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Thyroid metastases from renal cell carcinoma. Report of a case and review of the literature.

Metastases to thyroid gland are a rare occurrence in surgical practice. The most frequent primitive tumor is renal cell carcinoma. We report a case of thyroid metastasis from renal cell carcinoma in a 70-year-old man who underwent left nephrectomy ten years earlier, presented with a diagnosis of multinodular goiter, associated with thyroiditis and right laterocervical lymphadenopathy. A total and the surgical excision of laterocervical lymph node were performed. The results, according to the histological examination, were metastases from renal cell carcinoma, involving both the thyroid gland and the lymph node. Therefore, since the delay of presentation and the difficulties of diagnosis, we recommend log-term follow-up of the head and neck region, for those patients with renal cell carcinoma diagnosis.

Metastases to the thyroid gland are a rare occurrence in surgical practice. This might sound a little surprising, since the rich vascularization of the gland itself. The rarity of metastases in this organ is attributed to the fast blood flow and the high level of oxygen and iodine that could prevent the secondary localization of tumour cells[1]. Thyroid metastases represent approximately 1 to 2,4% of all the malignant nodules [2], while in autopsies series, the incidence overall rises up to 24% [3-4], suggesting that the condition is frequently undiagnosed. The most common primary site (48.1%) is renal cell carcinoma (RCC)[5-6], with a delay of presentation that could last until 20 years after the nephrectomy[7]. These secondary localizations have not typical symptoms and ultrasonography (US) and computed tomography (CT) findings do not differ from primitive thyroid tumours, making an early diagnosis almost impossible. Even cytological examination by fine needle aspiration biopsy (FNAB) seems to have uncertain results[8]. In this scenario, thyroidectomy might be a valid option in order to improve outcome and increase survival of patient affected by RCC metastases.

We present a case of a patient with thyroid metastasis from RCC, unexpectedly diagnosed after thyroidectomy for multinodular goitre with suspicion of malignancy.

Case Report

A 70-year-old white man, with personal history of hypertension, splenectomy and RCC for which he underwent left nephrectomy ten years earlier, was referred to our surgical division for a mass in the anterior region of the neck he had previously noticed. At clinical examination, the neck of the patient presented a swelling in the anterior region, and the thyroid resulted hard at the palpation; the inferior margins were impossible to determine,

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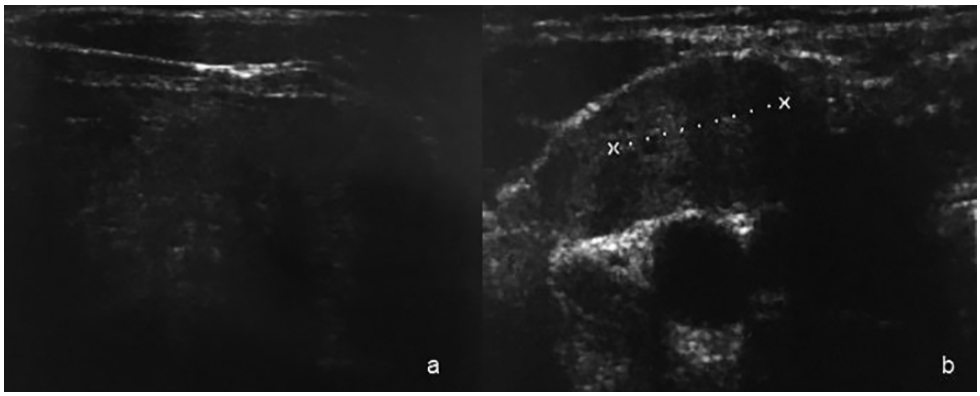

Fig. 1: A): ultrasonographic features of the left lobe nodule;B)ultrasonographic features of lymph node metastasis.

