Superior Vena Cava Syndrome in Men with Thymic Atypical Carcinoid

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Superior Vena Cava Syndrome in Men with Thymic Atypical Carcinoid (Neuroendocrine Tumor Grade 2)

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ABSTRACT

Introduction: Cases of neuroendocrine tumors (NET) can occur in various organs, generally in the form of gastroenteropancreatic (GEP-NET) and pulmonary tract (PNET). The incidence of thymic neuroendocrine tumors (TNET) is rare, accounting for less than 5% of thymic and mediastinal malignancies, and 0.4% of all neuroendocrine tumors. **Case presentation:** A 57-year-old man came to RSUP Dr. Mohammad Hoesin Palembang with complaints of coughing, bluish and curved blood vessels in the chest, and shortness of breath during activities that have been getting worse for six months. CT scan showed a tumor measuring 18.6 x 11.7 x 11 cm in the anterior mediastinum and pressing on the superior vena cava and abdominal aorta. TTNA and core biopsy with CT guidance showed NET Grade 2, mitoses 6/2 mm2, positive tumor cells with immunohistochemistry for synaptophysin, chromogranin, CD 56, AE1/AE3, and Ki67 9%. The patient received paclitaxel and carboplatin chemotherapy for 6 cycles. **Conclusion:** The prognosis for atypical carcinoid patients is 20-80% for a 5-year survival rate. Appropriate patient management is needed to improve the outcome of patients with primary thymic atypical carcinoid (NET, grade 2).

1. Introduction

Over the past 40 years, there has been a 6.4% annual growth in the number of cases with neuroendocrine tumors (NET). NET can occur in various organs, but often occurs in the gastroenteropancreatic (GEP-NET) and pulmonary tract (PNET).[1] Less than 5% of malignancies involving the thymus and mediastinum and 0.4 percent of all neuroendocrine tumors are thymic neuroendocrine tumors (TNETs). The annual incidence of TNET is 0.2 per 1.000.000 people.[2]

Neuroendocrine tumors in the thymus is classified into four subtypes by the World Health Organization (WHO) Classification of Tumours Thoracic Tumours 2020: atypical carcinoid (AC), small cell neuroendocrine carcinoma (LCNEC), typical carcinoid (TC), and small cell carcinoma (SmCC). It is important to differentiate TNET from lung cancer, primary extra thoracal tumor, and other diseases affecting the mediastinum. The incidence of low- to intermediate-grade neuroendocrine tumors (typical and atypical carcinoid tumors) in the mediastinum is less than 5%. It can occur at various ages and there

is a 3:1 male-to-female predisposition, along with endocrine involvement and paraneoplastic syndrome associations. The patient may get radiation and chemotherapy in addition to or instead of surgical treatment.[3]

Thymic Neuroendocrine Neoplasm (TNEN) is a comparatively aggressive tumour that has the potential to spread to other organs and become recurrent. The diagnosis of primary tumour neuroendocrine mediastinum is aided by clinical correlation and radiological evaluation. Prognosis of the case is determined by the time of disease is discovered and the time of treatment begins. The disease prognosis is better if early stadium, compared to cases where the advanced stadium. Atypical carcinoid prognosis with a 5-year survival rate of 60%. We described a 57-year-old male patient with thymic atypical carcinoid at the Department of Anatomical Pathology, RSUP Dr. Mohammad Hoesin Palembang.

2. Case Presentation

A 57-year-old construction worker complained of having trouble breathing during his work a year ago. Feeling constricted for three months ago, and it still hurts when sitting and sleeping as well as when moving. The patient has once coughed with blood patches, but never repeated. The patient reported having chronic chest discomfort that persisted for the previous three months, persisted during activities, and got worse.

