Metastasis of renal cell carcinoma to the parathyroid gland 16 years after radical nephrectomy: A case report

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Abstract. Renal cell carcinoma (RCC) has a high metastatic potential, and most commonly metastasizes via the bloodstream, although lymphatic metastases also occur. RCC is well-known for its propensity to metastasize to unusual sites, and late metastasis, even after a number of years, is common. The occurrence of RCC metastasis to the head and neck region is uncommon, and occurs primarily in the thyroid gland and in patients with widespread dissemination. Involvement of the parathyroid gland in metastatic carcinoma is extremely rare. In the present report, a case of metastasis confined to the parathyroid gland is described, likely with intrathyroidal localization, arising from a RCC that occurred 16 years after nephrectomy. A 66-year-old man was referred to the Department of Surgery of the University Hospital of Pisa (Pisa, Italy) with a preoperative fine-needle aspiration diagnosis of a follicular lesion in the context of nodular goiter of the thyroid gland. The previous medical history of the patient included a right nephrectomy for the treatment of clear cell RCC in February 1997. No other distant metastases were identified as of the latest follow-up in March 2014. At the time of thyroid surgery, the thyroid and parathyroid function tests were normal. The gross appearance of the surgical specimen was a multinodular goiter with a solid nodule measuring 33 mm on the left lobe of the thyroid gland. Microscopic examination revealed a completely encapsulated lesion consisting of clear cells arranged in a solid pattern and intermixed with fragments of parathyroid tissue. Following immunohistochemical examination, the clear cell lesion was negative for thyroid transcription factor-1 and thyroglobulin and strongly positive for epithelial membrane antigen, cluster of differentiation 10 and vimentin. To the best of our knowledge, this is the second case of metastasis to the parathyroid gland from a RCC reported in the literature.

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Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all malignant tumors in adults and its incidence is increasing; >39,000 new cases and 13,000 mortalities occurring annually in the United States at present (1,2). Active and passive cigarette smoking, obesity and hypertension are known risk factors (1). In addition, RCC appears to be more common in patients with end-stage renal failure, acquired renal cystic disease or tuberous sclerosis, compared with the general population (1).

Patients with RCC can present with local or systemic symptoms; however, most presentations are incidental (1). Local signs and symptoms include hematuria, flank pain or a palpable abdominal mass; while systemic symptoms can be due to metastases or paraneoplastic events largely related to secreted proteins, such as parathyroid hormone-related protein (causing hypercalcaemia), renin (causing hypertension), erythropoietin (causing erythrocytosis), and fever or wasting syndromes (3). Patients suspected of having a renal lesion should undergo complete physical examination and laboratory studies including complete blood count, serum chemistries, prothrombin time and partial thromboplastin time (1). Imaging studies should include computed tomography (CT) of the abdomen and pelvis with contrast, chest radiography and chest CT (1).

Among all histological variants of RCC, the clear cell type represents the most common, accounting for up to 80% of cases (1,2). Localized RCC generally carries a good prognosis, while extensive disease is essentially incurable; the 5-year survival rates are 91-100%, 74-96%, 59-70% and 16-32% for stage I, II, III and IV disease, respectively (4). Typically, RCC has a strong tendency to metastasize via the bloodstream. RCC usually metastasizes in the lung, bones, lymph node and cerebrum (1-4). Approximately 30-40% of patients exhibit metastatic disease at initial presentation, and 20% present with locally advanced disease, with the remainder having localized tumors (1,2). Around one-third of all patients with apparently localized disease will later develop metastasis, even a number of years after nephrectomy (3,4).

The principal treatment for localized RCC is surgical resection, including laparoscopic radical nephrectomy, hand-assisted laparoscopic nephrectomy, or open or laparoscopic partial nephrectomy (1). In the presence of metastatic disease, a radical nephrectomy in addition to metastasectomy may be considered (1). Compared with other cancers, chemotherapy is rather ineffective for RCC; numerous agents have been tested, with most showing response rates of <10% (5). Cytokine and targeted biological therapies may represent an alternative approaches (1).