and multiple nodes were appreciated, bilaterally. An US was performed, which showed thyroid gland globally enlarged, with prevalence of the left lobe. Right lobe was normoechoic, but inhomogeneous for the presence of several hypoechoic spots with undefined margins. Left lobe was hypoechoic, and largely occupied by a nodule of 42 x 33 mm approximately, with rich perinodular vascularization. The US mentioned as well a hypoechoic, homogeneous, solid, well-defined nodule, localized in the third level, poorly vascularized, suspicious for lymph node (Fig. 1). He took blood measurements of thyroid hormones; TSH was 9,49 mlU/L, while fT4, PTH, calcitonin resulted to be in the range of normality. Moreover, the patient underwent FNAB of both thyroid nodule and lateral cervical one, and while the cytological exam of the laterocevical mass showed "epithelial cells", the one of the nodule in the left lobe showed "lymphocytic cells", that rose the suspicion of Hashimoto's thyroiditis. At CT scan, thyroid appeared enlarged with prevalence of the left lobe, and mediastinal invasion with compression and deviation the trachea. Were reported as well few suspicious lateral cervical lymph nodes with inhomogeneous density. An abdominal US was performed as well, and the results were in the range of normality, except for the absence of the spleen and the left kidney; the right kidney resulted to be slightly hypertrophic and hypoechoic.

After completing the preoperative workup, a total thyroidectomy and the surgical excision of the right laterocervical lymphnode were simultaneously performed. During the surgery, thyroid resulted to be of hard-fibrous consistency, especially to the left side where the tissue appeared to be ligneous, and not separable from trachea and oesophagus. The total absence of cleavage plans made the nodule impossible to excise, and a notable gland residue was left in situ.

The histological exam of the gland showed a thyroid weighs 50 grams, with left lobe of cm 5.5 x 3.2 x 2.7, right lobe of cm 5 x 3.5 x 2.5, isthmus of cm 4 x 1.5 x 1, made by compact yellow tissue with multiple subcentimetrical nodes, and four fragment of tissue that appeared white when cut. Thyroid gland resulted to be almost entirely occupied by multiple nodes, merging into each others, of epithelial clear cells proliferation (Pan-CK+, Vimentin +, CD10+, Rcc+ Thyroglobulin-, HBME-1-). This result seemed to be compatible with renal clear cell carcinoma metastasis (Fig. 2). Moreover, six lymph nodes were found in the fragment of tissue, three of which resulted occupied by the same specimen of tissue of the gland. The post-operative period resulted to be slightly abnormal for hypocalcaemia. During third post-operative day calcium values resulted to be 7.7 mg/dL, for which endovenous substitutive therapy was started. The patient was discharged on seventh post-operative day, with calcium values of 8.52 mg/dL.

Discussion

Thyroid gland has a low frequency of clinical metastatic carcinoma, despite the rich vascularization of the gland. It seems to be related to the high oxygen and iodine concentration, to the highly rapid bloodstream of the thyroid, and to the filtering effect of lungs passage[1, 9, 10]. When this microenvironment results to be altered by situations such as goitre or thyroiditis, as it happened in our clinical case, the gland becomes a vulnerable territory for metastatic growths. Heffes et al., in the largest series of thyroid metastases from RCC, found pre-existing thyroid disease in 42% of the 36 cases[11-13].

Thyroid metastases represent approximately 1-2,4% of all the malignant nodules[2]; in autopsies series, the incidence overall is approximately from 1,9% to 24%[3-4], and the most common primary site of the tumour are the lungs. In clinical series, instead, the higher frequency of primitive malignancy is attributed to RCC[6]. In general, the most common non-thyroid malignancies metastasizing to the thyroid are RCC (48.1%), colorectal (10.4%), lung (8.3%), breast carcinoma (7.8%), and sarcoma (4.0%)[5]. There are no significative differences in the pattern of thyroid metastases, according to gender or side of the primary kidney tumour, as RCC has a high metastatic potential due to its hematogen and vascular features[14], invading the renal vein, and subsequently the inferior vena cava, the systemic arterial system and finally the thyroid arteries, gaining access the thyroid gland[15].