The patient has developed blue, twisted veins that extend from the skin of his chest to the nape and do not go away whether he sits or lies down throughout the last month (Figure 1A-B). Six kg of the 50 kg that was lost before being ill has been lost. No reports of having nocturnal sweats. No complaints of wheezing in the cold or at night. There are no symptoms of diarrhea, redness, oedema in the right or left leg, sexual dysfunction, or emotional instability.

The patient has smoked two packs a day for the past 21 years. No prior experience with drugs or alcohol. He has 20 years of experience as a construction worker, sanding walls and operating a cement mixer. When working, he doesn't use any kind of mask or other self-defence equipment.

JVP (jugular venous pressure) was measured physically at the neck (5+2) cm, and the lymph gland was not enlarged. Serum levels of CEA (1.6 ng/mL) and Cyfra 21-1 (1.99 ng/ml) were found to be normal in blood test results.

CT scans reveal masses in the right-to-left mediastinum, ranging in size from anterior to posterior: AP (antero-posterior) 11 cm, CC (cranio-caudal) 11.7 cm, and LL (latero-lateral) 18.6 cm. These masses compress and constrict the superior cava vein and extend to the proximal section of the abdomen paraaortic (Figure 1C-E). There appears to be an enlargement of the parathyroid lymph gland measuring 3,09x2,16 cm, 1,83 x 1,78 cm, and 3,01x2,54 cm in the lower right colli.

CT scan of the thorax with transthoracic needle aspiration (TTNA) in mediastinum showed multilayered cell architectures were identified in hypercellular populations with an erythrocyte background. Acinar, rosette, oval-shaped round, spindle, increased N/C ratio, chromatin salt and pepper, inconspicuous nucleus, and nuclear streaks make up a tiny fraction of the tumour. Plasma cells, neutrophils, lymphocytes, macrophages, fibrillar matrices, and degenerative cells are common (Figure 2B-D).

From a biopsy of the anterior mediastinum core, two tissue pieces measuring 1x0.1x0.1 cm and 0.6x0.1 were taken (Figure 2A). Preparation is derived from anterior mediastinum core biopsy, two tissue pieces revealed a mass of neuroendocrine growth pattern (organoid, trabecular, rosette formation, nested) or pseudoglandular (Figure 2E-G). Tumour cells are uniform with a polygonal shape, round to oval nuclei with salt and pepper chromatin as well as

inconspicuous nucleoli and moderate to abundant eosinophilic cytoplasm. Stroma is fine and highly vascularized, mitotic count is 6/2 mm^2 (Figure 2H).

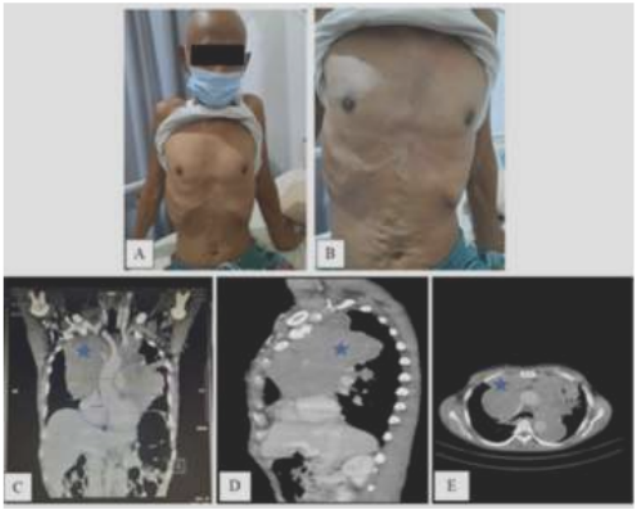

Figure 1. Signs of superior cava syndrome. A. Venectation of the patient's abdominal B. Venectation on thoracic anterior veins. C. Thorax CT scan with coronary section D. Sagittal segment CT scan. E. Axial section. The proximal paraaortic abdominals and the superior kava vein are both compressed and narrowed by the apparent mass in the mediastinum (asterisks mark) on the right-left side from anterior to posterior.

