Supplement

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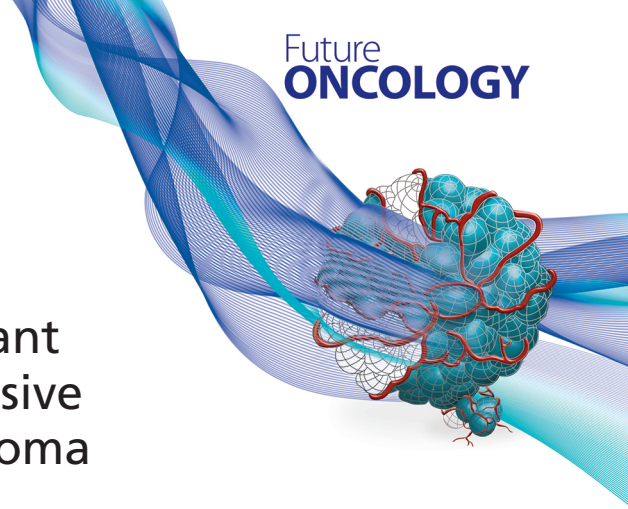

Case report: lenvatinib in neoadjuvant setting in a patient affected by invasive poorly differentiated thyroid carcinoma

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We report a case of an elderly woman presenting with a huge cervical mass invading the tracheal lumen. Diagnosed as invasive poorly differentiated thyroid cancer, after an endotracheal biopsy, stenting and radiotherapy, it was judged eligible for total thyroidectomy, but surgery was delayed due to pulmonary thromboembolism. The patient was therefore treated with lenvatinib with a neoadjuvant intent until hemodynamic stability was obtained. Thyroidectomy and radioiodine therapy were then performed and the postdose scan revealed an area of modest uptake in the anterior part of the neck. The patient is now in a good clinical status and she continues her follow-up program without any adjuvant therapy.

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Poorly differentiated thyroid cancer (PDTC) is a rare histotype of cancer [1–4]. Previously considered a tumor with intermediate characteristics between differentiated thyroid cancer (DTC) and anaplastic thyroid cancer (ATC), in 2004 it was recognized as a separate entity, with specific diagnostic criteria [3,4]. Since PDTC and ATC usually present as locally advanced tumors with common extrathyroidal extension [5], prognosis is poorer and clinical management is critical [6,7]. The clinical management of invasive thyroid cancer generally involves surgery and, if possible, radioiodine therapy [8]. Poor data are available regarding utility and efficacy in the available literature of neoadjuvant therapies in this setting [6,8–11]. Even tyrosine kinase inhibitors (TKIs), which have proved efficacy against radioiodine-refractory DTC increasing progression-free survival [12], have rarely been employed before thyroidectomy [13].

We report a case of an elderly woman presenting with a huge cervical mass invading the tracheal lumen, who was treated with lenvatinib with a neoadjuvant intent until hemodynamic stability was obtained.

Case report

The patient, an 81-year-old woman, had a personal anamnesis of HCV-related liver disease known since 1995, and of atrial fibrillation diagnosed in 2015 and treated with acetyl-salicylic acid and propafenone. Familial anamnesis revealed a multinodular goiter (MNG) in close relatives.

In November 2017, she complained of a persistent cough and dyspnea, refractory to the inhaled steroid therapy. Due to a growing sense of cervical encumbrance, a cervical ultrasound was performed. The examination revealed an MNG, with the major nodules of 18 and 40 mm, both solid and hypoechogenic, in the right and in the left

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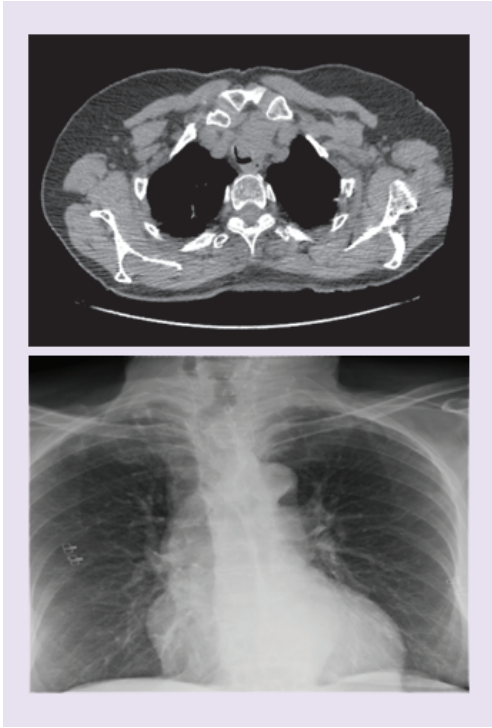

Figure 1. Tracheal dislocation and invasion by a cervico-mediastinal mass.

