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The challenges in diagnosis of thymic carcinoma

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***Abstract*---**Thymic Carcinoma (TC) is a rare tumor among the epithelial tumors of the thymus with a challenging diagnosis for pathologists. A case report, a 55-year-old male patient complained of coughing, chest pain, and intermittent shortness of breath for 2 weeks before being referred. Patient underwent radiological examination, surgery, histopathological examination and immunohistochemical examination to reach the definitive diagnosis. The histopathological examination of Thymic Squamous Cell Carcinoma was established with immunohistochemical examination.

***Keywords*---**Thymic Carcinoma, Histopathological Examination, Immunohistochemical examinaton.

Introduction

Epithelial tumors of the thymus consist of thymoma, thymic carcinoma and neuroendocrine tumors (Colby et al., 2017). Thymic carcinoma accounts for less than 1% - 4% of epithelial tumors of the thymus (Mlika et al., 2016). The most often location found in the mediastinum. Thymic Carcinoma is the most aggressive thymic epithelial tumor with a high degree of anaplastic histology, high proliferative activity, and a tendency to metastasize both intrathoracic and extrathoracic compared to thymoma (Sharma & Dawson, 2017) and has a poor prognosis (Miyamoto & Acoba, 2017). WHO Classification of Tumours Editorial Board, Thoracis tumours, 2021 stated that Thymic Carcinoma is a malignant neoplasm of the thymus which histologically does not resemble the normal thymic architecture as in thymoma and can occur at any age, mostly in the sixth decade with a mean age of 56 years and the percentage of men (56%) more than women.

There were 6 cases Thymic Carcinoma cases at Dr Soetomo General Academic Hospital Surabaya during 2014-2019 with an age range of 28-75 years.

Epithelial tumors of the thymus are usually discovered incidentally on radiological examination because there are no paraneoplastic syndromes or local symptoms associated with mediastinal mass compression. As many as two thirds of patients diagnosed with thymoma are asymptomatic. As many as 40% of patients most often come with complaints related to mediastinal mass effects, namely cough, chest pain, and tightness due to complications in the form of superior vena cava syndrome (Miyamoto & Acoba, 2017). The clinical symptoms of patients with thymic carcinoma and thymoma are very different. Paraneoplastic syndromes are rare in thymic carcinoma. The diagnosis of thymic carcinoma should be ruled out if there are clinical symptoms of Myasthenia Gravis. Myasthenia Gravis is a paraneoplastic syndrome that often occurs in thymoma because thymic carcinoma is rarely associated with an autoimmune syndrome compared to thymoma (Mlika et al., 2016).

Radiological examination CT scan of the thorax has an important role to see the characteristics of the tumor, stage and development. Thoracic MRI is very helpful to see the presence of tumor infiltration into the heart and great vessels or to differentiate malignancy from cysts. Fluorodeoxyglucose PET shows FDG uptake in Thymic Carcinoma compared to Thymoma (Miyamoto & Acoba, 2017). The clinical, radiological, and histopathological features are not typical of thymic carcinoma and neuroendocrine tumors. Thymic carcinoma is a diagnosis of exclusion because many cases of primary tumor metastases from other organs. This case report will elaborate the challenges of diagnosing thymic carcinoma.

Case Description

A 55-year-old male patient came to Dr Soetomo Academic General Hospital Surabaya with a referral from Peripheral Hospital in May 2019. The patient complained of coughing, chest pain, and intermittent shortness of breath for 2 weeks before being referred. The patient never complained of weakness in the upper and lower extremities. There was no history of smoking, cancer in the family, hypertension, diabetes mellitus, autoimmune and heart diseases. The patient's general condition was good and normal nutritional status. The results of the patient's laboratory examination showed within normal limits.