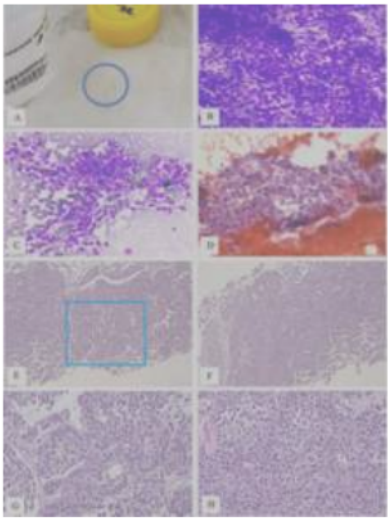

Figure 2. Thymic atypical carcinoid of mediastinum. A. Core biopsy from mediastinum. B. TTNA show hypercellular cluster of cells, consists of uniformised cells with nuclear streaking (200x). C. Nuclear moulding, rosette, round to oval cell with nuclear streaking (400x), MDT stain. D. "Small blue cell tumours," showing uniform cells which have a round to oval stippled nucleus and scant, pink granular cytoplasm, Papanicolaou stain (400x). F. Tumour showing trabecular and solid pattern, lobulated/organoid pattern (blue box) (H&E, 100x). G. Tumour cells are uniform with a polygonal shape, round to oval nuclei with salt and pepper chromatin as well as inconspicuous nucleoli and moderate to abundant eosinophilic vacuolated cytoplasm (H&E, 400x). H. Uniform, polygonal shaped, small cells with round/elongated or plasmacytoid shaped, atypical mitosis (blue arrow) (H&E, 400x).

The following immunohistochemical assays were performed: LCA (CD 45), AE1/AE3, Chromogranin, Synaptophysin, Ki67, and CD56. According to the findings, tumour cells were LCA (CD 45) negative (Figure 3). Tumour cells that are positive for synaptophysin, chromogranin, CD56, AE1/AE3, 9% of which are positive for Ki67. This finding is consistent with thymic atypical carcinoid (Neuroendocrine tumour grade 2). The patient was receiving chemotherapy for six cycles. paclitaxel 230 mg and carboplatin 440 mg for six cycles.

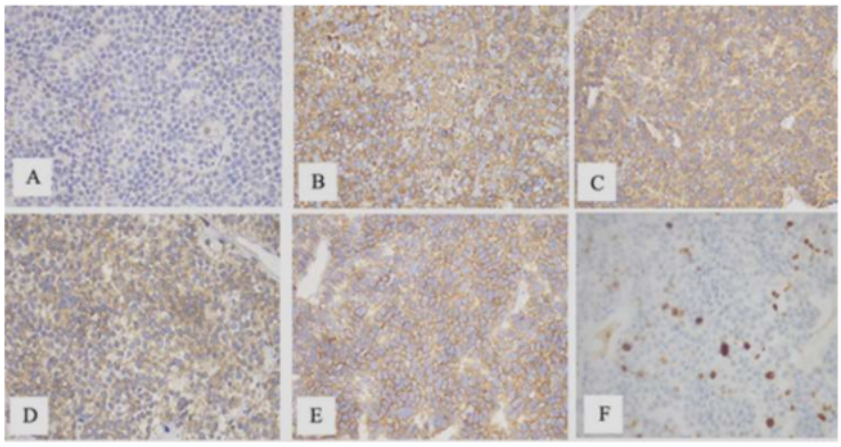

Figure 3. Immunohistochemistry of thymic atypical carcinoid. A LCA negative stain. B. Chromogranin diffusely and strongly positive. C. Synaptophysin positive in tumor cells. D. Positive staining for CD56 in cytoplasm tumor cells. E. Positive staining for cytokeratin AE1/AE3 in tumor cells. F. Low proliferative index with Ki67 immunostain (9%) (400x).