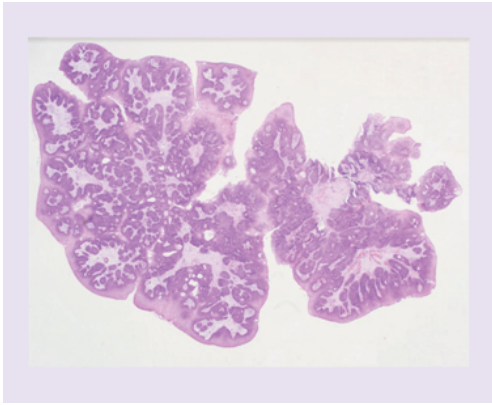

Figure 2. EE 20x tracheal polipoid lesion showing moderate to high-grade dysplasia. No signs of follicular thyroid cancer were detected.

lobe, respectively. A subsequent endocrinological evaluation advised a fine needle biopsy on both the nodules, but the examination was never carried out. Due to the worsening of the dyspnea, indeed, she underwent a high-resolution tomography of the neck, which revealed a huge cervico-madiastinal mass, apparently connected with left thyroid lobe, largely dislocating the trachea and invading the lumen (Figure 1). She was therefore referred to the emergency room of our hospital. A bronchoscopy confirmed the presence of an endotracheal vegetation obstructing approximately 80% of the lumen. Thus, the patient was admitted in the Pulmonology Operative Unit and few days later a new bronchoscopy was performed, a biopsy was taken and an endotracheal stent was positioned. A subsequent endocrinological evaluation posed the suspicion of an ATC, due to the radiological aspect and the rate of progression. The histological report on the tracheal biopsy, however, described a moderate- to high-grade dysplastic lesion of the tracheal wall. In that examination, thyroglobulin immunostaining was not performed because the initial histological report did not appear consistent with a thyroid lesion. Immuno-testing for cytokeratin 7 and 20, p40, TTF-1, Napsin-A and pS100 were performed instead and did not result as indicative of a thyroid origin (Figure 2).

The patient was treated with a cycle of external beam radiation therapy (20 Gy in five fractions) anyway.

In May, 2 months after the diagnosis, she was referred to the outpatient clinic of our Operative Unit. By that time, she presented with mild dyspnea, and a palpable hard and immobile cervical mass on the anterior left side