Radiological examination of a chest X-ray in April 2019 on showed a right parahilar and right paracardial nodule with a good bronchovascular pattern on the lung. Thoracic CT scan results showed multiple left and right lung nodules with contrast enhancement, with the largest size measured 2 cm in diameter in the right lung and 0.6 cm in diameter in the left lung; diffuse fibrosis in the left and right lungs partially attached to the left and right hemithorax walls; soft tissue mass cysts, inhomogeneous lobulated with contrast enhancement measured 3.1 x 3.8 x 4.5 cm on the right side retrosternally attached to the ascending aorta, superior vena cava and some part of right atrium. The conclusion was a mediastinal mass, can be metastatic or primary and suspicion of left and right lung metastases. The patient underwent a repeat chest X-ray at Dr Soetomo Academic General Hospital Surabaya in June 2019 and showed

multiple pulmonary nodules in the right paracardial and smaller nodules in the left paracardial.

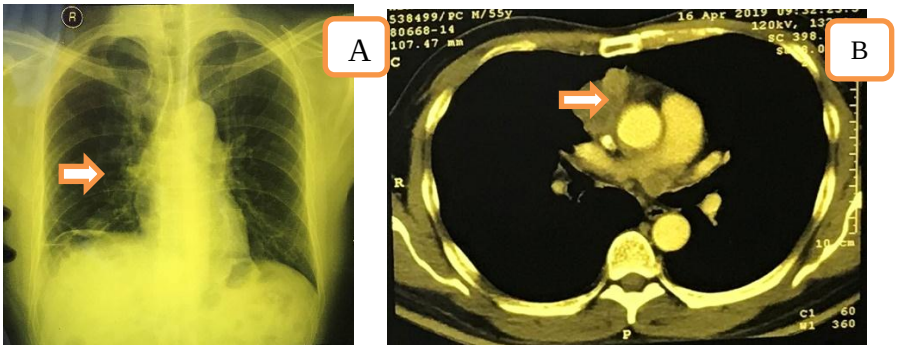

Figure 1. Radiological examination. A. Chest X-Ray B. Thoracic CT Scan

The patient was admitted to the hospital with a suspicious diagnosis of thymoma and planned for right thoracotomy and single right lung nodule excision. The patient underwent thymic tumor debulking excision thoracotomy with right lung wedge resection in June 2019 at Dr Soetomo Academic General Hospital Surabaya. During surgery, the thymic mass was found to be malignant, infiltrating pericardium, phrenic nerve and right atrium. The excision of thymic tumor was performed with partial resection of the pericardium and right phrenic nerve, and wedge resection was performed on the right inferior lobe nodule, clinically suspicious for metastatic process.

The surgical tissue was sent to the Anatomical Pathology laboratory for histopathological examination. Macroscopically we received 2 containers consisting of thymus tumor and lung nodules. The first container from thymus tumor contains 5 pieces of tissue, with total weight of 24 grams, measuring 1.8x1x0.5 cm – 5x3.3x1.7 cm, outer surface was rough, partially covered with fat, on the cut suction revealed a mass, sized 1.2x0.8x0.5cm to 1.7x1x0.8 cm, greyish-white, partially brownish, solid firm consistency. The second container from pulmonary nodule containing 1 piece of tissue weighing 9 grams measuring 4.2x3.5x1.8 cm, outer surface was rough partially smooth, on cut sections revealed a mass measuring 2.5x1.8x1.7 cm, greyish-white partly brownish, solid firm consistency ,with a small cystic space in the middle.