3. Discussion

The WHO 2020 classification system is used to categorize Thymic Neuroendocrine Neoplasm (TNEN) into three groups: low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and two high-grade carcinomas, which are small cell carcinoma (SmCC) and large cell neuroendocrine carcinoma (LCNEC). The tumours have neuroendocrine growth pattern (organoid, trabecular, rosette formation, nested) or pseudo glandular, follicular and papillary growth.[2] The anatomical location is significant since it has distinct risk factors, clinical symptoms, and molecular aetiology, even though the unification of neuroendocrine principles can occur in different organs.[3]

While only 0.4% of all neuroendocrine tumours are TNENs, the incidence rate of TNENs is 2-5% of all thymus abnormalities and typically affects elderly people. There is an elevated risk of low-grade to high-grade tumour transformation, metastasis to distant organs and lymph glands, and a correlation with death in all cases with TNEN.

Many discovered parallels between TNEN and NEN in the lungs. At least three similarities between NEN in the lungs and TNEN. TNEN is also associated with four histological subtypes of pulmonary NEN: typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell carcinoma (SmCC). Secondly, TC and AC in the lungs and thymus are possible in patients with

Multiple Endocrine Neoplasia (MEN) type 1. Third, there is no connection between smoking and the development of TC and AC in the thymus and lungs. Fourth, the risk of distant organ metastases and lymphatic metastases increases from TC, AC, LCNEC, to SmCC.

In comparison to females, males exhibit a greater differential in thymus TC than AC. In the thymus, the more prevalent subtypes are AC and LCNEC, but in the lungs, they are TC and SmCC. Patients with typical carcinoids tend to be male and average age of 49. The proportion of men to women is 3:1. Atypical carcinoids, which typically range in age from 18 to 82 years, are more common in older patients and have a greater incidence rate than typical carcinoids in the thymus. This 57-year-old male is consistent with the case.[3]

Clinically, TNEN can produce endocrine problems like paraneoplastic syndrome or create mild symptoms that are inadvertently discovered and related with local growth. The anterior mediastinum of the tumour in this patient is generating symptoms such as coughing, shortness of breath, and chest pain, which are interfering with day-to-day activities.

Because the lower respiratory tract contains neuroendocrine cells that secrete and release chemicals like bradykinin, prostaglandins, serotonin, calcitonin gene-related peptides (CGRP), heparin, and histamine, neuroendocrine-related disorders are frequently linked to metabolic abnormalities in the body. Neuroendocrine tumours in the lung and mediastinum can cause carcinoid syndrome in 5 percent of cases.[4] Cushing's syndrome may also be linked to neuroendocrine instances in the lung and mediastinum. The symptoms include diarrhoea, obesity, decreased appetite, flushing or redness in the face and chest, and cardiac disease connected to carcinoid syndrome. Sexual dysfunction, diarrhoea, face redness, or emotional disturbances were not reported by the patient. Therefore, functional neuroendocrine disorders are not clinically related to the patient's clinical symptoms.[5]

Physical examination of patients with violations on the mediastinum can vary, can also be affected by the accompanying disease previously suffered. Superior vena cava syndrome (SVCS) is a group of symptoms that can occur as a result of suppression of the superior vena cava by mediastinum tumours, both malignant and benign. This is because the mediastinum's structure has been invaded, and there is local compression of the tumour mass in the anterior mediastinum. These patients had normal physical examination results for the heart and no history of hypertension, asthma, or other chronic illnesses. Patients' physical examinations reveal venectation or dilatation of the veins in the neck and anterior thorax, as well as symptoms and signs of SVCS, such as cough, shortness of breath, weight loss, and chest pain.[6,7]

Mediastinal tumour that must be ruled out include lymphoma, thymoma, and thymic cancer. Patients with mediastinum tumours require additional testing, such as serum markers and thoracic radiography, to confirm the diagnosis. Thymic cancer and thymoma can be distinguished from one another by serum levels of CYFRA 21-1.[8]