Although RCC is well-known for its propensity to metastasize to unusual sites (6-13), the occurrence of RCC metastasis to the head and neck region is uncommon; this occurs primarily in the thyroid gland and in patients with widespread dissemination (9-13). In general, the involvement of the parathyroid gland in metastatic tumors is a very rare event (14-28). In the present study, a case of RCC metastasis to the parathyroid gland is reported. To the best of our knowledge, only one case of RCC metastasis to the parathyroid gland has been previously reported (28); however, the present case is the first report of intrathyroidal localization.

Case report

Patient. A 66-year-old Caucasian man was referred to the Department of Surgery of the University Hospital of Pisa (Pisa, Italy) in March 2013, with a preoperative fine-needle aspiration diagnosis of a follicular lesion in the context of nodular goiter of the thyroid gland. The previous medical history of the patient included a right radical nephrectomy for the treatment of clear cell RCC in February 1997. No other distant metastases were observed during follow-up. Scintigraphic bone scan imaging was negative for metastatic lesions. An abdominal ultrasonograpic examination revealed a nephrectomy scar on the right side, but the results were otherwise normal. Ultrasonographic examination of the neck region revealed the presence of nodular goiter of the thyroid gland with left predominance and slight deviation of the trachea without constriction, confirmed by CT examination of the neck region. Fine-needle aspiration was performed on two nodules of the apical and basal portion of the left lobe of the thyroid gland, measuring 40 and 33 mm, respectively. Cytological examination classified the apical nodule as a follicular lesion and the basal nodule as an unsatisfactory (non-diagnostic) smear, according to the 2nd edition of the Guidelines for Thyroid Cancer Management published by the British Thyroid Association (29). The patient underwent total thyroidectomy in March 2013. Laboratory findings on admission were as follows: Hemoglobin, 16.1 g/dl (normal range, 13.8-17.2 g/dl); hematocrit, 45.6% (normal range, 41-50%); erythrocyte count, 5,270,000/mm^3 (normal range, 4,400,000-5,800,000/mm^3); leukocyte count, 9,580/mm^3 (normal range, 3,800-10,800/mm^3); platelet count, 269,000/mm^3 (normal range, 130,000-400,000/mm^3); creatinine, 1.19 mg/dl (normal range, ≤1.2 mg/dl); and calcium 9.8 mg/dl (normal range, 8.5-10.3 mg/dl). Urine analysis was normal. Thyroid and parathyroid function tests were normal. Institutional approval from the ethics committee was obtained for the present study. Informed consent was obtained from the patient with regard to the use of the tumor samples.

