Large cell neuroendocrine carcinoma primarily in the pericardium: a case report and literature review

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To the Editor: A 40-year-old Chinese woman who complained of chest pain and compression, dyspnea that lasted for 3 months, and abdominal distension that lasted for 2 weeks was admitted at our hospital in September 2015. In early June 2015, she felt pain and compression behind the sternum after deep inspiration. Echocardiography showed mild pericardial effusion with normal left ventricular ejection fraction 63%. In July, these symptoms gradually worsened, while laboratory tests showed no abnormalities during routine blood examination, or in liver, kidney and thyroid functions. Two months later, the patient was choking and was having dyspnea even in a resting state and was unable to lie down at night. This was accompanied with poor appetite, abdominal distension, palpitation, decreased urine output, and edema in bilateral lower limbs. Echocardiography indicated moderate pericardial effusion which was not improved by diuresis. The patient's medical history includes uterus myoma for 7 years, and she was not exposed to drugs and radiation. She was not addicted to nicotine or alcohol and had no family history of tumor. In September 2015, she was admitted at our hospital. The blood pressure (BP) was 107/91 mmHg, and the heart rate (HR) was 103 beats/min. She looked acutely ill and she was resting in a semi-reclining position all day long. Distention of the jugular veins during inspiration, known as Kussmaul's sign, were observed. Superficial lymph nodes were not palpable. The heart sound was distant, and the pulsus paradoxus was also observed. The shifting dullness was suspected to be positive, with mild edema in lower limbs. The echocardiography showed widening of inferior vena cava (26 mm), and massive pericardial effusion which indicated cardiac tamponade. She was diagnosed with cardiac tamponade, and pericardial puncture and catheterization was operated immediately. The pericardial drainage was 250 to 400 mL per day with pericardial effusion turbid and bloody, and there were noticeable improvements in symptoms. The laboratory tests of drainage fluid showed white blood cell (WBC) 0 / High Performance Fortran (HPF), red blood cell (RBC) was large / HPF, adenosine deaminase (ADA) 13 U/L, lactic dehydrogenase (LD) 1500 U/L, CA125 256 U/mL. No tumor cells were found in pericardial effusion after repeated screening. The serum tumor markers were normal except for elevated CA125 (560 U/mL) and tissue polypeptide specific antigen (TPS) (389 U/L) T-spot. TB of both blood and pericardial effusion was negative. Other laboratory tests showed ALT 646 U/L, LD 653 U/L, total bilirubin 39 μmol/L, direct bilirubin 11 μmol/L; 24 h urine protein 0.33 g/24 h; Erythrocyte sedimentation rate, immunoglobulin, complement, anti-nuclear antibodies, lupus anticoagulant, antiphospholipid antibody, Coombs test were normal.

With drainage of effusion gradually decreased, liver function turned back to normal. In October 14, echocardiography was performed again showing thickening of pericardium and widening of inferior vena cava, which indicated constrictive pericarditis. The cubital vein pressure reached up to 30 cmH_2O. The contrast computer tomography (CT) and Fluorine-18-desoxyglucose positron emission tomography (18F-FDG-PET) /CT indicated lesions in the pericardium and atrioventricular spaces [Figure 1A–E], which had the potential to be malignant lesions. As the patient had constrictive pericarditis and no definite etiology, she was suggested to undergo pericardium biopsy for a definite diagnosis after multi-disciplinary consultations. Pericardiectomy was operated on October 21, 2015, and the pathology indicated (visceral and parietal pericardium) the malignant tumor with necrosis, without metastasis in lymph nodes of mediastinum (0/7) [Figure 1F–H]. Immunohistochemical staining showed

