among these synonyms, cystadenoma papillary lymphomatosum is widely recognized by pathologists because it reflects a tumor with a characteristic tissue shape. Papillary cystademona shows a bilayer epithelium with papillary protrusions in the cystoma, whereas lymphomatosum is associated with the lymphal tissue that surrounds and supports the tumor. Warthin was the first to endorse the term tumor, and has introduced Warthin's tumor as an easy-to-use designation ever since [5].

Barthin's tumor is a benign tumor of the salivary glands, especially in the parotid gland, usually cystic, 10% of all tumors are usually bilateral. Meanwhile, based on the histological image, the tumor is formed by a wide acinus with a papillary-cystic appearance. The epithelium is similar to the salivary ducts which are attached by dense lymphoid tissue that is visible in the lymphoid follicles [6].

Epidemiology

Warthin's tumor is a benign neoplasm arising in the salivary glands, especially in the parotid gland (70%), while Warthin's tumor in the submandibular gland (22%) and sublingual salivary glands and minor salivary glands (8%) are rare case. The ratio between malignant and benign tumors of the salivary glands also varies according to location, common location is in parotid glands 80% benign and 20% malignant, submandibular glands and sublingual glands 50% benign and malignant 50% and minor salivary glands 25% benign and 75% malignant [7, 8].

Benign salivary gland neoplasms are most often seen as slow growth, clearly defined. Symptoms such as pain, rapid growth, nerve weakness, and paresthesia and signs of cervical lymphadenopathy and the presence of fixation in the underlying skin or muscle indicate malignancy. Benign tumors of the salivary glands include pleomorphic adenomas, various types of monomorphic adenomas (including Warthins' tumors, oncocytomas, basal cell adenomas, canalicular adenomas, and myoepitheliomas), various types of ductal papillomas, and capillary hemangiomas. Pleomorphic adenoma accounts for 40% to 70% of all salivary gland tumors and occurs most often in the tail of the parotid gland. Pablo et.al conducted a retrospective study of 124 cases of salivary gland tumors, found 80% benign and 20% malignant. The most common locations were the parotid glands, namely 71%, submandibular glands 24% and minor salivary glands only 5%. In the case of benign tumors, there were plemorphic adenomas in 84% of the cases while Warthin's tumors alone accounted for 13% of the total cases of benign tumors [9, 10].

According to the Hamburg Salivary Gland Registry, the overall incidence of salivary gland tumors is 5 per 100,000 with an estimated 65% of these tumors being benign. Barthin's tumor ranks second after pleomorphic adenoma of the parotid gland, 90% of cases occur in the superficial lobe of the parotid gland and rarely in the deeper lobe (10%). And Barthin's tumors account for about 15% of all epithelial tumors of the parotid gland. Barthin's tumor is usually a cystic lesion in the tail of the parotid gland, is painless, slow-growing and occurs mainly in men between the 4th and 7th decades and is associated with smoking, which causes irritation of the ductal epithelium of the salivary gland, thereby stimulating tumorigenesis. They are often multicentral (12-20%), and about 10% are bilateral [4, 5, 10].

These tumors occur most frequently in old white people, as many as 10% of these tumors affect the 5th and 7th decades of age. The ratio between men and women is 3: 1 and accounts for about 5% of parotid benign tumors. In a retrospective comparative study of 96 cases of Warthin's tumor, the ratio of males to females was 3.3: 1, and it was found that warthin's tumors were 6.2% multifocal and bilateral. Meanwhile, in the research conducted by Helma *et al* towards 70 cases of Warthin's tumor with the conclusion that Warthin's tumor occurs mostly in men with a history of being smokers and the location of Warthin's dominant tumor is unilateral in the parotid gland [11, 12, 13].

In the case of Warthin's tumor, recurrences rarely occur and almost never turn into a malignancy. Malignancy change is estimated in only 0.1% of cases of Warthin's tumor. The incidence of postoperative recurrences is also very rare. Chulam *et al*., In their research concluded that both superficial and total parathyroidectomy surgery with good facial nerve evacuation did not result in recurrences during long-term monitoring [12, 13].

Salivary Glands Anatomy

The salivary glands are glands that open or secrete secretions into the oral cavity. Most of these are small glands in the sub mucosa or mucosa that line the epithelium of the mouth, tongue, palate, cheeks, and lips, and open into the oral cavity directly or through small ducts. However, there are much larger salivary glands (major salivary glands), namely the parotid, submandibular, and sublingual glands [14, 15]. In the following, we can see the anatomy of the salivary glands as shown in Figure 1.