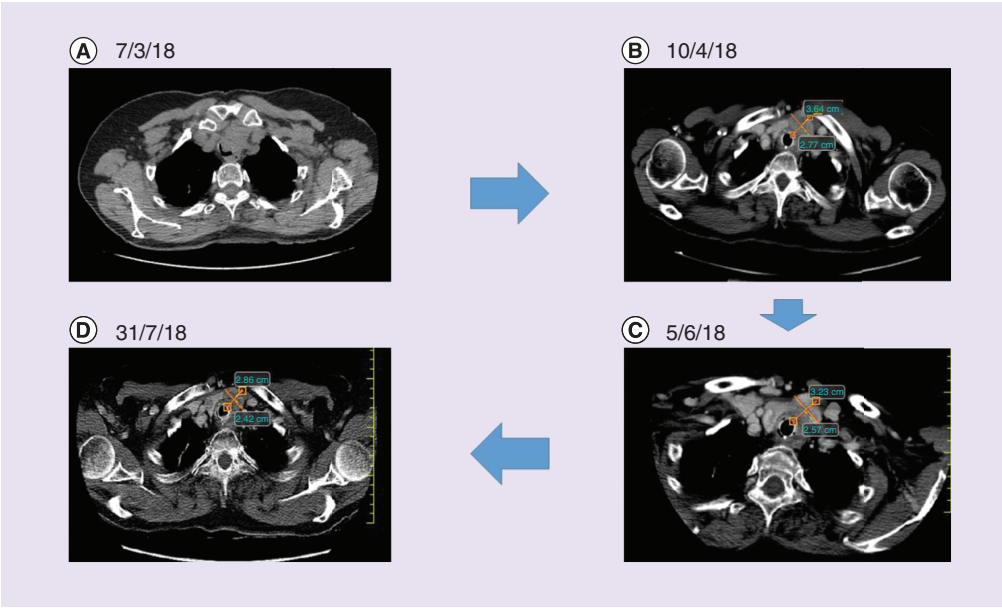

Figure 3. The effects of the treatments on the disease. Tumor size changes from **(A)** baseline: **(B)** first after tracheal stenting, **(C)** then after external radiation therapy and **(D)** after lenvatinib treatment.

of the neck. Thyroid ultrasound confirmed the presence of MNG, with the major lesion substantially stable from the previous evaluation. Blood examinations did not show any other remarkable finding (TSH: 0.78 mU/l; fT4: 13.81 pg/ml; thyroglobulin: 99.92 ng/ml; antithyroglobulin antibodies <20 U/ml; calcitonin <1.0 ng/l).

A biopsy was then performed directly on the mediastinal mass, and a thyroid carcinoma with follicular origin was diagnosed.

The thyroid disease management team (GIP) of our Institute therefore discussed the case and, after an accurate consultation with the patient and her relatives about risks and benefits of the different possible approaches, total thyroidectomy and subsequent radioiodine ablation therapy were programmed.

Unfortunately, just few days before surgery, a widespread pulmonary thromboembolism appeared, due to a deep venous thrombosis of the right lower limb: thyroidectomy was therefore delayed until the hemodynamic stability was restored, and an anticoagulant therapy was administered.

After the transfer to our Operative Unit, a TSH-suppressive therapy with levothyroxine was started and, considered the apparent high progression rate of the disease, low dose of lenvatinib (10 mg/die) was administered with neoadjuvant intent.

After 2 months, in early August, the patient was in a good clinical status, except for some lenvatinib-induced side effects, such as fatigue, upper limb dermatitis, lower limbs asthenia and a mild hypertension well controlled with amlodipine 5 mg/die. A mild dysphonia was also present. No more signs or symptoms of lower limbs thrombosis at the ultrasound nor of thromboembolism at the CT scan were present. The lesion size, on the other hand, was slightly reduced (Figure 3).

Surgery was carried out on 6 September, 2 weeks after lenvatinib discontinuation: a total thyroidectomy was performed, with partial resection of sternocleidomastoid muscle due to neoplastic invasion. During the surgical procedure, a gross neoplastic invasion of left sterno-thyroid muscle due to neoplastic invasion. During the surgical procedure, a gross neoplastic invasion of the left external tracheal wall was described, and the surgeon adopted a shaving technique, preserving the trachea. Left recurrent laryngeal nerve was found to be adherent to the neoplasm, from which was detached and preserved. Furthermore, a small share of thick and creamy liquid attributable to necrotic tissue was found, possibly due to previous radiotherapy and lenvatinib treatment.

Histological report described a poorly differentiated follicular derived thyroid carcinoma, invading surrounding soft tissues, with focal areas of squamous differentiation in its context (Figure 4).

A total of 10 days after thyroidectomy, the tracheal stent was removed, and a subsequent bronchoscopy showed a good re-epithelization of the internal tracheal wall, with a persistent slight narrowing of the lumen (Figure 5). In

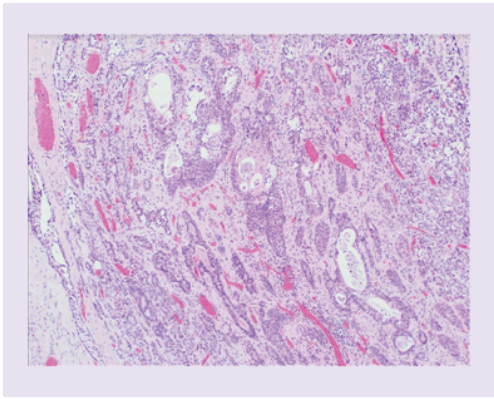

Figure 4. EE 200x follicular thyroid cancer with focal areas of squamous differentiation.