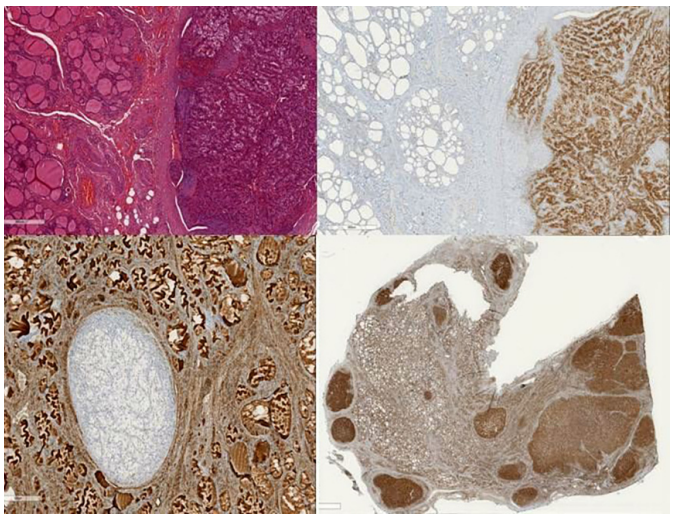

Fig. 2: Histological and Immunoistochemical characteristic of thyroid metastases from RCC.

Thyroid metastases usually present as a solitary nodule[5, 16, 17], and are more frequently a late finding, developing with a latency up to 20 years as a metachronous tumor[18,19], even thought 25% of are synchronous to the primitive disease[9, 14, 20].

Usually, thyroid metastases have not typical signs and symptoms, and do not differ from other primitive thyroid diseases, as they often present with neck swelling, dysphagia, dysphonia, and respiratory distress[17], while change in functioning are usually late and uncommon[6]. Usually metastases appear in glands in which thyroid tissue is damaged as a result of goitre, primary tumour, or thyroiditis, owing to its decreased oxygen and iodine content[5,11,21]; few authors have even reported episodes of thyroiditis after chemotherapy[22]. They could also be asymptomatic[20,23], and incidentally diagnosed during imaging, but more frequently the patient complain a fast growing neck mass[24,25], as it happened in our clinical case, in which, after ten years of latency, the patient developed a thyroid metastasis that grew in few months.

Diagnosis of thyroid metastases is a challenge, since they have non-specific imaging features and FNAB often provides uncertain cytological results. Metastatic disease in the thyroid gland tends to form a mass that mimics primary tumour, or even benign masses, with few or no suspicious US features[26], such as solid nodules, nonhomogeneous, hypoechoic, with noncircumscribed margins, absence of calcifications, and increased vascularity[3,5,19,28]. Even more sophisticated techniques, such as CT scans and MRI, cannot reliably differentiate between primitive lesions and metastases [28]. Radioscintigraphic imaging, using iodine-131 or technetium-99m, results inconclusive as well, since both primary and secondary lesions appear as cold nodule, unable to capture the radioisotopes [15, 29].

FNAB has been considered an important diagnostic tool, with high sensibility and specificity [8,30-32]; recently, though, FNAB resulted to be more frequently inaccurate, especially with RCC metastases [8,26,33-38], and the majority of nondiagnostic FNAB were reported to be benign or indeterminate [26,33,35-38]. The diagnostic inaccuracy of FNAB for metastatic thyroid lesions has been associated to several factors; first of all, the hypervascularization of the nodules, since it is associated with higher possibility of blood contamination, that makes cytological examination harder to perform [19,38,39].

Additionally, in order to diagnose RCC metastases, immunohistochemical staining is necessary, and it cannot be performed on FNA specimens, on which only cytological exam is possible[5,26,38]. Studies with immunohistochemical (IHC) markers such as PAX2, RCC marker, CD10, vimentin, alpha-metylacyl-CoA racemase [40] are important in the diagnostic process of this disease, and FNAB does not provide adequate tissue samples [35]. Moreover, it does not provide information on primitive disease and it cannot distinguish from high-grade malignancy and anaplastic carcinoma [34]. More invasive techniques such as CNB or open biopsies have been proposed, and they have been proven to diagnose metastatic RCC without further investigation [12,34,38,41].

