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INVITED REVIEW

Metastases to the Parathyroid Glands: A Comprehensive Literature Review of 127 Reported Cases

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Abstract Metastases to the head and neck organs are uncommon, potentially representing the initial presentation of an occult malignancy. Single case reports and small series report metastases to the parathyroid gland, but there is no large review of the literature on secondary tumors involving the parathyroid glands. A review of the English literature between 1950 and 2017 was performed of all metastases or secondary involvement of the parathyroid glands. One hundred and twenty-seven cases of metastatic tumors were reported, although potentially significantly unrepresented in autopsy series (parathyroid glands are not routinely examined) and due to reporting bias. Women were affected more commonly than men (5.8:1; 99 vs. 17, respectively), with a mean age at presentation of 58.5 years, when reported. The most common primary sites of malignancies that metastasized to the parathyroid glands were breast carcinomas (66.9%, n = 85), melanoma (11.8%, n = 15), and lung carcinoma (5.5%, n = 7), with carcinomas representing 86.6% of metastases. Metastases were nearly always identified as part of widely metastatic disease, with only five (3.2%) cases reported as isolated metastases. Tumor-to-tumor metastases comprised 5.5% of all metastases to the parathyroid glands (metastases to parathyroid adenoma). A significant clinical finding of metastases to the parathyroid glands was the development of deranged calcium homeostasis, well beyond the 9 (7.2%) cases with primary parathyroid gland disease present. Although concurrent conditions (renal disease; bone metastases) may partially affect calcium metabolism, the onset of calcium derangement seemed to coincide with parathyroid gland metastases and not systemic disease. In summary, metastases to the parathyroid glands are uncommon, potentially under-recognized in patients who have otherwise widely metastatic tumors. Women are affected more often than men, with breast carcinomas (66.9%) and melanoma (11.8%) the most common primary tumors. Calcium homeostasis is affected, probably as a result of parathyroid gland parenchymal destruction.

Keywords Parathyroid glands · Parathyroid neoplasms · Parathyroid hormone (PTH) · Comorbidity · Calcium · Metastatic tumors · Secondary neoplasms · Breast neoplasms · Lung neoplasms · Melanoma

Introduction

Many tumors metastasize to the head and neck region. However, if lymph node metastases are excluded, organ metastases are uncommon. Specifically, metastases to the parathyroid glands are seldom reported, with only isolated single case reports, small series or autopsy reports that include parathyroid gland involvement in generalized disease. Parathyroid gland tissue is seldom systematically evaluated during a typical autopsy [1, 2]. Great care is taken to preserve parathyroid gland function during thyroid gland surgery [3]. Symptoms, if present at all, are likely to be nonspecific in nature, and thus antemortem

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manifestations are rare. As a result, the actual incidence and prevalence of cancers metastatic to the parathyroid glands is unknown. One of the few studies to highlight metastases to the parathyroid glands was a prospective study of 160 consecutive cancer death autopsies, identifying parathyroid gland involvement by metastatic tumor in 11.9% of patients [4]. In other series, parathyroid gland involvement was identified in the context of widely metastatic disease, just one of many organs affected [5], while isolated metastases to the parathyroid gland in surgical pathology material as the only metastatic site is exceptional [3, 6–8]. The most comprehensive literature review on the topic thus far was by Shifrin et al. [5], with this report expanding the review of 15 articles to 28 articles in an attempt to more thoroughly elucidate the nature of the metastatic phenomenon.

Methods

A review of English publications between 1950 and 2017 was performed to identify all reported cases of metastases to the parathyroid glands [1–28]. The review was conducted via searches of PubMed and Google Scholar databases using various combinations of search terms “parathyroid gland”, “parathyroid”, “metastasis”, “metastases”, “cancer”, “malignancy”, “endocrine organ”, “autopsy”, “post-mortem”, “neoplasm”, “surgical pathology,” “melanoma”, “sarcoma” and “tumor-to-tumor”. Individual case reports, case series, surgical pathology studies, and autopsy studies were all included. Particular attention was applied to series from the same institution or by the same authors to reduce duplication. All leukemias and lymphomas and direct extension/invasion into the parathyroid gland from adjacent malignancies were excluded, as they are not regarded as true metastases.