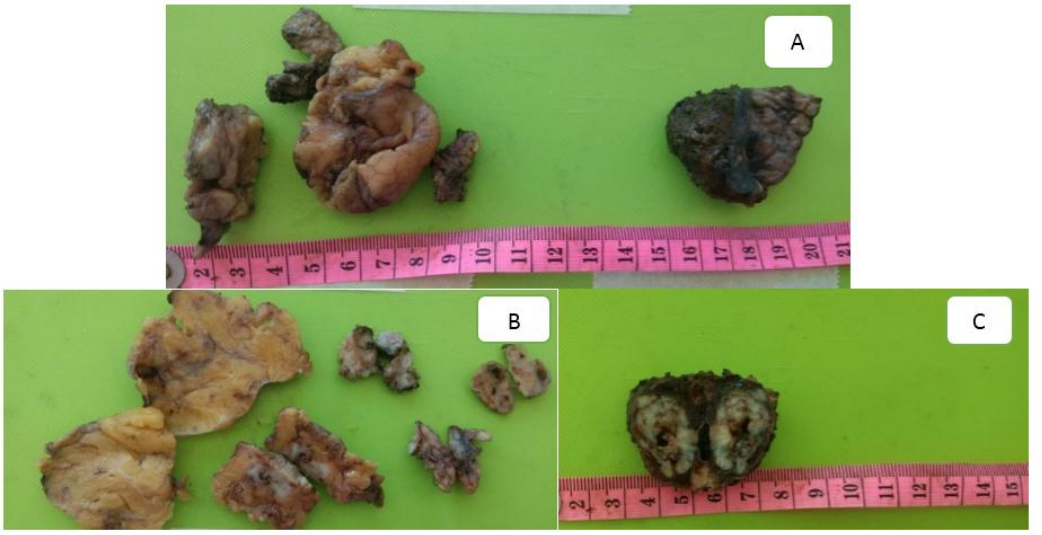

Figure 2. A. Surgical Specimen B. Cut section of Thymic Tumor C. Cut section of Lung Nodule

Microscopic examination of thymic tumor tissue showed tissue fragments with tumor growth consisted of proliferation of anaplastic epithelial cells, round to oval nucleus, pleomorphic, hyperchromatic, moderate amount of cytoplasm, mitoses > 35/10 High Power Field, tumor growing invasively into the fibrous stroma with an area of necrosis and hemorrhage. Microscopic examination of pulmonary nodule showed pieces of lung parenchyma tissue with tumor growth arranged in solid, nests and partially trabecular structures, consisted of a proliferation of round to oval, pleomorphic, hyperchromatic nuclear cells, prominent nucleoli, moderate amount of cytoplasm, mitoses 24/10 High Power Field. There were also foci of tumor growth with a perivascular space pattern along with infiltration of lymphoid cells with areas of necrosis and hemorrhage. Histopathological results concluded as Thymic carcinoma with a differential diagnosis of Thymoma B3 and carcinoma of the lung and continued with immunohistochemical examination with CD117, TTF-1, CK7, CD5 and P63 antibodies. Immunohistochemical examination of lung nodules showed that CK7 was negative in the tumor cell cytoplasm, TTF-1 was negative in the tumor cell nucleus, CD117 was positive in the tumor cell cytoplasm, CD5 was positive in the tumor cell membrane and P63 was positive in the tumor cell nucleus, thus concluded as thymic squamous cell carcinoma.