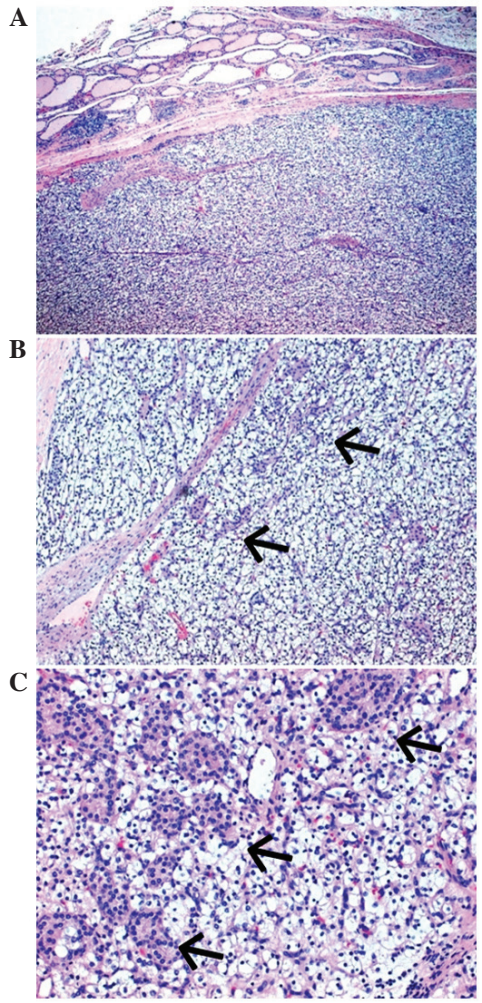

Figure 1. Hematoxylin and eosin-stained sections showing the intrathyroidal localization of the clear cell lesion. (A) The fully encapsulated lesion is surrounded by thyroid tissue and consists of clear cells arranged in a solid pattern of growth. Magnification, x4. (B) In the context of the clear cell lesion, there were scattered small nests of cells with a differing morphology (arrows indicate the scattered small nests of parathyroid tissue). Magnification, x10. (C) At major magnification, the close admixture of the clear cells with fragments of parathyroid tissue is evident (arrows indicate the scattered small nests of parathyroid tissue). Magnification, x20.

Specimens. Specimens were surgically obtained via total thyroidectomy. The thyroid weighed 35 g (normal range, 20-30 g) and measured 73x65x40 mm. Thyroid tissue was fixed in 10% neutral-buffered formalin and then dissected. A total of 13 samples (~20x20 mm) of all nodules and collateral parenchyma were collected and embedded in paraffin. Following slicing with a microtome, routine hematoxylin and eosin staining was performed on the section prior to histopathological examination according to standard protocols (30).

Immunohistochemistry. A paraffin block for immunohistochemical study was selected. Immunohistochemistry was performed using the avidin-biotin-peroxidase complex method according to the manufacturer's protocol (31). Tissue sections (5 μm thick) were deparaffinized in xylene and rehydrated in a graded ethanol series. Immunohistochemical analyses were performed automatically using the Ventana Benchmark immunostaining system (Ventana Medical Systems, Inc.,