Two articles included in this study, namely the Bumpers et al. and Cifuentes et al. articles presented cases from the same institution over the years 1959–1974 [14] and 1971–1990 [22]. Given a 4-year overlap, there may potentially be a small number of repeated cases. Further, the Viadana et al. article includes only breast carcinoma metastatic to endocrine organs, but does not separate out parathyroid glands specifically, but no doubt also has potential overlap [29]. Similar to the Viadana et al. paper, the Patel et al. article contained cases of metastases to the parathyroid gland amongst a larger analysis of autopsy or surgical pathology specimens, but did not provide details as to how many parathyroid metastasis cases were included, and thus were excluded from this analysis [29, 30].

Results

Table 1 includes a listing of all 127 cases of metastasis to the parathyroid glands reported and incorporated into this literature review [1–28]. The vast majority of the cases developed in female patients (n = 99), no doubt accounted for by the high number of breast carcinoma cases (n = 85), with the overall average age when reported, of 58.5 years. Women outnumbered men by 5.8:1 (85.3 vs. 14.7%, respectively). Carcinomas were the most common tumor type (86.6%, n = 110), followed by melanoma (11.8%, n = 15), and sarcoma (1.6%; n = 2). Within the carcinoma category, breast carcinoma (66.9%, n = 85) were most common (Fig. 1) [4, 6, 8, 9, 12, 14, 17–20, 22, 23, 29], with the majority ductal carcinoma, followed by lobular carcinoma, although in many cases the exact tumor type was unspecified (Table 2). Some suggest that lobular carcinomas are more likely to metastasize, but this finding was not identified by others. Similarly, lung and thymic carcinoma were often not further broken down, although neuroendocrine carcinomas (n = 3) were noted. Melanomas were identified from primarily skin primaries (n = 12), although anal and palate (mucosal) sites were also documented, along with an ocular tumor [1, 4, 16]. A soft tissue sarcoma and a rhabdomyosarcoma each metastasized to the parathyroid glands [4]. Thyroid neoplasms most commonly showed direct extension [31], but hematogenous metastases were noted in three cases (Fig. 2). Nearly all of the cases (n = 122) were part of widely disseminated disease at the time of the identification of the parathyroid gland involvement, with only 5 (3.2%) cases reported as isolated metastases [3, 6–8, 28].

Tumor-to-tumor metastasis is uncommon, defined as one tumor metastasizing to another tumor. In this review, 5.5% of the total reported cases of metastases to the parathyroid glands were shown to represent metastases to parathyroid gland adenomas (n = 7; Table 3). An additional three cases had underlying parathyroid hyperplasia affected by metastases [5, 8, 26].

Serum calcium levels were reported in only 58 patients. Of these patients, 23 (39.7%) experienced hypercalcemia while 17 patients (29.3%) experienced hypocalcemia, and the remaining patients were eucalcemic. Serum parathyroid hormone levels were reported in 12 patients, with 9 patients (75%) experiencing elevated levels, and only 1 patient (8.3%) reported with a reduced level. Reporting of numbers of parathyroid glands evaluated, number of glands affected and the percent of gland replaced by tumor was inconsistent. However, all eight patients reported to have nearly complete replacement of the parathyroid gland tissue by the metastatic deposit, had hypocalcemia [4, 11, 17, 19, 20, 23]. Four of these eight patients had parathyroid hormone (PTH) values measured, three had elevated PTH levels and one had a low PTH value. Thus, in the patients with elevated PTH levels,

Table 1 Literature review of 127 reported metastases to parathyroid glands (listed in chronological publication order) [1–28]

Author	Date	Sex	Primary	Tumor type	Tumor-to-tumor metastasis[a]
Woolner et al. [9]	1958	F	Breast	Lobular carcinoma	Yes
Drickman et al. [10]	1961	M	Rectum	Adenocarcinoma	
		F	Rectum	Adenocarcinoma	
King et al. [11]	1964	F	Breast	Lobular carcinoma	
Margolis et al. [12]	1969	F	Breast	Lobular carcinoma	Yes
Horwitz et al. [4]	1972	M	Lung	nr	
		M	Stomach	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Skin	Melanoma	
		F	Breast	nr	
		F	Thymus	Thymoma	
		F	Breast	nr	
		F	Skin	Melanoma	
		M	Thigh	Spindle cell sarcoma	
		F	Skin	Melanoma	
		F	Salivary gland	Mucoepidermoid carcinoma	
		M	Lung	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Tongue	nr	
		M	Skin	Melanoma	
		F	Breast	nr	
		M	Skin	Melanoma	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	nr	
		F	Breast	Lobular carcinoma	
		F	Skin	Melanoma	
		F	Breast	nr	
		F	Breast	nr	
		M	nr (Testis)	Carcinoma (? Seminoma)	
		F	Skin	Melanoma	
		M	Lung	nr	
		M	Prostate	nr	
		F	Breast	nr	
		F	Anus	Melanoma	
		F	Thigh	Rhabdomyosarcoma	
		F	Breast	nr	
		F	Breast	nr	
		M	Kidney	Clear cell renal cell carcinoma	
		F	Breast	nr	

