Metastatic Papillary Thyroid Carcinoma to the Maxilla: Case Report and Literature Review

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Abstract Metastatic tumors to the oral cavity are uncommon and a thyroid origin is considered exceedingly rare. A case of metastatic papillary thyroid carcinoma (PTC) presenting as a painful swelling in the right posterior maxilla of a 63-year-old male is reported here. The patient had been diagnosed with PTC 2 years ago and treated with thyroidectomy and radioactive iodine treatment. Radiographically, the metastatic lesion presented as a poorly-defined radiolucent lesion around an impacted maxillary third molar in the right maxilla. Histopathologic examination revealed features of PTC which was immunohistochemically positive for pancytokeratin, keratin 19 and thyroglobulin. Imaging studies revealed the presence of residual maxillary and neck disease as well as additional metastatic lesions in the sternum, ribs, and left tibia. A thorough review of the English language literature revealed only 36 previously published cases of thyroid cancer metastases to the oral cavity, the demographic and clinicopathologic features of which are summarized.

Keywords Oral metastasis · Papillary carcinoma · Thyroid cancer · Maxilla

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, constituting up to 80% of all thyroid cancers [1]. It presents as an asymptomatic slow-growing thyroid mass, sometimes found incidentally, with a relatively indolent behavior and a favorable prognosis [2].

The rate and location of metastatic spread varies according to the histologic subtype of thyroid cancer. Up to 6% of patients with well-differentiated thyroid carcinoma have been reported to develop distant metastasis, with a predilection for bones (43%) and lung (40%) [3]. Papillary thyroid carcinoma usually shows lymphatic invasion and frequently metastasizes to regional lymph nodes, although distant metastases are considerably less frequent [4]. On the other hand, follicular thyroid carcinomas are more prone to spread hematogenously, especially to the lung and bones with a rate of 5–20% [5]. In general, bone metastases are clinically diagnosed in 4–13% of patients with differentiated thyroid cancer, are more common in patients over 45 years old, usually symptomatic and often multicentric; the most common skeletal metastatic sites are the vertebrae (29%), pelvis (22%), ribs (17%) and femur (11%) [6].

Metastatic tumors to the oral cavity are uncommon representing about 1% of all oral malignancies [7, 8]. The most common metastatic site is the posterior body of the mandible (premolar-molar region) [9, 10]. Oral metastases usually originate from lung, breast, prostate, colon, and kidney [10, 11]. Thyroid carcinoma metastases to the jaws are rare with only a limited number of cases previously reported in the literature. Herein, we report a case of PTC metastasizing to the maxilla and present a comprehensive review of published cases of metastatic thyroid cancer to the oral cavity.

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Case Report

A 63-year-old man was referred by his general practitioner to an Oral Surgery Clinic for the management of a painful swelling of the right posterior maxilla. Two years ago, the patient was diagnosed with PTC treated with thyroidectomy. Subsequently, the patient received radioactive iodine in therapeutic doses twice and was kept on thyroxine suppression therapy; however, serum thyroglobulin levels were gradually elevated, indicating residual active disease.

Clinically, a painful, hard swelling of the right posterior maxilla was noticed. Panoramic radiograph revealed a poorly-defined radiolucent lesion around an impacted third molar in the right maxilla (Fig. 1). Surgical excision of the impacted tooth and removal of the surrounding soft tissue was performed.

Histopathologic examination of the specimen revealed malignant epithelial cells arranged in solid masses and islands; the neoplastic cells were oval to round with vesicular and occasional clear and/or grooved nuclei and exhibited moderate pleomorphism with few atypical mitotic figures (Fig. 2). Immunohistochemical analysis revealed positivity against pancytokeratin, keratin 19 and thyroglobulin (Fig. 2b insets). Based on the nuclear features and the immunohistochemical profile of the tumor along with the history of thyroid cancer, a final diagnosis of metastatic PTC was made. Bone scintigraphy (Fig. 3) and computed tomography (Fig. 4) confirmed the presence of metastatic disease in the maxilla and maxillary sinus, also revealing the presence of residual neck disease and additional metastatic lesions in the sternum, ribs, and left tibia.