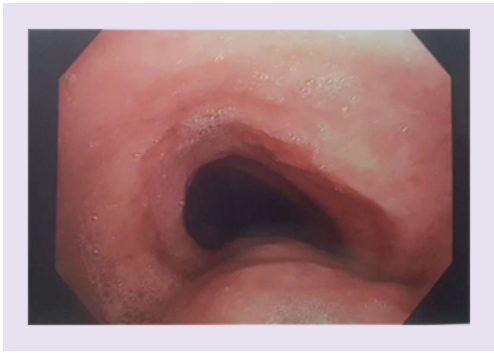

Figure 5. Bronchoscopy performed after stent removal. 'Good re-epithelization of the internal tracheal wall, with a persistent slight narrowing of the lumen'.

that occasion, checking the other parts of the investigable respiratory tract, a hyperemic area of irregular mucosa was found, and biopsies were carried out, but they just revealed a normal bronchial mucosa, without any neoplastic cell.

At the last clinical evaluation performed on 19 October, the patient was asymptomatic, and no more dysphonia was reported. A 10 kg weight loss during the previous 8 months was noted. The neck ultrasound showed the presence of hyperecogenic scar tissue, without evidence of disease recurrence or persistence and no pathologic lymph nodes were described. Basal Tg was barely detectable (0.3 ng/ml) in course of L-T4 therapy (TSH: 3.33 mU/l) with negative antithyroglobulin antibodies, and even during rhTSH stimulation no increase was noted (Tg: 0.2 ng/ml; TSH: 136.8 mU/l)

The whole-body scan (rxWBS) performed after the therapeutic administration of 150 mCi of 131-I showed a mild uptake of the radioisotope in the anterior part of the neck, without any other signal of recurrent or metastatic iodine-gaining disease.

Discussion

Respiratory tract invasion from aggressive thyroid cancer is an uncommon but challenging situation presenting in approximately 1–15% of patients affected by thyroid cancer, and it is mostly related to aggressive histotypes, often poorly or totally undifferentiated carcinomas [4,14]. Squamous differentiation can occasionally occur, even if squamous cell thyroid carcinoma, defined as a tumor totally or almost entirely composed by squamous cells, is an extremely rare condition characterized by a very bad prognosis [15,16]. In our patient, after the first suspicion of ATC due to the radiological aspect and aggressive behavior of the tumor, a squamous cell thyroid carcinoma was suspected because of the histologic report of a squamous differentiation and of the tracheal invasion radiologically supposed. Another hypothesis, which had to be considered, was the presence of a primary squamous tracheal neoplasm invading surrounding tissues and thyroid gland: such kind of lesions, though rare, may occasionally be misdiagnosed for thyroid tumors [17]. Primary tracheal tumors, often malignant, are mostly represented by squamous cell carcinoma and cystic-adenoid carcinoma, and their prognosis is largely influenced by the grade of invasion of the adjacent organs and tissues [17,18]. In this last hypothesis, assuming a gross extratracheal extension and thyroid invasion, we could speculate a life expectancy between approximately 5 and 15 months [18]. On the

other hand, the more likely diagnosis of de-differentiated thyroid cancers, led to a significantly different prognosis varying from few months, in case of anaplastic cancers, to several years for PDTCs [19]. Even considering PDTCs presenting with aero-digestive tract invasion, the prognosis remains better than the one of an invasive tracheal tumor, with a median disease specific survival of up to 5 years [7].

Further investigations and revisions of the histological specimen performed after the thyroidectomy confirmed the intraluminal tracheal mass as a papillary dysplastic lesion, with no signs of thyroidal elements nor invasion of the basal membranes and negative for thyroglobulin immunostaining. It can be proposed that this lesion could be a sort of a reactive process of tracheal mucosa to the underlying primary thyroid neoplasia.

Another issue we had to consider was the cost–benefit ratio of an invasive approach with radical or nearly radical intent in an elderly patient. In this regard, no specific recommendation is provided by 2015 American Thyroid Association Guidelines on the Thyroid Nodule [8]. A multimodal approach was used in this patient, based on clinical assessment and available evidence [10,11]. Intensity-modulated radiotherapy proved to have some benefits in cases where surgery was not feasible or when a gross residual disease was present [11,20]. A review published by McLeod *et al.* in the same year about this topic pointed out the increased risks of invasive procedures related to senescence, due to comorbidity, concomitant therapies and decreased performance status. On the other hand, in the elderly patient the incidence of aggressive and less DTCs is higher, and disease specific mortality exponentially increases with age. Authors concluded that all treatments approved for the tumor treatment in the adult can be applied in the elderly, but a specific risk–benefit evaluation should be always carried out, considering performance status and comorbidities, and some approaches slightly modified, such as the extent of surgery or the entity of TSH suppression [21].