Table 1 (continued)

Author	Date	Sex	Primary	Tumor type	Tumor-to-tumor metastasis[a]
		F	Breast	nr	
Borden et al. [13]	1976	M	Skin	Melanoma	
Cifuentes et al. [14]	1979	F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
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		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
Schwartz et al. [15]	1982	F	Kidney	Clear cell renal carcinoma	Yes
de la Monte et al. [16]	1983	nr	nr	Melanoma	
		nr	nr	Melanoma	
		nr	nr	Melanoma	
		nr	nr	Melanoma	
		nr	nr	Melanoma	
Watanabe et al. [17]		F	Breast	Ductal adenocarcinoma	
de la Monte et al. [18]	1984	F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	

Table 1 (continued)

Author	Date	Sex	Primary	Tumor type	Tumor-to-tumor metastasis[a]
		F	Breast	Lobular carcinoma	
Inoshita et al. [1]	1985	M	Hard palate	Melanoma	Yes
Gattuso et al. [2]	1988	nr	Lung	Small cell carcinoma	
		nr	Lung	Large cell carcinoma	
Hermus et al. [19]		F	Breast	Mammary carcinoma	
Goddard et al. [20]	1990	F	Breast	Lobular carcinoma	
Benisovich et al. [21]	1991	F	Lung	Adenocarcinoma	Yes
Bumpers et al. [22]	1993	F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Ductal adenocarcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
		F	Breast	Lobular carcinoma	
Mariette et al. [23]		F	Breast	nr	
Tang et al. [24]	2002	nr	Thyroid	Papillary thyroid carcinoma	
		nr	Thyroid	Papillary thyroid carcinoma	
Pazaitou-Panayiotou et al. [25]	2005	n/r	Thyroid	Differentiated thyroid carcinoma	
Venkatraman et al. [26]	2006	F	Lung	Adenocarcinoma	PH
Fulciniti et al. [6]	2010	F	Breast	Ductal adenocarcinoma	Yes
Lee, HE et al. [7]	2011	M	Liver	Hepatocellular carcinoma	Yes
Chrisoulidou et al. [3]	2012	nr	Thyroid	Follicular thyroid carcinoma	
Lee et al. [8]	2013	F	Breast	Ductal adenocarcinoma	PH
Shifrin et al. [5]		M	Thymus	Well differentiated neuroendocrine carcinoma	PH
Ofo et al. [27]	2014	M	Kidney	Clear cell renal cell carcinoma	
Torregrossa et al. [28]	2016	M	Kidney	Clear cell renal cell carcinoma (intrathyroidal parathyroid gland)	

[a] *PH* parathyroid gland hyperplasia, *nr* not reported

it would seem that the remaining parathyroid gland tissue was responding appropriately to the hypocalcemia from a different cause, and resulting in elevated PTH levels.

Discussion

This English literature review from 1950 to 2017 selected 127 reported cases of metastatic disease, which secondarily affected the parathyroid gland tissue. It is likely that clinically significant disease identified during life is uncommon, but that when there is widely disseminated disease, parathyroid gland involvement by metastatic tumors is probably significantly underreported. Horwitz et al. [4] reported a prospective study of 160 cancer patient autopsies, with 11.9% of patients having at least one parathyroid gland with metastatic involvement. de la Monte et al. [16] identified parathyroid gland metastases in 28% of patients with melanoma. In another study, de la Monte et al. [18] reported 6% of 187 patients with breast cancer showed parathyroid gland metastases, while Bumpers et al. [22] reported 24% of patients who died of breast cancer had parathyroid gland involvement. Further, Cifuentes et al. [14] reported that when a parathyroid gland was affected by metastatic breast cancer, an average of 18 other sites throughout the body also contained metastases. Horwitz et al. [4] also reported