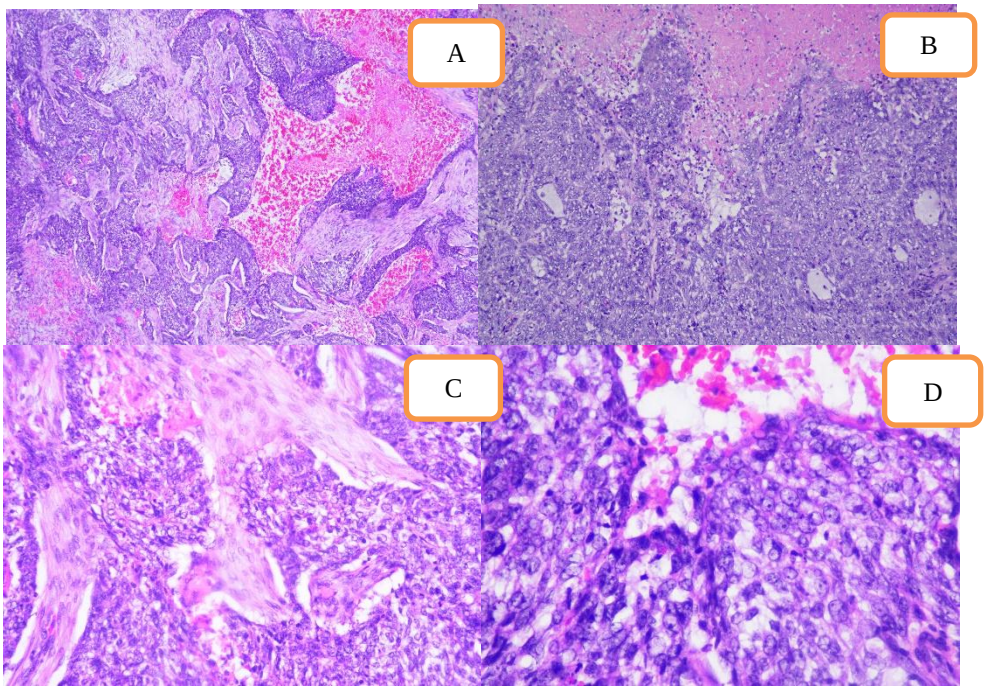

Figure 3. Microscopic examination of thymic tumor showed tumor growth consisted of proliferation of anaplastic epithelial cells, round to oval nucleus, pleomorphic, hyperchromatic, moderate amount of cytoplasm, tumor growing invasively into the fibrous stroma with an area of necrosis and hemorrhage. A. HE 40x B. HE 100x C. HE 200x D. HE 400x.

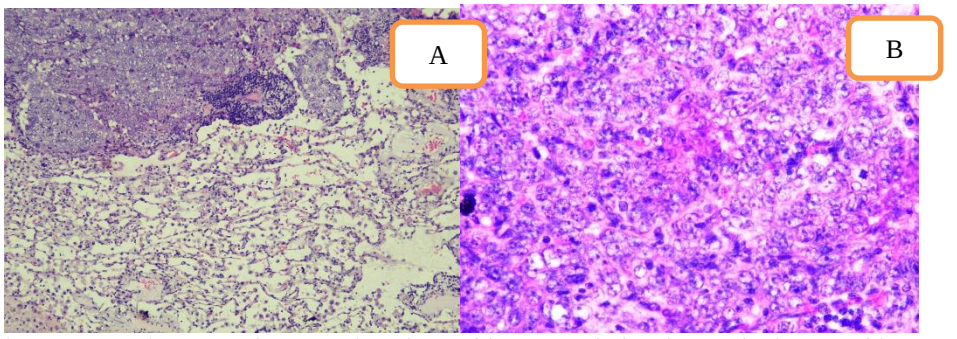

Figure 4. Microscopic examination of lung nodule showed pieces of lung parenchyma tissue with tumor growth arranged in solid, nests and partially trabecular structures, consisted of a proliferation of round to oval, pleomorphic, hyperchromatic, prominent nucleoli, moderate amount of cytoplasm. A. HE 200x B. HE 400x.

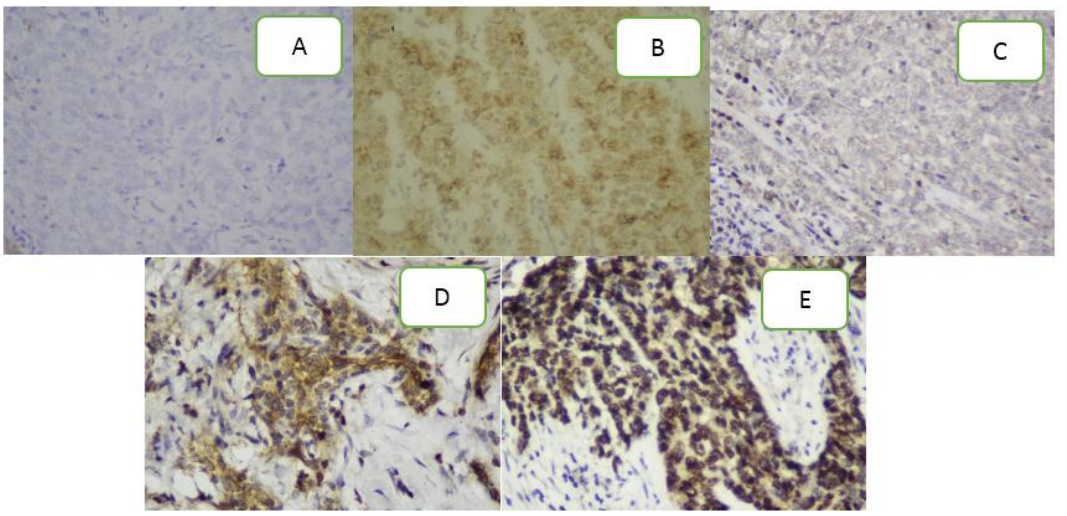

Figure 5. Immunohistochemical Examination in the thymic tumor
A. Negative staining of CK7 antibody B. Positive staining of CD117 antibody
C. Negative staining of TTF-1 antibody D. Positive staining of CD5 antibody
E. Positive staining of P63 antibody