Recommended treatment included surgical debulking of the neck disease and administration of a new therapeutic

Fig. 1 Panoramic radiograph revealing a poorly-defined radiolucent lesion around an impacted third molar in the right maxilla

Fig. 2 Photomicrographs showing moderately pleomorphic malignant oval to rounded epithelial cells with vesicular and occasional clear and/or grooved nuclei (hematoxylin and eosin, **a** 100X, **b** 200X). Insets: Immunohistochemical stains revealing tumor cell positivity against pancytokeratin (CK, 200X), keratin 19 (K19, 200X) and thyroglobulin (Tg, 200X)

dose of I-131, but the patient refused to comply and elected for radiotherapy of the maxilla and chest. He underwent 13 sessions of radiotherapy and received in total 39 Gy, resulting in transient reduction of the cervical mass and amelioration of his symptoms (i.e. difficulty in swallowing and pain in the sternum). After the completion of the radiotherapy, the patient was recommended a new surgical debulking of the cervical mass which had become firm. In the setting of pre-surgical screening, a new fine needle aspiration (FNA) of the cervical mass was performed, which revealed the persistence of dedifferentiated (anaplastic) thyroid carcinoma. Thus, the patient's condition was deemed inoperable and he was treated with chemotherapy (6 cycles every 3 weeks; combination of cisplatin and adriamycin) as palliative therapy. At last follow-up, 2 years after the diagnosis of the maxillary metastasis, the patient was alive but with widespread metastatic disease.

Fig. 3 Bone scintigraphy with TC99 m MDP showing increased uptake indicative of metastatic disease in the right maxilla and sternum

Discussion

Metastatic tumors to the oral cavity are relatively rare, representing approximately 1% of all oral malignancies [7, 8]. In a recent large retrospective study, the most common malignancies to give oral metastases were breast cancer (in women) and lung cancer (in men); other common primary sites were prostate, colon, kidney, adrenal gland, liver, and female genital organs [10–13]. Metastatic thyroid carcinoma to the oral tissues is a rare event. In large series and reviews of metastatic tumors to the jaws, primary thyroid origin ranged from about 4–6.5% [10, 14, 15].

Our comprehensive review of published cases of metastatic thyroid cancer to the oral tissues (with sufficient information pertinent to individual cases) revealed only 37 cases (including our case), the salient features of which are summarized in Table 1 [7, 9, 15–42]. The mean age of patients was 60.6 years (among 33 patients with available information). Although there was a wide age range (13–87), only two patients were younger than 40; most patients ($n = 12$), including ours, were in the 7th decade of life, followed by the 6th decade ($n = 8$) and the 8th decade ($n = 5$). Considering that the mean age of diagnosis of well-differentiated thyroid carcinoma is about 40 years for papillary and 50 years for follicular, the somewhat older ages of patients with metastatic disease to the mouth may reflect the time needed for the development and detection of the metastatic lesions. Among 34 patients with available gender information, 25 (73.5%) were female and 9 (26.5%) were male. The observed female predilection can be attributed to the greater preponderance of thyroid cancer in women compared to men [5, 9, 26].

Fig. 4 Computed tomography revealing space-occupying metastatic disease in the right maxilla and maxillary sinus (a), as well as osteolytic metastasis in the sternum (b)

With regard to the histologic subtype of the primary thyroid cancer, most oral metastases originated from a follicular thyroid carcinoma (20 out of 36 with available data; 55.5%). Papillary thyroid carcinoma accounted for 8 (22.2%) cases, including the case reported here. Single cases of Hurthle cell, medullary, and poorly differentiated carcinoma were reported, while in 5 cases, the primary tumor was reported as thyroid carcinoma or adenocarcinoma without further specification. In general, the oral metastatic tumor preserved the histologic features of the primary tumor. The predilection for oral metastases from

Table 1 Published case reports of metastatic thyroid carcinoma to the oral cavity