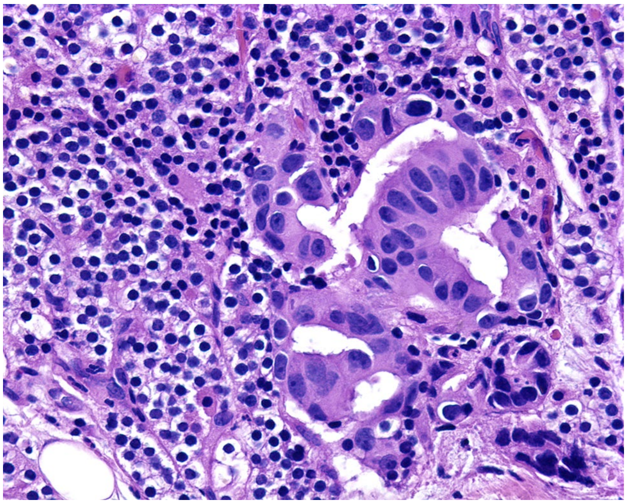

Fig. 1 Pleomorphic ductal cells are arranged in a glandular formation, representing metastatic breast ductal adenocarcinoma to the parathyroid gland parenchyma

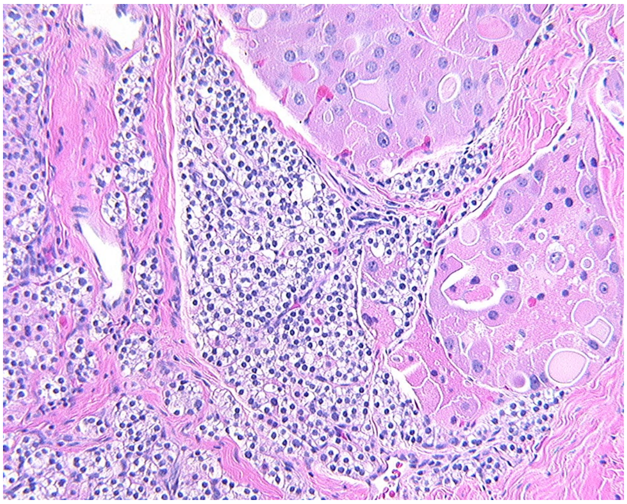

Fig. 2 Tumor deposits of an oncocytic follicular thyroid carcinoma identified within parathyroid gland tissue

Table 2 Primary sites of 127 reported malignancies metastatic to the parathyroid glands

Primary site	Number of cases
Breast (adenocarcinoma)	85
Skin melanoma	13
Lung (adenocarcinoma and neuroendocrine carcinomas)	7
Unknown	6
Thyroid carcinoma (differentiated)	4
Kidney clear cell renal cell carcinoma	4
Thymic tumors	2
Soft tissue sarcoma (thigh)	2
Rectum adenocarcinoma	2
Liver hepatocellular carcinoma	1
Hard palate melanoma	1
Stomach adenocarcinoma	1
Salivary gland (mucoepidermoid carcinoma)	1
Tongue	1
Prostate adenocarcinoma	1
Anus melanoma	1

that parathyroid gland involvement was part of widespread metastases (bone, liver, lymph nodes, lungs, spleen, kidney, heart, gastrointestinal tract, genital system, brain and skin) in addition to other endocrine organs affected (adrenal glands, pituitary gland, thyroid gland and pancreas). Bumpers et al. [22] reported 35% of patients who died of breast cancer had multiple endocrine organs involved with metastatic breast cancer. Thus, it can be extrapolated, in the vast majority of cases, parathyroid gland metastases present as part of widely disseminated disease. Thus, the identification of only 127 cases reported in the literature is probably due to a selection and publication bias, with parathyroid gland involvement in metastatic disease much more common than suggested.

If one considers the incidence of new cancers diagnosed each year, with breast, lung, prostate, colorectal and melanoma listed in descending order of frequency (Cancer Facts & Figures 2017, American Cancer Society, Atlanta, Georgia, accessed 07/10/2017), it is perhaps not surprising that breast (66.9%), melanoma (11.8%) and lung (5.5%) account for the most common tumors that metastasize to the parathyroid glands. However, disease burden, lymphovascular supply, and perhaps embryologic considerations must also be taken into consideration, with reporting bias of tumor types that cause the most disease-related death also contributing. Metastatic pathways may be related, with thyroid, parathyroid, thymus and anterior pituitary derived from branchial arches, via the foregut ultimately. Thus, metastases to these organs are also documented in other foregut derived organs like stomach and pancreas [16]. Functional relationships as suggested by calcium regulation, which include bone, kidney, thyroid and parathyroid glands, may also account for patterns of organ involvement, while several endocrine organs are also commonly simultaneously affected (adrenal, pituitary, parathyroid, thyroid and pancreas) [4, 14, 16, 18, 22]. Thus, the single case reports of isolated metastatic disease to the parathyroid glands alone, as the only metastatic finding in living patients are exceptional [3, 6–8], with widespread disease the more likely scenario. It is of note that metastatic renal cell carcinoma (clear cell carcinoma specifically) to parathyroid glands is very infrequently reported [4, 15, 27, 28], even though late and widespread metastases from renal cell carcinoma are well known [32]. Importantly, the differential diagnostic consideration of a metastatic clear cell carcinoma within the clear cell parathyroid gland parenchyma