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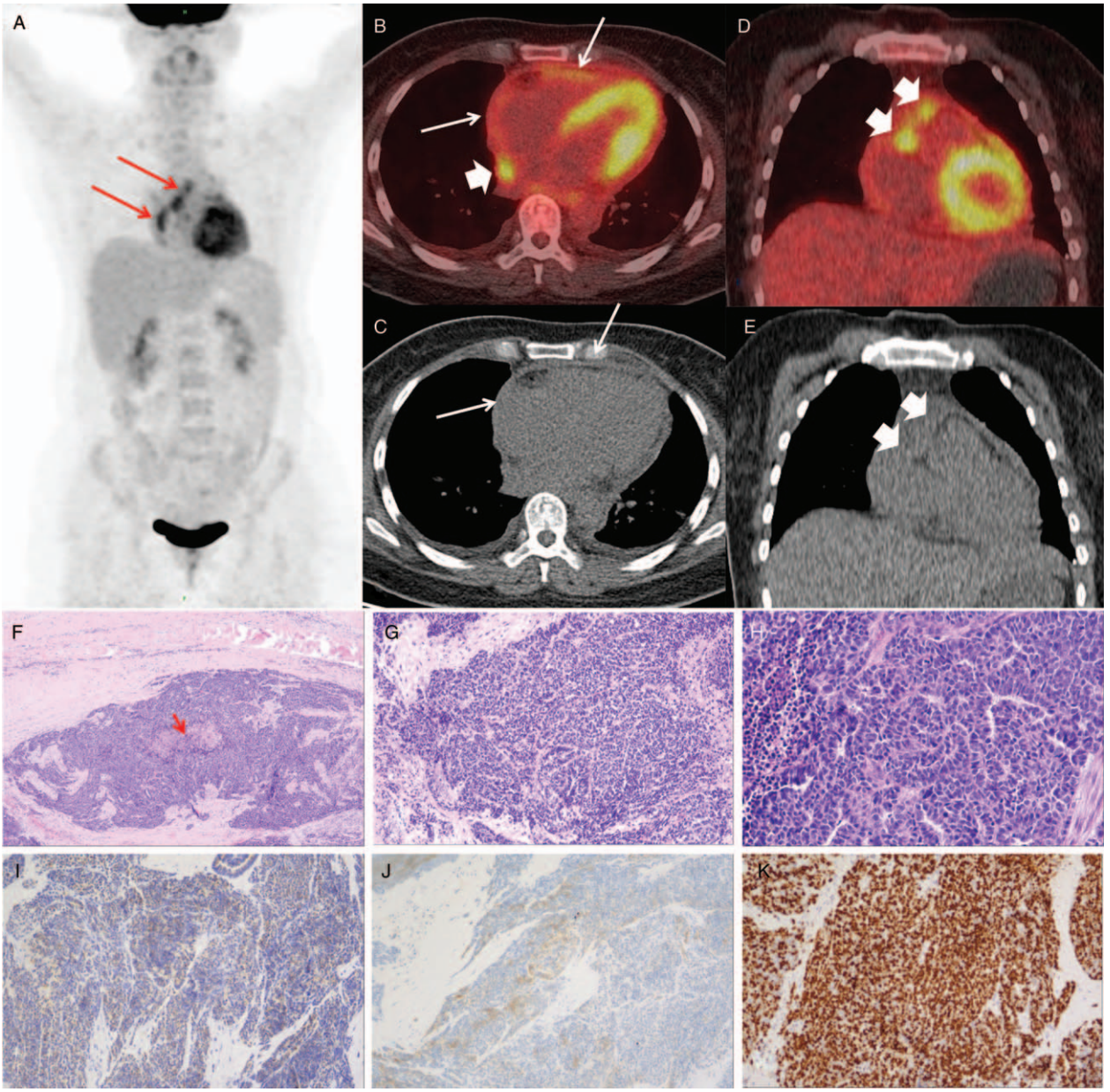

Figure 1: Images of PET-CT and histology of the specimens of pericardium. (A) Maximum intensity projection of fluorine-18-deoxyglucose positron emission tomography (18F-FDG-PET) showed multiple nodular increased FDG activity in mediastinum (arrows). (B) Axial PET/CT fusion and (C) coregistered CT showed diffuse thickening of pericardium with unevenly increased FDG uptake (arrows). There was nodular hypermetabolic lesion in pericardium (arrow head). Bilateral pleural effusion was also noted. (D) Coronal PET/CT fusion and (E) coregistered CT also showed multiple FDG-avid lesions in pericardium (SUVmax 6.0). (F) Solid nests with large zones of necrosis in the middle of the tumor (arrows) (hematoxylin and eosin, original magnification $\times$40). (G) The tumor showed organoid nesting, trabecular growth, rosette-like structures forming cribriform patterns (hematoxylin and eosin, original magnification $\times$100). (H) The tumor cells are generally large, with abundant cytoplasm, mitotic counts $>$ 10 mitoses per 2 mm^2 (hematoxylin and eosin, original magnification $\times$200). (I) Partially positive for synapsin. (J) Partially positive for CD56(NK-1). (K) Ki-67 index was 90%.

cytokeratin (CK; AE1/AE3) (+), synaptophysin (partial +), CD56 (NK-1) (partial +), chromogranin A (−), Ki-67 (index90%), CK5/6 (−), CK7 (−), CD99(−), carcinoembryonic antigen (−), calretinin (−), mesothelial cell (−), S-100 (−), vimentin (partial +), CD20 (−), thyroid transcription factor-1 (TTF-1)(−), CD117 (−), CD5 (partial +) [Figure 1I–K]. Based on the results of immunohistochemical staining, pathology of the lesion] conformed to large cell neuroendocrine carcinoma (LCNEC). In addition, somatostatin receptor imaging after the surgery revealed high expression of somatostatin receptor in both the inside and outside of aortic arch and anterior of descending aorta, with no signs of tumor in other locations. The patient was recommended for treatment at Department of Oncology. After discharge, she was only treated based on her symptoms and not for LCNEC. Eventually, she died in February 2017.