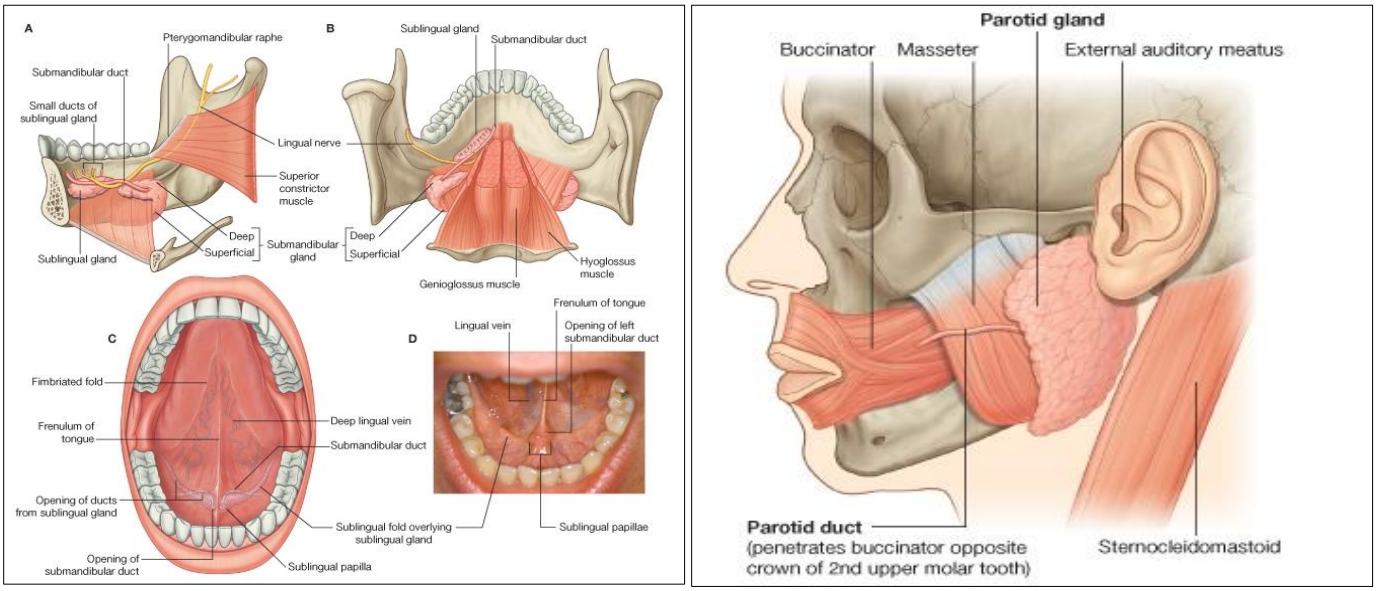

Fig 1: Anatomy of the Salivary Glands [15]

Parotid Glands

The parotid glands lie outside the boundaries of the oral cavity in a triangular arrangement of shallow trenches formed by the following anatomical structures, as sternocleidomastoid muscle behind; front mandibular ramus; and the superior and trench floor is formed by the external acoustic meatus and the posterior aspect of the zygomatic arch. The parotid duct passes anteriorly on the outer surface of the masseter muscle and then turns medially through the buccinator muscle of the cheek and opens into the oral cavity adjacent to the crown of the upper second molar teeth. The parotid glands cover the external carotid artery, retromandibular vein, and the origin of the extra cranial part of the facial nerve [VII] [15].

Submandibular glands

The submandibular gland extends smaller than the parotid gland, but larger than the sublingual gland. Each shaped hook. The submandibular duct arises from the inner medial side of the gland in the oral cavity and passes in front to open at the apex of the small sublingual papilla beside the base of the frenulum of the tongue. The lingual nerve rotates under the submandibular duct, traversing first the lateral side and then the medial side of the duct, the nerve descending anteromedial through the floor of the oral cavity and then up to the tongue [15].

Sublingual Glands

The sublingual glands are the smallest of the three major salivary glands. Each is almond-shaped and immediately lateral to the submandibular duct and associated with the lingual nerve in the floor of the oral cavity. The superior margin of the sublingual gland gives rise to a longitudinal fold of the mucosa (sublingual fold), which extends from the posterolateral aspect of the floor of the oral cavity to the sublingual papilla beside the base of the frenulum of the tongue in the anterior midline. The sublingual gland drains into the oral cavity through various small ducts that open to the top of the sublingual fold [15].