Table 3 Seven cases of tumor-to-tumor metastasis involving the parathyroid gland [1, 6, 7, 9, 12, 15, 21]

Article	Primary malignancy	Primary tumor site	Secondary tumor
Woolner et al. [9]	Carcinoma	Breast	Parathyroid adenoma
Margolis et al. [12]	Poorly differentiated adenocarcinoma	Breast	Parathyroid adenoma
Schwartz et al. [15]	Clear cell carcinoma	Kidney	Parathyroid adenoma
Inoshita et al. [1]	Melanoma	Hard palate	Parathyroid adenoma
Benisovich et al. [21]	Adenocarcinoma	Lung	Parathyroid adenoma
Fulciniti et al. [6]	Infiltrating ductal carcinoma	Breast	Parathyroid adenoma
Lee et al. [7]	Hepatocellular carcinoma	Liver	Parathyroid adenoma

may prove challenging since both tumors could be PAX8 and RCC immunoreactive. However, a positive reaction with CAIX and CD10 and a negative reaction with chromogranin and parathyroid hormone studies would help confirm a renal cell carcinoma.

Tumor-to-tumor metastases are a well-documented, albeit uncommon, finding. Endocrine organs, kidney, lung, and liver all have a significant blood flow, expressly related to functional requirements of the organ. Blood flow is disrupted by the development of a neoplasm or in the setting of hyperplasia. Thus, the disrupted blood supply or change in blood flow results in entrapment of tumor emboli within the tumor, and tumor-to-tumor metastasis may be seen [1, 6, 7, 9, 12, 21, 32, 33]. All of the tumor-to-tumor metastases in the reported cases were to parathyroid gland adenoma (Table 3). However, several cases also developed in parathyroid gland hyperplasia, another potential source of abnormal architecture and blood flow.

The parathyroid glands function in calcium homeostasis, with PTH secretion integrally related to the interplay of calcium metabolism by bone, kidney, skin and gastrointestinal functions. As such, deranged calcium metabolism reflected through hyper- or hypocalcemia, would be an expected finding. While the calcium levels were not reported in many of the patients, when it was reported, 68.4% of patients experienced either hypercalcemia (38.6%) or hypocalcemia (29.8%) during evaluation. If the patients with parathyroid gland adenoma and hyperplasia are removed from further consideration (n = 9), a significant cohort of patients still manifested calcium abnormalities. Serum parathyroid hormone levels were elevated in 75% of patients tested, while reduced in only 8.3%. These findings may suggest that at least part of the serum calcium abnormalities may be accounted for by destruction or replacement of the parathyroid gland parenchyma by the neoplastic infiltrate, while other factors in cancer patients (low albumin due to cachexia; gut absorption; renal function; bone metastases releasing calcium; paraneoplastic syndromes related to parathyroid hormone related peptide or malignant hyperthermia) contribute to calcium and parathyroid hormone alterations [4, 5, 11, 13, 17, 19–21, 23]. The inability of the glands to produce parathyroid hormone could lead to clinical hypocalcemia, while destruction of the gland by a rapidly growing tumor could also lead to release of stored PTH, flooding PTH into the peripheral circulation and causing abnormal serum calcium levels [5].

In summary, metastatic malignancies to the parathyroid glands usually present in middle aged to older women, who have widely disseminated disease. Breast carcinomas represent the majority of tumors (66.9%), while melanomas are also identified quite commonly (11.8%). Tumor-to-tumor metastases are uncommon (5.5%). Calcium homeostasis is frequently affected, more disproportionately than disseminated disease would suggest, probably as a result of parathyroid gland parenchymal destruction. Thus, parathyroid gland involvement should be considered in patients who have metastatic disease and calcium alterations.

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Compliance with Ethical Standards

Conflict of interest All authors declare that he/she has not conflict of interest as it relates to this research project.

Ethical Approval All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board (IRB #5968), which did not require informed consent.

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