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EDITORIAL – ENDOCRINE TUMORS

Just a Little Bit of Anaplastic Thyroid Cancer?

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Anaplastic thyroid cancer (ATC) is one of the most aggressive human malignancies, with long-term survival as a rare event, even after complete surgical resection or complete response to multimodal therapy.[1] Due to the poor prognosis of ATC, all cases are classified as stage IV according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system and stratified as stage IVA (localized disease), stage IVB (locoregional disease), or stage IVC (distant metastasis) based on the extent of disease at presentation.

Patients with ATC often present with a rapidly growing neck mass and symptoms associated with local invasion and may have a known history of a goiter, differentiated thyroid cancer, or no thyroid disorders. Rarely, a focus of ATC may be found on pathology after thyroidectomy that is coexisting with differentiated thyroid cancer (commonly papillary thyroid cancer [PTC] followed by follicular thyroid cancer and Hürthle cell carcinoma) or poorly differentiated thyroid cancer.

Important prognostic factors for ATC patients that are associated with worse survival include extent of disease (TNM stage IVC > IVB > IVA), age of 50–65 years or older, tumor larger than 5–6 cm, Charlson–Deyo comorbidity index greater than 2, positive tumor margins status in those with surgical resection, and the presence of concomitant BRAF/RAS and TERT promoter mutations compared with mutation in only one of the genes.[2]

The dedifferentiation of differentiated thyroid cancer to ATC is not uncommon, and lines of evidence supporting that this does occur include (1) the finding of an ATC focus in a differentiated thyroid cancer on pathology, (2) ATC occurring in patients previously treated for differentiated thyroid cancer, (3) genetic studies showing shared common driver mutation in both differentiated thyroid cancer and ATC (in some cases of coexisting PTC and ATC) with a higher gene mutation burden in ATC, and (4) transgenic mouse models of BRAF and TP53 mutations showing progression from PTC to poorly differentiated thyroid cancer to ATC with time.

In this issue of *Annals of Surgical Oncology*, Greenberg and colleagues[3] report on the outcome for patients with coexisting PTC and ATC (co-PTC/ATC) versus that for patients with only PTC and only ATC using data from the National Cancer Database (NCDB). They report that the overall survival for patients with co-PTC/ATC was intermediate to that of patients with only PTC (best) and ATC (worst) and was worse for patients older than 55 years as well as for those with a Charlson-Deyo score of 2 or higher, positive lymph nodes, lymphovascular invasion, distant metastases, or positive surgical margins.[3]

The authors also report that radioactive iodine and external beam radiation treatment for patients with co-PTC/ATC were associated with a better overall survival than for those who did not receive such treatment. Co-PTC/ATC accounted for 16.4 % of the ATC cases in this study, similar to other studies.[4] The authors' finding that co-PTC/ATC may represent an intermediate clinical entity is supported by their finding that clinical and pathologic features such as age at diagnosis, proportion of women, and rates of tumors larger than 4 cm, multifocality, extrathyroidal extension, and distant metastases were between those for patients with only PTC and ATC, and by their finding that among patients with co-PTC/ATC without any aggressive prognostic features, overall survival was still intermediate to that of patients with PTC and ATC.

Consistent with current guidelines and the known therapeutic efficacy of radioiodine ablation for PTC and external beam radiation therapy for ATC, radioiodine

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ablation therapy was less commonly administered for patients with Co-PTC/ATC than for patients with PTC, but more commonly than for those with ATC, and external beam radiation therapy was more commonly administered for patients with co-PTC/ATC than for patients with only PTC, but less commonly than for patients with only ATC. The investigators also found that total thyroidectomy and radioiodine ablation therapy were associated with longer overall survival for patients with co-PTC/ATC.

Given the rarity of ATC and the sparse data on co-PTC/ATC, the study findings are an important contribution to the literature and shed some light on the prognosis and impact of treatment for patients with co-PTC/ATC. However, the study by Greenberg and associates[3] is limited by several shortcomings inherent to the use of data such as data in the NCDB. First and foremost, the component of ATC in the cases defined as co-PTC/ATCare unknown and could range from just a little bit of ATC (a microscopic focus) to most sites of disease involving distant metastasis. Although acknowledged as a limitation by the authors, this likely dictated the presence of the adverse features they observed, as well as treatment utilization and response to treatment (radioiodine ablation and external beam radiation).

Another important limitation of the study was the definition used to classify cases of co-PTC/ATC (all PTC that were grade 4). This is because the diagnosis of ATC on histology and especially on fine-needle aspiration cytology can be difficult, and because the interpretation of tumor grade for thyroid cancer is subjective without established or validated criteria (e.g., mitotic index. Ki67) to ensure its accuracy. Although mutation data are not available in the NCDB, expeditious mutation analysis for targetable genetic alterations (BRAF V600E, RET, and TRK fusions) at the diagnosis of ATC is important because patients can have exceptional responses to agents targeting these alterations, which in some cases can result in a short-lived complete response or make surgical resection possible (neoadjuvant therapy).[4]

In summary, the likely better prognosis for patients with co-PTC/ATC than for patients with only ATC should lead to improved discussions with patients regarding their prognosis and expected response to specific treatment, justifying the selection of an aggressive management strategy if there is just a little bit of anaplastic thyroid cancer.

DISCLOSURES The author declares no conflicts of interest.

REFERENCES

1. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ Jr, et al. American thyroid association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2021;31:337–86.
2. Xu B, Fuchs T, Dogan S, et al. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, immunophenotypic, and molecular study of 360 cases. *Thyroid*. 2020;30:1505–17.
3. Greenberg JA, Moore MD, Thiesmeyer JW, Egan CE, Lee YJ, Christos P, et al. Coexisting papillary and anaplastic thyroid cancer: elucidating the spectrum of aggressive behavior. *Ann Surg Oncol*. 2022. https://doi.org/10.1245/s10434-022-12553-6.
4. Ragazzi M, Torricelli F, Donati B, Ciarrocchi A, de Biase D, Tallini G, et al. Coexisting well-differentiated and anaplastic thyroid carcinoma in the same primary resection specimen: immunophenotypic and genetic comparison of the two components in a consecutive series of 13 cases and a review of the literature. *Virchows Arch*. 2021;478:265–81.