Authors	Age	Gender	Location	Histological diagnosis	Time to metastasis	Treatment of metastasis	Other metastatic sites	Outcome (length of follow-up)
Meyer and Shklar [7]	51	F	Mandible	Adenocarcinoma	NA	NA	None	NA
McDaniel et al. [16]	77	F	Right mandible	Follicular thyroid Ca	First manifestation	Hemimandibulectomy and parotidectomy	None	Alive FOD (4 years)
	48	F	Left mandible	Follicular thyroid Ca	First manifestation	NA	NA	NA
Al Ani [17]	60	F	Right mandible	Follicular thyroid Ca	First manifestation	NA	NA	NA
Ripp et al. [18]	61	F	Right mandible	Thyroid Ca	First manifestation ^a	Cobalt teletherapy	Widespread	DOD (1 year)
Draper et al. [19]	NA	F	Mandible	Follicular thyroid Ca	NA	Radiotherapy	Skull	NA
Stypulkowska et al. [20]	NA	NA	Mandible	Adenocarcinoma	1 year	Symptomatic	NA	DOD ($\leq$ 1 year)
	NA	NA	Mandible	Adenocarcinoma	First manifestation	Symptomatic	NA	DOD ($\leq$ 1 year)
Osguthorpe and Bratton [21]	53	M	Right mandible	Follicular thyroid Ca	First manifestation	Partial mandibulectomy	None	Alive FOD (3 years)
Nishimura et al. [22]	74	F	Right mandible	Follicular thyroid Ca	First manifestation ^b	Chemotherapy	Vertebra	Alive (4 months)
Parichatikanond et al. [23]	51	F	Left mandible	Papillary thyroid Ca (follicular variant)	First manifestation	Chemotherapy, radiotherapy, hemimandibulectomy	Ribs, lung	Alive with disease (4.5 years)
	42	F	Left mandible	Follicular thyroid Ca	First manifestation	Hemimandibulectomy	NA	NA
Tovi et al. [24]	33	M	Left mandible	Follicular thyroid Ca	First manifestation ^c	Radioactive iodine therapy	Vertebrae, mediastinum, parietal bone, femur	Died of thyroid crisis (17 days)
Markitziu et al. [25]	69	F	Left mandible and parotid	Papillary thyroid Ca (follicular variant)	First manifestation ^d	Radiotherapy and chemotherapy	NA	Alive FOD (1.5 years)
Kahn and McCord [26]	82	F	Anterior mandible	Follicular thyroid Ca	32 years	Radiotherapy, radioactive iodine therapy, resection	Mediastinum, tibia, lungs and pelvis ^e	Died FOD (1.5 years)
Whitaker et al. [27]	87	M	Dorsal tongue and lower lip	Follicular thyroid Ca	First manifestation ^f	Surgical removal, radioactive iodine therapy	Lung	Alive with disease (4 months)
Vural and Hanna [9]	64	F	Right mandible and infratemporal fossa	Follicular thyroid Ca	First manifestation	Radical resection and radioactive iodine therapy	Multiple skeletal metastatic lesions	NA
Erdag et al. [15]	53	F	Right mandible and infratemporal fossa	Papillary thyroid Ca (follicular variant)	4 years	Resection and radioactive iodine therapy	Vertebra and humerus	Alive with disease (2.5 years)
Agarwal et al. [28]	45	F	Left mandible	Follicular thyroid Ca	First manifestation ^g	Hemimandibulectomy	NA	NA
Anil et al. [29]	61	F	Right mandible	Follicular thyroid Ca	8 years	NA	NA	NA
Piatelli et al. [30]	54	F	Right maxillary gingiva	Medullary thyroid Ca	4 months	Surgical removal	Cervical lymph nodes	Alive FOD (4 years)
Colella et al. [31]	50	F	Right mandible	Papillary thyroid Ca	5 years	NA	NA	NA

