Multidisciplinary approach to follicular thyroid carcinoma with giant mandibular and multiple sites metastases

Case report

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Loredana De Pasquale*, Dimitri Rabbiosi**, Alessandro Bardazzi**, Luca Autelitano**, Giacomina Pierina Moro*, Giorgio Ghilardi*

"San Paolo" Hospital, Milan, Italy
**Endocrine Surgery, Department of General Surgery*
***Department of Maxillofacial Surgery*

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Metastatic tumors generally have poor prognosis, with short survival period and rarely indication to surgical treatment. In case of thyroid-differentiated cancer with distant metastases, prognosis is usually better, because of the possibility of treating metastasis by Radio Ablation by ^{131}Iodine, after surgery. We report the case of a 65 years old woman, presenting with a giant mandibular metastasis from follicular thyroid carcinoma, originating from a cervico-mediastinal non-functioning goiter, with lung metastases. After the diagnostic work-up, she underwent left hemi-mandibulectomy, reconstruction by the placement of a precustomized titanium plate with condylar prosthesis and total thyroidectomy. Subsequently the Patient was treated by Radio Ablation by ^{131} Iodine, in four consecutive sessions. She is alive with no progression of the neoplasm after forty-six months follow-up. Even in advanced differentiated thyroid carcinoma, surgery should be taken into consideration, to treat the patient by complementary therapies and to improve the prognosis in term of survival.

KEY WORDS: Advanced differentiated thyroid carcinoma, Metastatic differentiated thyroid carcinoma

Introduction

Follicular and papillary carcinomas are subtypes of differentiated thyroid cancer (DTC) and account for 90% of cases of all thyroid tumors [1]. The treatment of DTC includes total thyroidectomy, Radio Ablation by ^{131} Iodine (RAI) and levo-thyroxine (LT4) replacement at TSH suppressing doses. Conventional chemotherapy and external beam radiotherapy (EBRT) have proven scarcely effective against metastases [2]. After the age of 40, 10% of patients with papillary thyroid cancer (PTC), 25% of patients with follicular thyroid cancer (FTC) and 35% of patients with Hurtle cell thyroid cancer (HTC) develop distant metastases [4,5]. Approximately 10%-15% of patients with DTC present with, or subsequently develop, distant metastases and bone is the preferred target in 2-13% [4]. Bone is the second site of metastasis in DTC, accounting for as much as 25 to 44 % of metastatic patients, while lung is the most commonly involved organ (up to 70%). Multiple sites are involved in 10%-20% of patients at diagnosis [6]. A recent study on 444 metastatic DTC patients showed that bone metastases are more frequent in FTC (7-28%) compared to PTC (1.4-7%) patients [4]. The overall prognosis for patients with DTC is good, with a 10-year survival rate of 80-95% [4], while in metastatic DTC patients, the 10-year survival rate drops to 40%: poor prognostic factors

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Correspondence to: Loredana De Pasquale, M.D., Endocrine and Breast Surgery, Surgery Department, Azienda Ospedaliera, Polo Universitario "San Paolo", Via A. di Rudinì 8, 20142 Milano, Italy (e-mail: loredana.depasquale@ao-sanpaolo.it)

include age, aggressive histology, aggressive variants of thyroid cancer, metastases with poor ^{131} Iodine (^{131}) uptake and extra-pulmonary or multiple site metastases [4]. The peculiarity of metastatic DTC is the possibility to treat distant metastasis using RAI, after the removal of the primary tumor.

We report a case of a giant mandibular metastasis from FTC, originating from a cervico-mediastinal multinodular non-functioning goiter, treated by a multi-disciplinary approach.

Case Report

A 65 years old woman was referred to the Maxillofacial Surgery outpatient clinic, complaining of a large painful mass, developing on the left inferior part of her face. Her dentist had prescribed oral antibiotics, despite which the mass had continued to grow over a period of four weeks, causing increasing difficulty in mastication and finally in feeding (Fig. 1).

The woman had a ten year history of cervical goiter, which had been monitored elsewhere. Three years previously, the gland was noted to have increased in size and had partially descended into the anterior mediastinum: an option for thyroidectomy was discussed with the patient. She refused the operation repeatedly, because she was asymptomatic and the mass did not alter the shape of her neck significantly. Moreover, in the same period the patient had the diagnosis of an intra-cranial meningioma, treated by radiotherapy. The woman had no family predisposition for thyroid disease, was mildly obese and had peripheral arteriopathy, but no other comorbilties of note.