Radiological evaluation emerges as a method that can support the mediastinum tumour diagnosis.[9] TTNA lung patients with atypical carcinoids displayed patterns of distributed cells during the cytological investigation, showing neuroendocrine growth pattern (organoid, trabecular, rosette formation, nested) or pseudo glandular, follicular and papillary growth. Tumour cells have a consistent polygonal shape, round to oval nuclei, with chromatin that is salt and pepper, inconspicuous nucleoli and moderate to abundant eosinophilic cytoplasm. Nevertheless, cytological analysis is insufficient to differentiate between atypical and typical carcinoides.[10] In general, the NET picture is similar to the microscopic appearance of patients' carcinoid tumors.[5,11]

A differential diagnosis with a typical carcinoid can be ruled out due to the 6/2 mm^2 atypical mitosis. Mitosis on typical carcinoid <2/2mm^2. Mitotic count of NET intermediate grade in thymus is 2-10 mitosis/2 mm^2 (average 6.5 mitosis/2 mm^2). Ki67 test results were 9% (low proliferative index). It matches the Ki67 index on atypical carcinoids up to 30%. The diagnosis of neuroendocrine tumours cannot be confirmed without an immunohistochemistry analysis. First-line (Chromogranin A and Synaptophysin) and second-line antibodies are the ones that are employed (NSE, CD56, and CD57). If the response is positive for two out of the three antibodies utilized, then the result is considered positive.[12]

Based on the definitive diagnosis obtained, patients received chemotherapy using paclitaxel and carboplatin for six cycles. Patients unable to get surgical treatment for non-small cell lung cancer may benefit from combination therapy utilizing carboplatin and active, well-tolerated paclitaxel.[13]The dose relationship with the response to paclitaxel and the comparison results with other platinum-based regimes are still to be determined.[14]

The prognosis of cases is determined by the time the disease is discovered and the start of treatment.[15] The prognosis improves with early detection as compared to cases that receive therapy at an advanced stage and have a poor outcome.[16] Five-year survival rate for patients with atypical carcinoid is 60%.[11]

Genetic abnormalities TC/NET grade 1 (G1) traits minimal genetic anomalies. Chromosome abnormalities occurring 1q, 5, 6q, 7q, 8q, 10, 11q, 12q, 13q, 18q, 20, 21q, and 22q, and chromosome deletion 1, 2p, 4p, 8, 10p, 11p, 15q, 17p, 18p, dan 22q. A genetic mutation in TC has not been reported. In comparison to TC, AC/NET grade 2 has a greater number of genetic alterations—that is, fewer than LCNEC or SCNEC.[3] However, the histologically significant differences between these four subtypes remain a challenge.[5,17]

In terms of morphology, immunohistochemistry, and molecular differences, intermediate grade NET can be easily identified from poorly differentiated, high grade LCNEC. High-grade LCNECs displayed the opposite immunohistochemical profile but with a high mitotic index, whereas intermediate-grade tumours contained ATRX mutations, a chromogranin positive and EZH2 negative morphology, and a moderate number of mitoses. *NF1* is mutated genetically in both tumour populations. The tumour is still listed as LCNEC by the World Health Organization, but research indicates that it is actually a carcinoid tumour with a high mitosis index, which can be distinguished from the conventional type due to differences in systemic management, such as immunotherapy.[5,18]

A definitive diagnosis will be challenging to establish due to the constraints of core biopsies, particularly for low grade tumours. Immunohistochemistry, utilizing epithelial markers like keratin, as well as chromogranin and synaptophysin, would be highly beneficial in determining the diagnosis. The TNEN classification will provide appropriate patient performance optimization and follow-up.[18]

4. Conclusion

A 57-year-old construction worker has complained of coughing and dyspnoea for a year, along with abdominal and chest vascular dilatation. The laboratory blood indicators CYFRA 21-1 and CEA are both within normal ranges. Thymic atypical carcinoid (Neuroendocrine Tumor, grade 2) can be definitively diagnosed based on clinical symptoms, laboratory, CT scan, TTNA, histological diagnosis, and immunohistochemistry.

