Extended Abstract

Distinguishing between thymic carcinoma and lung carcinoma: a medical oncologist's perspective

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Thymic carcinomas account for approximately 20% of all thymic epithelial tumors (TETs), have distinct histologic and molecular characteristics, and the potential to grow rapidly and limit survival (1-3). The World Health Organization defines several histologic subtypes of thymic carcinoma (1). Of these subtypes, thymic squamous cell carcinoma is the most common, accounting for 70–80% of all cases. These tumors share morphological and immunophenotypic features with squamous cell cancers of the lung, which constitute approximately 20% of all non-small cell lung cancers (NSCLCs) (1,4). Although clinical and radiological features along with morphologic and immunophenotypic findings (2) can help to distinguish between thymic carcinomas and NSCLCs, in some cases it can be difficult to make a distinction between these tumors. Nevertheless, it is important to distinguish between thymic carcinoma and NSCLC due to differences in the clinical presentation, natural history, and management of these diseases. Tumor location, metastases, growth rate, underlying risk factors, and concomitant paraneoplastic autoimmune disease (AD), if present, can help differentiate between NSCLCs and thymic carcinomas with otherwise similar morphologies.

The location of the primary tumor and the pattern of metastasis can provide clues about the underlying tumor type. Patients with NSCLC generally present with a primary tumor in the lung parenchyma, and distant metastases are present in more than half the cases at the time of initial diagnosis (5). Brain and bone metastases are observed in up to 40% of patients (6,7). In contrast, thymic carcinomas typically arise in the prevascular (anterior) mediastinum and invade local structures such as the pleura or pericardium (8). Although extrathoracic spread occurs, especially later in the course of the disease, brain metastases are rare with an incidence of less than 5% (9).

NSCLCs generally grow faster than thymic carcinomas with a median doubling time of 131 (range, 39–221) days for squamous cell lung carcinoma (10). In contrast, advanced thymic carcinomas have a longer median doubling time of 205 (range, 43–653) days (11).

Identification of underlying risk factors and concurrent paraneoplastic ADs can both help establish a diagnosis. Risk factors for NSCLC include history of tobacco smoking, occupational and environmental exposures, ionizing radiation, and genetic predispositions (12). In contrast, there are no established risk factors to date for thymic carcinoma. Paraneoplastic ADs are observed in about 10% of patients with lung cancer and approximately 6% of patients with thymic carcinoma (13,14). Endocrine disorders, such as hypercalcemia of malignancy, are the most common paraneoplastic ADs associated with NSCLC (15), whereas paraneoplastic autoimmunity, although uncommon, is more likely to manifest as myasthenia gravis in association with thymic carcinoma (14).

Treatment planning in cases of diagnostic uncertainty requires an understanding of areas of overlapping clinical activity of systemic therapies, a potential role for targeted therapy, benefits and risks of immunotherapy, and indications for local therapy.

Treatment of metastatic NSCLC is guided by histology, the presence of actionable genomic targets, and programed death ligand-1 expression on tumor cells. In the absence of actionable targets and contraindications to immunotherapy, frontline treatment of metastatic NSCLC

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consists of a platinum-doublet chemotherapy with an immune checkpoint inhibitor (ICI) or an ICI alone (16,17). Similarly, unresectable thymic carcinoma is also treated with platinum-based combination chemotherapy, such as cisplatin with doxorubicin and cyclophosphamide (PAC regimen) or carboplatin with paclitaxel (18,19). In cases where it is difficult to distinguish between NSCLC and thymic carcinoma, treatment with carboplatin and paclitaxel can be considered due to overlapping clinical activity.

In tumors harboring actionable genomic changes, the choice of treatment is determined by the presence of druggable targets. The list of targetable genomic alterations in NSCLCs has expanded rapidly in recent years, and approximately 40% of NSCLCs are expected to harbor a druggable genomic alteration (16,17). In contrast, thymic carcinomas rarely harbor actionable mutations or other genomic targets (3). *KIT* mutations are present in less than 10% of thymic carcinomas and can potentially be targeted with KIT inhibitors, such as imatinib, or multikinase inhibitors that target *KIT*, such as sunitinib (20).

The role of ICIs in cases where it is difficult to differentiate between lung and thymic carcinoma merits special attention. For NSCLC, ICIs have an established role for many indications including upfront treatment of advanced disease, maintenance therapy, consolidation after chemoradiation, and in cases of unresectable or recurrent disease (16,17). In contrast, the indication for use of ICIs for thymic carcinoma is limited to the use of pembrolizumab for treatment of relapsed disease in patients with no history of paraneoplastic autoimmunity (19,21). Patients with thymic carcinoma receiving pembrolizumab require close monitoring since the risk of developing severe treatment-related, immune-mediated toxicity is two to five-fold higher compared with patients with NSCLC receiving ICIs (15% *vs.* 3–6%) (16,21). Therefore, in cases of diagnostic uncertainty, ICIs should only be used in carefully selected patients where the potential benefits are likely to outweigh the risks of treatment. The following factors should inform the decision to use ICIs under these circumstances:

- ICIs are generally contraindicated in patients with an active AD with a few exceptions, such as well controlled autoimmune thyroid disease or type I diabetes mellitus, vitiligo, or psoriasis.
- Patients with TETs, including thymic carcinoma, appear to be at a particularly high risk for developing severe and potentially life-threatening muscle-directed or neuromuscular immune-mediated toxicity (22). Therefore, ICIs are contraindicated in patients with a history of myasthenia gravis, polymyositis, myocarditis, or neurological ADs, whether active or in remission.
- In patients with TETs, detectable titers of acetylcholine receptor (AChR) autoantibodies before initiation of treatment with an ICI tends to be strongly associated with subsequent development of immune-mediated myositis (23). Hence, we recommend testing for AChR antibodies before starting immunotherapy in cases where it is difficult to establish a conclusive diagnosis of NSCLC *vs.* thymic carcinoma, and not offering ICIs to patients with detectable AChR antibodies even in the absence of a clinical history of AD.
- For patients with a squamous cell carcinoma where a thymic origin cannot be ruled out, individuals being treated with immunotherapy should undergo close clinical monitoring and serial testing of creatine kinase and aldolase to monitor for development of immune-mediated myositis.

Finally, local therapies including surgery and radiation therapy should be considered, when indicated, for the management of both NSCLC and thymic carcinoma (17,19). In both tumor types, surgery is generally indicated for patients with early stage, locally advanced, or oligometastatic disease. Furthermore, definitive radiation therapy can be used for management of both NSCLC and thymic carcinoma in patients with locally advanced or unresectable disease, or as adjuvant therapy after complete surgical resection.

In conclusion, some cases of NSCLC and thymic carcinoma are difficult to distinguish from one another due to shared histologic and radiological features. Therefore, multidisciplinary evaluation is essential to establish the correct diagnosis and plan appropriate management. If a conclusive diagnosis cannot be established, it is advisable to choose treatment regimens with overlapping clinical activity. Multi-modality therapy should be considered when indicated. Targeted therapy driven by genomic data finds a role in the management of NSCLC more often than thymic carcinoma. Lastly, the use of ICIs should be carefully considered in case of diagnostic uncertainty due to substantial differences in the risk of immune-mediated toxicity. Further research is required to establish diagnostic signatures for thymic carcinoma in order to help distinguish it from NSCLC. Ultimately, establishment of the correct diagnosis is fundamental in guiding the treating physician through the expected disease course, appropriate treatment

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modalities, and potential complications.

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