At clinical examination, the left side of her mandible was almost completely occupied by a large and painful mass, of hard consistency, fixed and tender to palpation. The mass bulged buccally and lingually, displacing the tongue medially. This had led to a malocclusion with deviation of the mandible to the left and a left-sided open bite. No signs of thyroid over-activity were noted. The patient's neck was short and large. The thyroid was not obvious on inspection, but the large goiter was easily palpable with the left lobe considerably larger than the right, disappearing within the mediastinum.

The orthopantomograph (OPG) showed an osteolytic lesion involving the left hemi-mandible from first premolar to condyle. The CT confirmed the clinical suspicious of severe soft tissue involvement. Extension was buccal and lingual, developing to the floor of mouth and the submandibular space inferiorly, and superiorly to the infra-temporal fossa with infiltration of the temporalis muscle and the parotid (Fig. 2).

A biopsy was performed of the mandibular lesion under local anesthesia, returning a histological result of "metastasis by follicular thyroid carcinoma".

The patient underwent neck ultrasound, which confirmed a consistent enlargement of the thyroid gland, with multiple nodules, the greatest one on the left side with mediastinal extension. All the nodular lesions had peripheral vascularization. There was no evidence of pathological lymph nodes. Neck and chest CT demonstrated a very large and heterogeneous left thyroid lobe,

Fig. 1: The 65 years old female patient at referral: the left-sided face swelling is evident, while the neck appears normal. (The patients gave us her agreement for this picture publication).

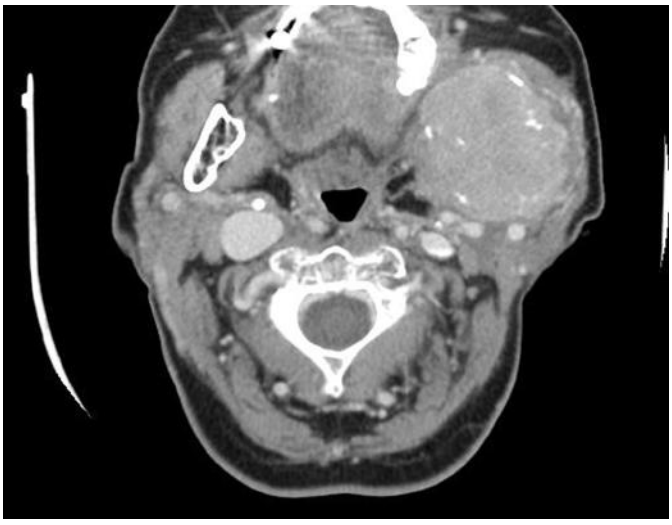

Fig. 2: CT scan of the mandible shows a large osteolytic lesion of the left mandible infiltrating the surrounding soft tissues.

extending into the anterior mediastinum to the innominate vein, with a lateral deviation of the trachea and multiple sub-centimeters nodules at both lungs.
A Fine Needle Aspiration biopsy (FNAb) of the greatest nodule of the left thyroid lobe was performed, in order to exclude the loss of differentiation of the tumor. The diagnosis was of "follicular neoplasm".
The patient underwent total thyroidectomy and partial mandibulectomy, through two distinct surgical approaches. Thyroidectomy was performed through a large cervical incision. There was no evidence of local invasion or lymph node involvement.
The mandibular metastasis required a left hemimandibulectomy distal to the lower left canine and disarticulation of the condyle. Extensive resection of the surrounding soft tissues was performed, with sacrifice of the left oral floor, masseter, buccinator and part of temporalis muscles. To achieve a radical resection the maxillofacial surgeons also performed a left supra-omohyoid neck dissection. During the resection important anatomical structures, such as the lingual and hypoglossal nerves, the internal carotid artery and its branches and the facial nerve, were identified and preserved.
The mandibular reconstruction required the placement of a precustomized titanium plate with condylar prosthesis (Fig. 3).
Definitive histological examination of the removed tissues gave the result of follicular carcinoma with diffuse vascular infiltration of the left and right lobes of the thyroid extending to the capsule on the left side. No lymph nodes were involved. The metastatic infiltration of the mandible was confirmed by the definitive histological evaluation (pT3, N0, M1).
One month after the resection, the patient underwent ^{131}Iodine ablation (120 mCi). The result of the scan, three days after this treatment documented the presence of cervical post-surgical thyroid residual tissue and the presence of metastatic lesions in the skull, right clavicle, lung, lumbar vertebrae and left coxo-femural joint; none of these metastasis were showed by pre-operatively imaging.
The CT scan 5 months following RAI, did not show any neoplastic tissue in the thyroid region and in the mandible. Unmodified metastatic nodules were described in both lungs; multiple new suspected lymph nodes were showed in the upper mediastinum, in the aorto-pulmonary space and at the tracheal carina. The bone scintigraphy confirmed the presence of metastasis of the right clavicle, the left 10th rib, the lumbar vertebrae and the skull but not of the left coxo-femural joint.
Nine months after the original operation the patients underwent a second RAI treatment, which did not produce any significant results.