Table 1 continued

Authors	Age	Gender	Location	Histological diagnosis	Time to metastasis	Treatment of metastasis	Other metastatic sites	Outcome (length of follow-up)
Ostrosky et al. [32]	72	M	Anterior mandible	Follicular thyroid Ca	First manifestation	Resection	None	NA
Bodner et al. [33]	65	M	Right mandible	Hurtle cell thyroid Ca	NA	Supportive	Widespread	DOD (2 months)
Liu et al. [34]	66	M	Masticator space and mandible	Papillary thyroid Ca (follicular variant)	22 years	Radical resection and radioactive iodine therapy	Scapula	Alive FOD
Tamoliakis et al. [35]	69	F	Mandible	Papillary thyroid Ca	NA	Inoperable	NA	DOD (1 month)
Kaveri et al. [36]	NA	NA	Mandible	Thyroid Ca	NA	Resection	NA	NA
	65	M	Left mandible	Follicular thyroid Ca	First manifestation	NA	Ribs	NA
Antunes and Antunes [37]	13	F	Maxilla	Papillary thyroid Ca	NA	NA	NA	NA
	64	F	Mandible	Follicular thyroid Ca	NA	NA	NA	NA
	75	F	Mandible	Follicular thyroid Ca	NA	NA	NA	NA
Ismail et al. [38]	70	F	Left mandible	Follicular thyroid Ca	First manifestation	NA	Hilar lymph nodes	NA
Algahtani et al. [39]	66	F	Left mandible	Follicular thyroid Ca	First manifestation	Segmental mandibulectomy	Cervical lymph nodes	NA
Nishikawa et al. [40]	83	F	Anterior mandible	Poorly-differentiated thyroid Ca	2 years	None	Lung	DOD (1 year and 7 months)
Kumar et al. [41]	58	F	Left mandible	Follicular thyroid Ca	First manifestation	Segmental mandibulectomy	None	Alive FOD (2 years)
Daley and Darling [42]	57	M	Anterior mandibular gingiva	NA	NA	NA	NA	NA
Present case	63	M	Right posterior maxilla and maxillary sinus	Papillary thyroid Ca	2 years	Radiotherapy, chemotherapy	Sternum, ribs, left tibia	Alive with disease (2 years)

NA not available, FOD free of disease, DOD died of disease

^a Subtotal thyroidectomy had been performed 12 years earlier; the histologic report had indicated the presence of bizarre embryonic elements with unusual mitotic configurations

^b The patient was aware of a slowly growing tumor in the neck for 10 years

^c Total thyroidectomy had been performed 10 years earlier with a benign diagnosis of adenoma. Re-examination of the thyroid specimen at the time of the mandibular metastasis revealed follicular carcinoma

^d Total thyroidectomy had been performed 2 years earlier with a benign diagnosis of goiter. Re-examination of the thyroid specimen at the time of the mandibular metastasis revealed papillary thyroid carcinoma (follicular variant)

^e Metastatic disease involving different sites developed at various time points (4–32 years) following thyroidectomy due to the presence of an unspecified tumor

^f Subtotal thyroidectomy had been performed 17 years earlier. Re-examination of the thyroid specimen at the time of the oral metastasis revealed follicular carcinoma

^g Synchronous occurrence of the thyroid tumor and the mandibular metastasis

follicular thyroid carcinoma is attributed to the blood-stream dissemination of the latter.

Interestingly, in more than half of the cases (19/37), the oral metastasis was specified as the first manifestation of an unknown primary thyroid cancer, while in 8 cases the temporal relationship between diagnosis of the primary and metastatic disease was not specified. In the remaining cases, the time from diagnosis of the primary thyroid tumor to the development of the oral metastasis ranged widely from 4 months to 32 years. Hirshberg et al. [14], in their large review of metastatic tumors to the oral cavity (independent of primary site), reported that oral metastasis was the first clinical sign of an undiscovered distant malignancy in 23% of cases. Therefore, it appears that oral metastases of thyroid cancer are more likely to present as the first clinical sign of the disease compared with the whole of metastatic malignancies to the oral cavity. Characteristically, in one of the cases published by Nishimura et al. [22], the primary thyroid carcinoma was undetectable by clinical and radiographic means for about 2 years following the detection of metastatic lesions in the mandible, ribs, and lung. Nonetheless, it should be noted that in a number of previously unknown thyroid carcinomas metastatic to the oral cavity, there was a history of a growing tumor in the neck or previous thyroidectomies with inconclusive or incorrect diagnoses. On the other hand, the occasional development of metastatic lesions many years after the initial diagnosis of thyroid cancer supports the notion that the growth rate of a thyroid carcinoma may be very slow so that metastatic lesions may remain dormant and thus undetected for long periods [26].