Histopathological analysis is, in fact, superior diagnostic performance compared to cytological one [42], and histologically RCC is characterized by high content of lipid material and glycogen (PAS positive) [10,15,29,44], as well as the absence of mucin. This is, though, a nonspecific finding [45].

IHC provides important information in RCC metastases diagnosis. Usually, metastases result to be negative for thyroglobulin, calcitonin, TTF-1, CEA while primitive disease are usually positive [15,17,21,26], remembering that only 20% to 30% of anaplastic carcinomas stain for thyroglobuline [19,43]. RCC metastases, on the other hand, are more frequently positive for CD10, vimentin, EMA, cytokeratin [11,14,21,23,25,44,46,47]. In our case, immunohistochemical results and clinical history of the patient led to the final diagnosis.

Prognosis of this condition usually depends on several factors, such as isolated metastases with absence of multiple organ disease; possibility of complete excision of the metastatic focus; histological characteristics of the primitive tumour; slow growth with absence of symptoms; long time interval between tumour resection and development of the metastases; extensive necrosis in the resected piece [6,15,16,26,48,49]. Overall prognosis is usually poor, since 35% to 80% of patients present multiple organ dissemination at the diagnosis of thyroid involvement [5,6,48], but local control of the disease could offer good survival rates, and surgical treatment is supported either way [50,51]: with curative intent, if primitive tumour has been resected and there are no signs of metastases in other organs [52]; with palliative intent, avoiding airways obstruction and respiratory distress, in aggressive cases with fast growth [16,19,48,53].

The aim of surgical approach is to excise metastases with adequate margins, and while in localized, unilateral diseases lobectomy or isthmectomy have been considered,

in multifocal diseases total thyroidectomy is to prefer [6], even though some authors suggested that conservative surgery might be more frequently associated with positive margins [54-56]. Despite that, since metastases are not sensitive to radioactive iodine, total thyroidectomy is not mandatory as long as adequate margins are achieved[6]. With aggressive operative approaches and total excision of the disease, median survival reaches approximately 5 years after the diagnosis [19,57-59]. Regional lymph node involvement is rare, and prophylactic neck dissection is not required [6,54,60-62], but regional lymphatic should be assessed preoperatively, since RCC has a tendency to invade towards internal jugular vein [6,54]. In patients who cannot be thyroidectomised, methods to prolong survival include medical therapy, immunotherapy (e.g., interferon-), multikinase inhibitors (sunitinib, sorafenib, axitinib, pazopanib), antivascular endothelial growth factor agents (bevacizumab), and mammalian target of rapamycin inhibitors (temsirolimus, everolimus)[15].
Since the difficulties in diagnosis and the delay of presentation, long-term follow up of the head and neck region should be standardized for those patient with a history of RCC, and a metastasis should be suspected in cases of thyroid disease, even years after the presentation of the primitive tumour. To thorax and abdomen CT scans, routinely performed, should be added head and neck scans, especially in high-risk cases. Anyway, after diagnosis of thyroid metastasis is made, surgical approach, if technically possible, is more advisable, since it improves both survival and quality of life of the patient.

Riassunto

Le metastasi tiroidee hanno una percentuale di incidenza molto bassa, le più frequenti sono quelle dovute al carcinoma renale. In questo lavoro presentiamo il caso di in un paziente di sesso maschile di 70 anni, sottoposto circa 10 anni prima a nefrectomia sinistra per carcinoma renale. Il paziente è giunto alla nostra osservazione con diagnosi preoperatoria di gozzo multinodulare associato a tiroidite autoimmunitaria ed a linfadenopatia laterocervicale destra. Il paziente è stato sottoposto a tiroidectomia totale ed asportazione chirurgica del linfonodo laterocervicale destro. L'esame istologico ha esitato nella diagnosi di metastasi da carcinoma renale interessanti sia uno dei noduli tiroidei che il linfonodo laterocervicale. In considerazione del ritardo di presentazione e delle difficoltà diagnostiche, è consigliabile nei pazienti affetti da carcinoma renale anche un accurato follow-up a lungo termine del distretto testa-collo.

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