Vascularization, Limfatics and Innervation

The blood vessels that provide vascularization of the parotid gland originate from the external carotid artery and from its adjacent branches to the gland. The submandibular and sublingual glands are supplied by branches of the facial and lingual arteries. Veins from the parotid gland are passed to the external jugular vein, and veins from the submandibular and sublingual glands drain into the lingual and facial veins. Lymphatic vessels from the parotid gland drain into nodes that are in or in the gland. The parotid node then drains into the superficial and deep cervical nodes. Lymphatics from the submandibular and sublingual glands drain mainly to the submandibular glands and then to the deep cervical glands, partly to the juguloomyohyoid nodes [15, 16].

The parasympathetic innervation to all the salivary glands in the oral cavity originates from the facial nerve branches [VII], which join the maxillary [V2] and mandibular [V3] branches of the nerves to reach their target destination. The parotid gland, receives parasympathetic innervation from fibers that initially travel in the glossopharyngeal nerve [IX], which eventually join the mandibular nerve branches [V3] in the infratemporal fossa [15, 16].

Clinical Manifestation

The clinical symptoms that arise are the appearance of masses in the facial area (parotid), in the angulus of the mandible (parotid and submandibular), neck (submandibular) or swelling of the floor of the mouth (sublingual). A rapid enlargement of the mass leading to abnormalities such as infection, cystic degeneration, hemorrhage or malignancy. Benign salivary gland tumors are usually mobile and for masses or benign tumors originating from the parotid, there is no impairment of facial nerve function. Malignant lesions usually cause symptoms such as facial nerve disorders, rapid growth, paresthesias, fixed lesions and enlarged cervical lymph nodes. Benign parotid tumors often present as painless, slow-growing masses often caudal to the parotid glands [16, 17].

Diagnosis

The diagnosis should be asked about previous radiation to the head-neck area, operations that have been performed on the salivary glands and certain diseases that can cause swelling of these glands (diabetes, cirrhosis, hepatitis, alcoholism). Also drugs such as opiates, antihypertension, phenothiazine derivatives, diazepam, and chlordiazepoksid can cause swelling, because these drugs decrease the function of the salivary glands. Clinical inspection can be determined whether there is abnormal swelling or the condition of the skin and mucous membrane interfere facial nerve functions. Sometimes on inspection it is clear that there is fixation to the surrounding tissue, and immediately the presence of trismus is evident. The sufferer should also be examined from behind, to be able to see any asymmetries that might escape our attention [17, 18].

Careful palpation can lead to an accurate assessment of tumor localization, size (in cm), shape, consistency, and relationship to surroundings and if possible, palpation should be done bimanual. Systematic palpation of the neck for lymphadenopathy and rare Warthin's tumor should also be performed. On investigations, cytologic examination (small needle biopsy) is very important in the diagnosis of swelling in a suspected salivary gland tumor. But, using this method, generally a temporary working diagnosis can be achieved and in the majority of benign clinical and cytologic tumors, no additional imaging studies are required [18, 19].

X-rays of the head and neck may show the presence or absence of bone disorders or may also be important for differential diagnostics (salivary gland stones, calcified lymph nodes). Chest X-ray is required for possible hematogenous metastases. Using ecography or CT might be an option, but even better with MRI, an overview of the limiting nature and space relationships of the tumor can be obtained. Size, localization, its location inside or outside the lymph nodes could be visualisation. Pleomorphic adenoma can be differentiated from other salivary gland tumors by MRI. This method cannot differentiate between benign and malignant tumors. Contrast X-ray of the parotid glands and submandibular glands (sialography) is required for further investigation of inflammation (chronic) or calcification and can be useful for a differential diagnosis [18, 19].

The differential diagnosis of salivary gland tumors is not only benign but must also consider the malignant type. A variety of other benign neoplastic involving the salivary glands should be considered, papillary duct adenoma, sebaceous adenoma, classic schwannoma, congenital epithelial tumor, cavernous hemangioma and ectopic extra glandular tissue. Fine needle aspiration is very useful in determining whether an asymptomatic mass in the parotid gland region or in the submandibular space is whether the gland is true or not. Treatment options can be determined based on the present invention [19, 20].

Treatment

The main treatment for salivary gland tumors is surgery. Radiotherapy as postoperative adjuvant therapy is given only as indicated, or given to inoperable salivary gland carcinoma. Chemotherapy is only given as an adjuvant, although it is still under study, and the results are not satisfactory.