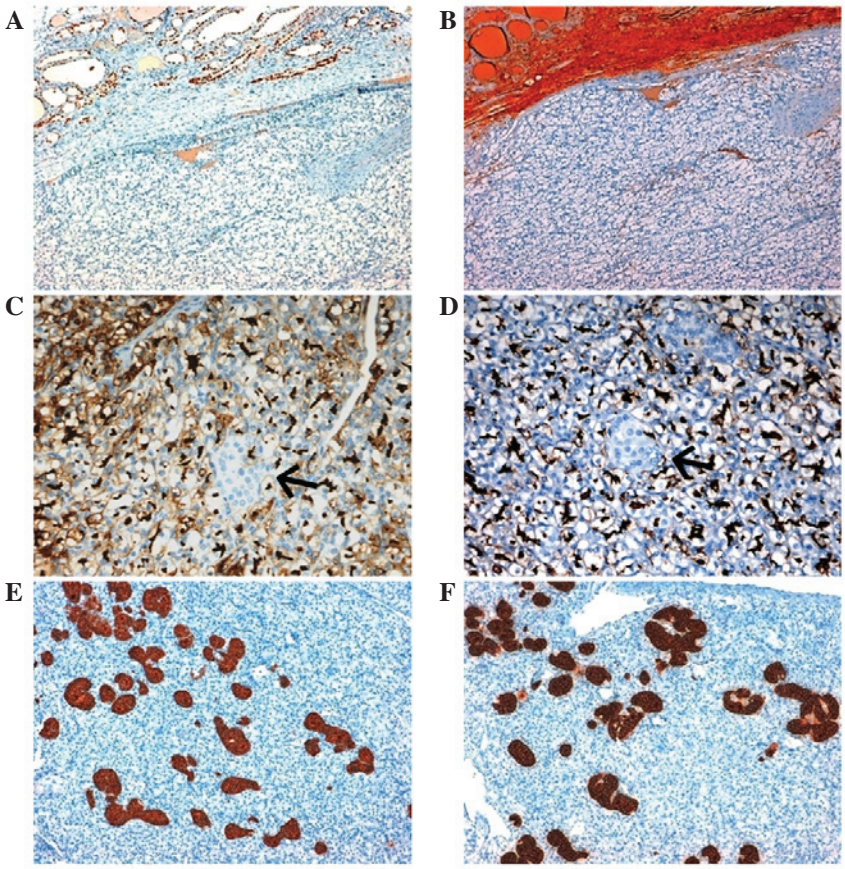

Figure 2. Immunohistochemical staining images. (A) Immunostaining for thyroid transcription factor-1 and (B) thyroglobulin revealed the absence of reactivity in the clear cell lesion in comparison to the adjacent thyroid tissue, used as an internal positive control. Magnification, x10. Immunostaining for (C) cluster of differentation 10 and (D) epithelial membrane antigen revealed the strong reactivity of the clear cell lesion. There was a notable absence of immunoreactivity in the scattered small nests of parathyroid cells (arrows indicate the scattered small nests of parathyroid tissue). Magnification, x20. The residual small nests of parathyroid cells were strongly immunoreactive to (E) chromogranin A and (F) parathyroid hormone. Magnification, x10.

Tucson, AZ, USA) with primary antibodies (all obtained from Ventana Medical Systems, Inc.) against the following: Thyroid transcription factor-1 (clone SP141; #790-4756; rabbit monoclonal; 5.7 μg/ml), thyroglobulin (clone 2H11+6E1; #760-2671; mouse monoclonal; 0.22 μg/ml), cluster of differentiation (CD)10 (clone SP67; #790-4506; rabbit monoclonal; 4.9 μg/ml), epithelial membrane antigen (EMA; clone E29; #790-4463; mouse monoclonal; 0.54 μg/ml), vimentin (clone V9; #790-2917; mouse monoclonal; 2.5 μg/ml), chromogranin A (clone LK2H10; #760-2519; mouse monoclonal; 1 μg/ml), parathyroid hormone (clone MRQ-31; #760-4532; mouse monoclonal; 0.08 μg/ml) and calcitonin (clone SP17; #760-4705; rabbit monoclonal; 0.56 μg/ml). All antibodies were pre-diluted as above. Universal UltraView 3,3'-diaminobenzidine chromogen detection system method (#760-091; Ventana Medical Systems, Inc.) was utilized as a chromogen, and commercial hematoxylin was used for counterstaining, according to the manufacturer's protocol.

Results. Specimens were obtained from a 66-year-old man who underwent thyroidectomy following examination and evaluation. The gross appearance of the surgical specimen was a multinodular goiter with two nodules of solid consistency in the left lobe measuring 33 and 40 mm, respectively; notably, the nodule measuring 33 mm exhibited a bright yellow color. Microscopic examination (Leica Microscope DM400B; Leica Microsystems, Wetzlar, Germany; x4, x10, x20 and x40 magnifications) revealed a multinodular goiter with abundant colloid on the right lobe of the thyroid gland, associated with two small foci of the classic variant of papillary thyroid carcinoma, sized 1 and 4 mm, respectively. On the left lobe, the nodule measuring 40 mm was an adenomatous nodule with a prevalent microfollicular pattern of growth, while the nodule measuring 33 mm was a completely encapsulated lesion consisting of cells with abundant clear cytoplasm arranged in a solid pattern of growth, with a prominent sinusoidal vascular network. In the context of this lesion, there was intermingling of the clear cells with scattered small solid nests of cells with differing morphology (abundant deeply granular and eosinophilic cytoplasm; Fig. 1). Immunohistochemical analyses revealed that the neoplastic population with clear cell morphology was completely negative for thyroid transcription factor-1, thyroglobulin, chromogranin A, calcitonin and parathyroid hormone, and strongly positive for CD10, EMA and vimentin (Fig. 2). Notably, the small nests of cells intermixed with clear cells were strongly positive for chromogranin A and parathyroid hormone and negative for all other antibodies (Fig. 2). Taken together, the morphological and immunohistochemical data suggested a definitive histological diagnosis of metastatic clear cell RCC to the parathyroid gland, likely with intrathyroidal localization.