Fig. 3: Intraoperative view: left hemimandibulectomy completed. Positioning of the precustomized mandibular and condylar plate premolded.

Fig. 4: Cosmetic result five months after the operation.

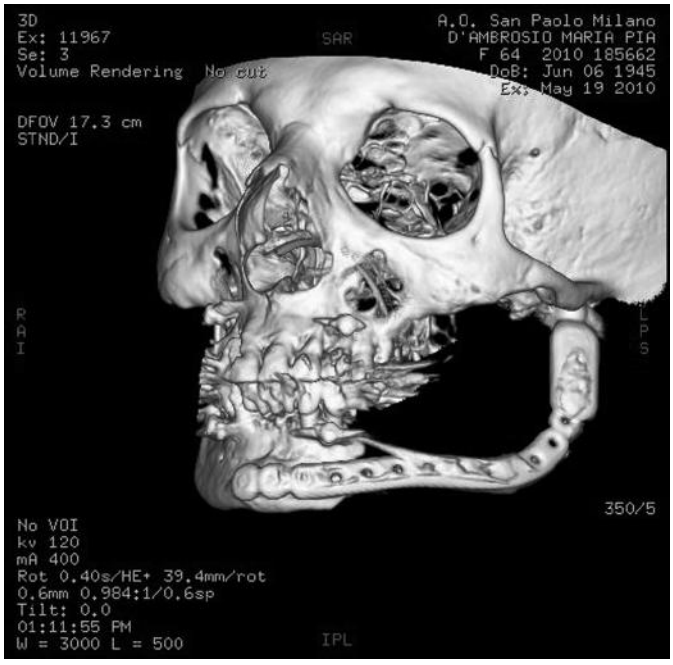

Fig. 5: 3D TC reconstruction five months after the operation.

Fourteen months following the operation the patient underwent a third cycle of RAI and administration of 4 mg of Zoledronic Acid (Zometa) i.v. After this treatment a total body CT scan could not detect any evidence of skull metastasis, however all the other lesions persisted unmodified. Neither neck nor mandibular recurrences were documented.
Forty-six months after the intervention the patient is well and in good general condition, after the fourth RAI. All the metastatic lesions previously described are unmodified. No local recurrences were described.
The maxillofacial surgical team has reviewed the patient monthly for the first 9 months after the resection and confirmed excellent healing of the surgical site with note of a stable occlusion and minimal aesthetic deficit (Fig.4). The three-dimensional CT showed a good reconstruction and the achievement of acceptable skeletal and morphological symmetry (Fig. 5).