Discussion

Thymic Carcinoma is a rare epithelial tumor in the thymus (Tseng, 2011). The incidence rate is 0.13 per 100,000 population per year and occurs in the fifth decade with a male predominance (Sharma & Dawson, 2017). This case occurred in a male patient aged 55 years and this is in accordance with the literature.

The patient complained of coughing, chest pain, and intermittent shortness of breath for 2 weeks in this case and there was no complaint or history of Myasthenia Gravis. Literatures mentioned that many cases were found incidentally on radiological examination due to local symptoms related to the compression effect of the mediastinal mass or the presence of a paraneoplastic syndrome (Report, 2017). Paraneoplastic syndromes such as Myasthenia Gravis are very rarely associated with thymic carcinoma. Myasthenia Gravis is very often associated with Thymoma type A, AB, or B (Gravis, 2015). The standard radiologic examination for thymic tumors is chest CT scan with contrast because it allows exploration of the mediastinum and pleura from the apex to the costodiaphragmatic region. CT scan is better than MRI for the diagnosis of anterior mediastinal masses except for cystic lesions (Girard et al., 2015).

Microscopic examination of thymic carcinoma showed a proliferation of large polygonal cells arranged in a sheet, islet, and cord pattern and growth into the stroma with inflammatory cell infiltration. Tumor cells with large vesicular or hyperchromatic nuclei, prominent nucleoli and eosinophilic cytoplasm, mitoses and foci of necrosis were also found (Venuta et al., 2010). Microscopic examination of this patient was concluded as Thymic Carcinoma with differential diagnosis of Thymoma B3, and carcinoma of the lung.

Immunohistochemical examination was performed to confirm the origin of epithelial tumor cells using cytokeratin antibodies, EMA, CD117, CD5, MUC1 (Mlika et al., 2016). CD5 and CD117 antibodies is very useful in establishing the diagnosis of Thymic Carcinoma. Expression of c-kit antibodies occurs more in thymic carcinoma than in thymoma. Thymic carcinoma shows strong immunoreactivity to p63 which is a marker of squamous cell differentiation, whereas thymoma B3 is not immunoreactive to p63 (Gravis, 2015). Metastases carcinoma are frequently observed in the liver, lungs, or bones, and lymph node metastasis in mediastinum is extremely rare. The histopathological type is adenocarcinoma in most cases whereas Squamous Cell Carcinoma is rare (Agca & Kosif, 2018). Thymic Squamous Cell Carcinoma are imunoreactive for pancytokeratins, and most positive for p63/p40. CD5 and CD117 are frequently expressed in thymic Squamous Cell Carcinoma (75-85%) but rarely expressed in thymomas (usually <5%) (WHO Classification of Tumours Editorial Board, Thoracis tumours, 2021). Carcinoma of the lung is divided into two, namely Small Cell Lung Carcinoma and Non Small Cell Lung Carcinoma which is very rare which metastasizes to the thymus, giving positive results with CK7 and TTF-1 antibodies on immunohistochemistry (Report, 2017). Immunohistochemistry of TTF-1 and CK7 was performed on the patient due to the presence of a pulmonary nodule with a differential diagnosis of lung carcinoma. The patient's immunohistochemistry results were positive for CD117, CD5, P63 and negative for CK7, TTF-1 so that the diagnosis of Thymoma B3 and carcinoma of the lung could be ruled out.

Conclusion

Thymic Carcinoma is a rare epithelial tumors in the thymus. The diagnosis of thymic carcinoma is made by excluding other diagnoses such as metastases, thymoma or carcinoma of the lung and bronchial tree. The role of the pathologist is not only to determine the criteria for malignancy but also to determine the histologic subtypes which are difficult due to the similiarity of the morphology with other tumor presented in the thymus and lung.

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