Discussion

In the present study, a rare case of nodular goiter of the thyroid gland concurrent with metastatic RCC involving an intrathyroidal parathyroid gland, without disseminated systemic metastasis and without clinical signs of parathyroid disease, was reported. Typically, RCC exhibits a high metastatic potential, and most commonly metastasizes via the bloodstream, although lymphatic metastasis also occurs (1,2). In order of frequency, RCC more commonly metastasizes to the lung, bone, liver, brain and skin (1,2). RCC is well-known for its propensity to metastasize to unusual sites, even a number of years after nephrectomy (6-13). Metastases from RCC to the head and neck region are very rare (9-13), with the thyroid gland accounting for a large percentage of cases (32-34).

Several studies have indicated that thyroid glands affected by various pathologies (nodular goiter, thyroiditis, benign and malignant neoplasms) are more likely to harbor metastatic disease compared with normal glands, most likely due to an abnormal blood supply leading to decreased oxygen and iodine content (32-34). The actual incidence of parathyroid gland involvement in neoplastic patients with widespread metastases largely remains to be elucidated (21). Even in cases of diffuse systemic dissemination of neoplastic disease, the observation of parathyroid involvement is very rare, perhaps because parathyroid gland are seldom evaluated at autopsy (21).

In a previous study, the incidence of parathyroid gland involvement with metastatic tumors has been between 0.2 and 11.9% among patients with a known history of cancer (21). In autopsy studies, the metastatic involvement of parathyroid gland has typically been observed in patients with systemic dissemination (18,21). Furthermore, as parathyroid involvement occurred in patients with extensive metastases in other organs, it has been suggested that this event may represent a symptom of late-stage cancers (18). In clinical series, the metastatic involvement of the parathyroid gland occurred more commonly as a solitary lesion without systemic dissemination (24-27). The previously reported cases of metastatic carcinoma affecting the parathyroid gland originated from the breast, lung, skin (malignant melanoma), liver and hemolymphatic system (chronic lymphocytic leukemia) (14-27).

The metastatic involvement of the parathyroid gland may be associated with altered parathyroid function, including hypoparathyroidism (17,19) and hyperparathyroidism (24-27). In certain circumstances, metastasis to the parathyroid gland has been proposed as an alternative mechanism of 'malignant hypercalcemia', occurring in a peculiar subgroup of patients with widespread metastatic malignant neoplasm (22). By contrast, the occurrence of hypoparathyroidism and hypocalcemia in metastatic cancers affecting the parathyroid gland as result of parathyroid destruction by the tumor is rarely observed (17,19). The occurrence of metastasis in parathyroid glands affected by other pathologies, primarily adenoma and hyperplasia, may be justified by the abnormal blood supply as compared with normal parathyroid tissue (15,16,20,25,26). Secondary involvement of the parathyroid gland may be the consequence not only of distant metastasis but also of direct extension, more commonly by thyroid and laryngeal carcinomas (32,35,36). Involvement of the parathyroid gland with papillary thyroid carcinoma has been observed in 20/911 cases, primarily due to direct extension, however, 2% were due to metastasis (36).

In the present case, the patient underwent total thyroidectomy, due to a preoperative diagnosis of a follicular lesion in the context of nodular goiter of the thyroid gland. Histopathological examination highlighted the presence of an encapsulated clear cell lesion in the context of nodular goiter, associated with the presence of small foci of papillary thyroid microcarcinoma. Initially, the differential diagnosis between a thyroid lesion with clear cell morphology and a metastatic localization was taken into consideration. Data from the initial immunohistochemical tests uncovered the metastatic nature of the lesion, supported by the absence of immunoreactivity for thyroid transcription factor-1 and thyroglobulin and the presence of immunoreactivity for CD10, EMA and vimentin. Notably, additional immunohistochemical analyses revealed the atypical immunoprofile of the scattered solid nests, which were strongly positive for chromogranin A and parathyroid hormone.

To the best of our knowledge, this is the second case reported in the literature of solitary metastasis confined to the parathyroid gland from clear cell RCC, which occurred 16 years after nephrectomy in a patient with no clinical signs of parathyroid disease.

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