Both the jaws and the oral soft tissues may be affected by metastatic cancer with a predilection for the mandible and the gingiva, respectively [14]. In general, oral metastases to the maxilla are rare, corresponding to less than one-fifth of all metastatic tumors to the jaws [37]. In our review, the vast majority of oral metastases from thyroid cancer were located in the mandible (32/37; 86.5%). Only two cases (including the case presented here) were located in the maxilla, while there were three cases of oral soft tissue metastasis affecting the maxillary gingiva, the mandibular gingiva, and the tongue/lower lip, respectively [27, 30, 37]. It has been suggested that the predilection of metastasis to the ramus and angle of the mandible reflects the rich blood circulation in the medullary cavity of these regions [9, 10]. Noteworthy is that in a number of metastatic thyroid cancer cases to the jaws (including the case presented here), there was also involvement of adjacent structures, such as the parotid, infratemporal fossa, and masticator space and sinus.

Metastatic tumors to the jaws may cause symptoms such as pain, swelling, tooth mobility, and paresthesia [33, 39]. Paresthesia in the mental area, referred to as numb chin

syndrome, may be a sign of metastatic disease to the jaws [38]. In addition, loosening of teeth may result in tooth extractions which preceded the diagnosis of metastasis in 55 out of 390 cases reviewed by Hirshberg et al. [10]. Interestingly, oral metastases may mimic an inflammatory condition, such as periodontitis, periapical lesions, osteomyelitis, or pericoronitis or present as a pathologic fracture [26, 39]. It should be noted that metastatic follicular thyroid carcinoma frequently has a highly vascular nature, often causing pulsation and/or bruit on auscultation and eliciting a clinical diagnosis of arteriovenous malformation; in such cases, preoperative angiographic evaluation and devascularisation by embolization and/or ligation are necessary precautions to avoid potentially significant bleeding [9, 18, 22, 24, 26, 32, 41].

Radiographically, jaw metastases usually present as poorly-defined radiolucent lesions, while carcinomas of the breast or prostate may also appear radiopaque or mixed due to stimulation of new bone formation; alveolar bone loss and widening of periodontal ligament may also occur [38]. It is possible that a jaw metastasis is sometimes radiographically undetectable; such lesions may be detected with bone scintigraphy [33]. It has been reported that metastatic lesions of follicular and papillary thyroid carcinomas are osteolytic and appear radiolucent usually with an irregular, indistinct scalloped margin, while medullary thyroid cancer may give osteoblastic bone metastasis [15, 26, 43].

The treatment of oral metastases of thyroid carcinoma has varied extensively from palliative to various combinations of surgical resection, radioactive iodine treatment, radiotherapy, and/or chemotherapy. It has been recommended that surgical resection of the metastatic tumor in conjunction with total thyroidectomy (if not performed earlier), followed by radioactive iodine treatment and/or external-beam radiation may afford better survival [5, 9, 15, 32]. Nonetheless, the treatment decision depends on various factors, including the operability of the metastatic lesions and the presence of a solitary metastatic focus versus multiple metastatic lesions. In widespread metastatic disease, treatment is usually palliative [30].

Prognosis of patients with distant thyroid cancer metastases is generally poor, with an average of 40% of patients alive 4 years after the diagnosis of metastasis and an overall 10-year survival rate of 27% for bone metastases of differentiated thyroid carcinoma [26, 38, 44]. In our review, follow-up information was available in 19 out of 37 cases, although the length of the follow-up varied considerably from 2 months to 4.5 years): 10 patients were reported as alive (6 of them being free of disease) and 8 patients died (7 of them due to the disease). It must be noticed that even an isolated bone metastasis is frequently indicative of widespread metastatic disease [5, 9]. Based on

our review, in 17 out of 22 cases with available information, the oral metastases were accompanied by other, usually skeletal, metastases. On the other hand, early detection of metastatic disease may improve treatment effectiveness and the overall survival rate.

In conclusion, metastatic tumors to the jaws are rare and associated with a poor prognosis. Origin from a primary thyroid cancer, including PTC, is exceedingly rare, with only a limited number of reported cases. Since the clinical signs and symptoms are most often vague, mimicking other oral conditions, a patient's thorough medical history is indispensable. Nonetheless, oral metastases may represent the first manifestation of an unknown thyroid cancer. Histologic findings consistent with a metastatic tumor from the thyroid should be confirmed by appropriate immunohistochemical studies. In such cases, a thorough diagnostic work-up is necessary for detection of the primary site and any additional metastatic sites.

Conflict of interest The authors declare that they have no conflict of interest.

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