5. References

1. Effraimidis G, Knigge U, Rossing M, Oturai P, Rasmussen ÅK, Feldt-Rasmussen U.

Multiple endocrine neoplasia type 1 (MEN-1) and neuroendocrine neoplasms (NENs). Semin Cancer Biol 2022 (2);79:141–62.

2. Dinter H, Bohnenberger H, Beck J, Bornemann-kolatzki K, Schütz E, Küffer S, et al. Molecular classi fi cation of neuroendocrine tumors of the thymus 2019;14(8):1472–83.
3. WHO Classification of Tumours Editorial Board Thoracic tumour. WHO Classification of Tumours. 5th ed. Vol. 5. Lyon, France: International Agency for Research on Cancer; 2021. 400–460 p.
4. Subash N, Papali MM, Bahadur KP, Avanthika C, Jhaveri S, Thannir S, et al. Recent advances in the diagnosis and management of carcinoid syndrome. Dis Mon 2022;68(7):10-22.
5. Rekhtman N. Lung neuroendocrine neoplasms: recent progress and persistent challenges. Mod Pathol 2022;35(1):36–50.
6. Kalowitz D, Weiner M. Mediastinal Mass and Superior Vena Cava Syndrome. In Cohen's Comprehensive Thoracic Anesthesia. In: Cohen E, editor. Cohen's Comprehensive Thoracic Anesthesia. English: Elsevier; 2022. p. 501–15.
7. Wan JF, Bezjak A. Superior vena cava syndrome. Emerg Med Clin North Am 2018;81(2):59–65.
8. Shiiya H, Ujiie H, Hida Y, Kato T, Kaga K, Wakasa S, et al. Elevated serum CYFRA 21-1 level as a diagnostic marker for thymic carcinoma. Thorac cancer 2021;12(21):2933–42.
9. Liu H, Liu L, Chen Y. Thymic carcinoid mimicking mediastinal lymphoma on (18)F-FDG PET/CT. J Nucl Cardiol Off Publ Am Soc Nucl Cardiol 2021;28(3):1193–5.
10. Mody D, Krishnamurthy S, Anton R, Thrall M, Caraway N, Stewart, J, et al. Diagnostic Pathology Cytopathology. 2nd ed. 102-142, editor. New York: Elsevier; 2018. 2-80 p.
11. Zhang C, Myers JL. Atlas of Lung Pathology. New York: Springer; 2018. 203–255 p.
12. Allen TC, Suster S. Pathology of the Pleura and Mediastinum. US Aatypical: Springer; 2018. 440–465 p.
13. Tsoukalas N, Baxevanos P, Aravantinou F, Tolia M, Galanopoulos M, Tsapakidis K, et al. Advances on systemic treatment for lung neuroendocrine neoplasms. Ann Transl Med 2018;6(8):1-46.
14. Melosky B. Advanced typical and atypical carcinoid tumours of the lung: management recommendations. Curr Oncol 2018;25(6):86–93.
15. Hugo T, Marcelo P, Helano F, Milton B, Rachel R. Outcomes of patients with metastatic neuroendocrine lung neoplasms: typical versus atypical carcinoids. Braz J Oncol 2021;17:1–6.
16. Torniai M, Scortichini L, Tronconi F, Rubini C, Morgese F, Rinaldi S, et al. Systemic treatment for lung carcinoids: from bench to bedside. Clin Transl Med 2019;8(1):1–19.
17. Bohnenberger H, Ströbel P. Recent advances and conceptual changes in the classification of neuroendocrine tumors of the thymus 2021;1(1):129–35.
18. Lavini C, Moran CA, Morandi U, Schoenhuber R. Thymus Gland Pathology. Milan: Springer; 2008. 55–111 p.

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