At last, the decision to use lenvatinib in a neoadjuvant setting, can surely be matter of discussion. The role of a TKI in the treatment of the thyroid cancer is now limited to those cases that still show progression after primary treatments (surgery and radioiodine therapy) and local ablation therapies, and even in such cases, a careful evaluation of their risk/efficacy ratio is recommended [8,22].

Little is known about their role before or instead of surgery. Some benefits have been documented, especially by Japanese authors, on progression-free survival of patients affected by ATC [23,24], and Phase II studies are now ongoing with this purpose [25] in order to produce stronger evidence and recommendations [26]. Very few data have been reported, instead, about the role of a TKI in neoadjuvant setting in patient with a differentiated or PDTC: at our knowledge, just sporadic cases have been described. Tsuboi *et al.* reported a case in which lenvatinib use allowed surgical resection of a papillary thyroid tumor initially judged inoperable after 84% reduction of its volume [27], similarly Steward *et al.* obtained a considerable regression of tumor volume from a 73-year-old woman affected by invasive follicular-variant of papillary thyroid cancer after treatment with sorafenib and subsequently with lenvatinib, and this made thyroidectomy possible [28].

It is not possible to evaluate the direct effect of lenvatinib on the neoplasia; in the histological report, necrotic foci were absent. A diffuse intraneoplastic fibrous stromal component with calcifications was described, instead, but it is not clearly attributable to lenvatinib treatment. On the other hand, the 'small share of thick and creamy liquid attributable to necrotic tissue' described by the surgeon could be a consequence of lenvatinib treatment.

Since lenvatinib has a powerful inhibitory effect on angiogenesis, targeting the VEGF receptor among the other tyrosine kinases, bleeding and fistula creation represent one of the major concerns for its use in this setting, especially when the trachea or esophagus are involved [29]. These type of side effects are known from the earliest times of use of the drug [30]; they can be very severe, and a complete recovery can be very slow and difficult [31]. On the other hand, this risk can be avoided if the drug is administered with caution and starting with a very low dosage [29,30].

For this reason, in our case, lenvatinib was administered at the minimum dose with a documented efficacy profile, in order to minimize side effects in a patient with a good performance status but with several comorbidities. We witnessed a substantial stability of the lesion size during the 3 months of therapy: sincerely it would be difficult to clarify whether this was due to the lenvatinib itself or it was the result of the previous radiotherapy, of tumor natural history or all of them. What we can say is that this solution lead to a therapeutic goal that we would have hardly expected at the time of the diagnosis, with acceptable side effects and with no significant reduction of patient's performance status after 8 months from the beginning of the treatments.

Future perspective

New evidence is expected to clarify the role of TKIs when surgery is postponed or contraindicated. Phase II studies are now ongoing with this purpose.

Summary points

- A correct diagnosis of head and neck neoplasms is mandatory to define patient's prognosis and the most appropriate treatment, but in some cases a correct case definition is not simple.
- Squamous differentiation in the context of a thyroid carcinoma is rare and has a bad prognostic significance. It has to be put in differential diagnosis with the squamous carcinoma of the trachea, which is even rarer.
- Elderly patient should be eligible for all treatments approved for thyroid cancer in the adults, but they have to be evaluated in terms of the risk–benefit ratio, considering comorbidities, performance status and additional therapies that could modify clinical course.
- To date, not enough data are available to recommend the use of tyrosine kinase inhibitors with neoadjuvant purpose in the case of delayed surgery or inoperable patients, but their role in this setting appears of great interest.
- In case of airways or vessels neoplastic invasion, the use of a tyrosine kinase inhibitor, especially lenvatinib, should be cautiously balanced with the risk of bleeding and fistula creation.

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Informed consent disclosure

Written informed consent to keep personal and clinical data and to use them for research purposes was obtained from the patient at the beginning of the therapy.

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