Discussion

The incidence of metastases of the maxillo-facial region, mandible included, is extremely low, about 1-3% [7-9] In the literature, single cases are more commonly described; only few reviews with consistent number of patients arereported [4, 10,11]. An Indian review [10] shows that the origin of the primary tumor is variable and seems related to the age and sex of the patient. In the first decade of life the most frequent origin of metastasis is from adrenal and brain, in the second from bone, in the fifth, sixth and seventh, in females from breast and thyroid. In males there is no a preferential primary neoplasm. From another review of English literature [11], it emerges that the great part of well-documented jaw metastases are diagnosed in the fifth, sixth and seventh decades and generally originate in the female from breast, adrenal, colon, genital and thyroid cancer, while in males from lung, prostate, kidney, bone and adrenal neoplasms [11]. Prognosis for patients with this kind of metastasis is generally poor, with a mean survival period of six months [10]. Maxillofacial metastasis from thyroid cancer seem to result in a better prognosis: in the above mentioned Indian review, one case of jaw metastasis from thyroid cancer is reported, with a survival period of three years, after thyroid and jaw resection and ^{131} radio ablation [11] a treatment similar to the one described by the authors of this paper.
The case previously presented offers many points for discussion.
The first one is the rationale for treating such an advanced tumor with an aggressive surgical approach, as the one adopted by the authors. DTC of the thyroid is a particularly malignant neoplasm, with a capacity to up-take radioactive iodine. This property, maintained by the tumor if the cells are well differentiated, allows a complementary treatment to surgery, particularly in metastatic cases. The removal of the thyroid gland and of the extensive mandibular metastasis, as described in the presented case, permitted the treatment of metastasis by RAI. Pre-operatively both lesions were biopsied: the thyroid FNAb and an incisional biopsy of the mandible were both consistent with a differentiated thyroid carcinoma. No anaplastic cells were found. The patient was obese and had peripheral arteriopathy, but had no other significant co-morbidity. She was also experiencing severe symptoms and functional deficit especially in terms of feeding, which were interfering with her quality of life. Without an aggressive treatment she was at risk of developing obstructive airway symptoms and there would be not been possibilities for treating distant metastasis by RAI.
From a maxillofacial point of view, the main challenge was the reconstruction and the rehabilitation of the temporomandibular joint in particular. The mandibular reconstruction has always represented an important aspect of maxillofacial surgery; site, size of the defect and the surrounding soft tissues are three main factors that define the residual morphological and functional deficit [12]. Since the 1980s the gold standard for reconstruction of the mandible has been the use of microvascular free flaps [12-16]. The reported case, however, presented specific requirements that discourage the surgeons to reconstruct the defect with a microvascular flap. The patient was obese and had significant peripheral arteriopathy. The prolonged surgical time required for the reconstruction would have added to an already long time for the resection of the thyroid and the left madibular masses. The likely development of further bone metastasis also discouraged the use of a fibula free flap, which would otherwise have been considered the first option as a donor site.
The mandibular tumour was metastatic and the treatment of the primary lesion would have most likely required further radiotherapy to be done as soon as possible after the operation. The post-operative radiotherapy contraindicted the use of alternative reconstructive techniques such as an osteochondral graft [17,18].
A decision was then made to reconstruct the left mandible with a customized titanium prosthesis with condylar extension. This significantly reduced the length of the operation, nevertheless mantaining a satisfactory aesthetic and functional outcome. The immediate reconstruction of the TMJ guaranteed good mandibular motility and avoided the loss of ipsilateral mandibular height, maintaining the patient's normal occlusion. The crucial element with this kind of reconstruction is a close follow up of the patient because the titanium condyle could potentially cause the erosion of the glenoid fossa and the subsequent displacement of the prostesis in the middle cranial fossa [17,18].
After the operation the patient underwent RAI, with a further and more accurate stadiation than pre-operatively, by total body scintigraphy: other bone metastases, not previously detected, were documented at skull, clavicle, left rib and lumbar vertebrae. This finding allowed better planning of post-operative treatment, with an adequate dosage

of ^{131}I and other adjunctive therapies, such as Zoledronic acid (Zometa). In the literature the use of biphosphonates seems to be useful for the treatment of bone metastases from thyroid carcinoma [19]. After four RAI treatments and medical therapy, there is evidence of regression of skull lesions and the other lesions have not evolved.
Currently the woman is alive after forty-six months and does not complain of any symptoms.

Conclusion

Metastatic tumours generally have a poor prognosis with a short survival period after the diagnosis. In cases of thyroid-differentiated cancer with distant metastases, prognosis is usually better, because of the possibility of a multidisciplinary approach, in particular postoperative RAI. Even in advanced DTC, surgery should be taken into consideration, in order to treat the patient by other complementary therapies and to improve the prognosis in term of survival.

Riassunto

I tumori metastatici in genere hanno una cattiva prognosi, con sopravvivenza breve e raramente sono candidabili al trattamento chirurgico. Nel caso dei carcinomi differenziati della tiroide, la prognosi è solitamente migliore, grazie alla possibilità di un approcio multidisciplinare e soprattutto al trattamento radiometabolico dei secodarismi, dopo l'asportazione del tumore primitivo. Il caso presentato riguarda una donna di 65 anni, che è giunta alla nostra osservazione per una tumefazione mandibolare, risultata successivamente una metastasi da carcinoma follicolare della tiroide, a partenza da un voluminoso gozzo cervico-mediastinico normofunzionante, con ulteriori secondarismi a livello polmonare. Dopo un accurato studio pre-operatorio la Paziente è stata sottoposta a resezione della mandibola sinistra con ricostruzione mediante una protesi metallica e a tiroidectomia totale. Successivamente è stata trattata con quattro cicli di terapia radiometabolica con buona risposta. La Paziente è viva, senza ulteriore progressione di malattia a un follow-up di quarantasei mesi. Anche nei casi di tumori differnziati della tiroide in fase metastatica, l'opzione chirurgica va presa in considerazione per consentire alle terapie complementari di migliorare la prognosi in termini di sopravvivenza.

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