Operable tumor [21, 22, 23, 24]

a. Primary therapy (surgery). The treatment option for parotid gland neoplasms is surgery. Most of the benign and malignant parotid tumors can be treated with superficial or total parotidectomy according to the location of the tumor by preservation of the facilitative nerve. Superficial parotidectomy is the procedure of removing the tumor mass with the superficial lobe parotid gland. Performed on benign superficial lobe parotid tumors. Total parotidectomy is the removal of the tumor mass with all parts of the parotid gland performed on:

1. Parotid malignant tumors that do not have extraparenkim extension and n.VII
2. Parotid benign tumor affecting the deep lobe
3. Extended total parotidectomy, performed on: Parotid malignant tumors that already have extraparenkim extension or n.VII
4. Radical neck desection (RND), performed on: There are metastases k.g.b. neck which are still operable

b. Additional therapy

Although the primary therapy for malignant salivary gland tumors is surgery, radiation therapy is also recommended because it has a beneficial effect when combined with surgery in increasing the therapeutic outcome. In addition, it acts as a primary therapy for nonresectable tumors. There are circumstances in which radiation therapy is indicated, namely:

1. High grade malignancy
2. There is still macroscopic or microscopic residue
3. Tumor attached to the nerve (n.fasialis, n.lingualis, n. hypoglossus, n. Accessories)
4. Each T3, T4
5. Carcinoma residif
6. Profundus lobe parotid carcinoma

Radiotherapy should be started 4-6 weeks after surgery to give adequate surgical wound healing, especially if the nerve has been transferred. Local radiotherapy is given to the operating field covering the incision scar as much as 50 Gy in 5 weeks. Ipsilateral regional / neck radiotherapy is given for T3, T4, or high grade malignancy. Both conventional and neutron-beam radiation therapy have been advocated as single-treatment modalities for T1 and T2 malignant salivary gland neoplasms. This approach is controversial, but it can be considered if there are real contraindications to surgery.

Inoperable tumors [21, 22, 23, 24]

a. The main therapy

Radiotherapy: 65 - 70 Gy in 7-8 weeks

b. Additional therapy

hemotherapy: The indication for chemotherapy is a patient with an inoperable tumor. Partial or complete response has been achieved in up to 50% of patients, which usually lasts 5-8 months and may include significant pain control. Most patients have cystic adenoid carcinoma, mucoepidermoid carcinoma, or adenocarcinoma. Currently, paclitaxel is the most frequently used agent. Although chemotherapy alone does not improve survival rates, the integration of radiation and chemotherapy has been shown to improve local control and show improvements in the

management of salivary gland malignancies.

1. For types of adenocarcinoma (adenoid cystic carcinoma, adenocarcinoma, malignant mixed tumor, acinic cell carcinoma)
- -adriamycin 50mg / m2 iv on day 1
- -5 fluorouracil 500mg / m2 iv on day 1
- -sisplatin 100mg / m2 iv on day 2 (repeated every 3 weeks)

2. For squamous cell carcinoma types (squamous cell carcinoma, mucoepidermoid carcinoma)
- -methotrexate 50mg / m2 iv on days 1 and 7
- -sisplatin 100mg / m2 iv on day 2 (repeated every 3 weeks)

Lymph node metastases (N) [21,22,23,24]

a. The main therapy
- Operable: radical neck dissection (RND)
- Inoperable: radiotherapy 40 Gy / + chemotherapy preoperatively, then evaluated
- becomes operable then RND
- remains inoperable then radiotherapy is continued until 70Gy

b. Additional therapy

Ipsilateral neck radiotherapy 40 Gy

Distant Metastases (M)

Palliative therapy: chemotherapy

a. For types of adenocarcinoma (adenoid cystic carcinoma, adenocarcinoma, malignant mixed tumor, acinic cell carcinoma)
- Adriamycin 50mg / m2 iv on day 1
- 5 fluorouracil 500mg / m2 iv on day 1
- sisplatin 100mg / m2 iv on day 2 (repeated every 3 weeks)

b. For squamous cell carcinoma types (squamous cell carcinoma, mucoepidermoid carcinoma)
- -methotrexate 50mg / m2 iv on days 1 and 7
- -sisplatin 100mg / m2 iv on day 2 (repeated every 3 weeks)

Prognosis

The prognosis for salivary gland cancer depends on staging, histology, type of cancer, patient age, and adequacy of evidence from surgical removal. The most important prognostic factor is cancer staging. Furthermore the most important factor is the histologic grade of the cancer. Low-grade cancers such as acinic cell cancer and low-grade mucoepidermoid are now usually stage 1 stage 2 cancer and have a good prognosis, 10-year with a survival rate of 80%. On the other hand, 10 years of survival following treatment from high-grade staging 3 and 4. Such as adenocarcinoma, squamous cell carcinoma, and high-grade mucoepidermoid carcinoma [24, 25].

Conclusion

The prognosis for salivary gland cancer depends on staging, histology, type of cancer, patient age, and adequacy of evidence from surgical removal. The most important prognostic factor is cancer staging. Furthermore, the most important factor is the histologic grade of the cancer

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