LCNEC is an aggressive and a relatively new category of neuroendocrine tumor, which is most commonly detected in the lung and it can be occasionally found in a variety of extrapulmonary sites including gastrointestinal, genitourinary tracts[1] and even mediastinum.[2] However, primary LCNEC in pericardium has not yet been reported.

Thus, we referred to the classification of neuroendocrine tumor and diagnostic criteria of LCNEC in lung. In the revised 2015 World Health Organization (WHO) classification of lung tumors,[3] neuroendocrine tumors are classified into nine entities, with the three most common ones being small cell carcinoma, large cell neuroendocrine carcinoma and carcinoid tumors. Based on the differentiation grade, neuroendocrine tumors are classified with low-grade typical carcinoid, intermediate-grade atypical carcinoid, high-grade LCNEC and small cell carcinoma. Generally, the diagnosis is based on both neuroendocrine morphology and the immunohistochemical demonstration of specific neuroendocrine markers. Morphologically, it is the large cell carcinoma in which tumor cells are typically more than three times greater than the diameter of resting lymphocytes, with moderate, often eosinophilic cytoplasm and prominent nucleoli. Mitotic activity is usually brisk with >10 mitotic counts in 2 mm^2 of viable tumor [10 HPF] that is essential, and large areas of necrosis that are typically visible. For neuroendocrine morphology, it usually presents as ganoid nesting, palisading, rosettes, and trabeculae.[4] One unequivocally positive neuroendocrine marker is sufficient to confirm the diagnosis including synaptophysin, chromogranin A or CD56, while CD56 expression alone must be interpreted with caution. As there might be potential overlap in the morphology of LCNEC and basaloid squamous cell carcinoma, negative squamous markers (p40 or p63) in TTF-1 (a pneumocyte marker)–negative tumors may indicate LCNEC.

Owing to the lack of literature on primary pericardial LCNEC and even mediastinal LCNEC,[2] the optimal treatment strategies for these conditions have not yet been decided. Considering the similar biological characteristics and survival curves as those observed in small cell lung cancer (SCLC),[5] LCNEC is supposed to be treated with similar strategies as small-cell carcinoma consisting of platinum/etoposide. Some LCNEC involving the expression of somatostatin receptors may greatly benefit from treatment with somatostatin analogues and peptide receptor radionuclide therapy (PRRT). Octreotide, a synthetic somatostatin analog, is common therapeutic choice combined with chemotherapy. Radiotherapy is considered as probably beneficial in LCNEC due to its high potential for metastasis in LCNEC, which is an indicator of poor prognosis.

Since it is challenging to differentiate LCNEC from small cell carcinoma, atypical carcinoid and non-small cell lung cancer (NSCLC), especially so in biopsy/cytology specimens, the diagnosis of LCNEC can only be made in resection specimens.[3] In this case, though the biopsy of pericardium was of high risk, the patient was presented with pericardial tamponade at disease onset and was diagnosed with constrictive pericarditis, a nonspecific but life-threatening medical condition, the most severe complication of tumor involved with pericardium, which was a definite indication for surgery. In the end, the patient was operated, and the tumor excision led to the pathological diagnosis.

The present case study reported on a middle aged female patient, with no history of smoking, which is inconsistent with the typical epidemiological features of pulmonary LCNEC, and which indicate the heterogeneity of this kind of carcinoma, leading to difficulty in diagnosis. As we know, this is the first case of LCNEC primarily in pericardium. The patient presented with pericardial tamponade as the onset symptom and was finally diagnosed by pericardiectomy. Physicians are supposed to consider malignant tumors in these patients, and further evaluations such as imaging and surgery are necessary to establish the pathology. In addition, any abnormalities found on laboratory tests should be considered, especially neuroendocrine markers. Only then, it is possible to make a more accurate diagnosis and to provide the patient with timely treatment, thus eventually improving the patient's prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the article. The patient understands that her name and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest

None.

References

1. Tu YA, Chen YL, Lin MC, Chen CA, Cheng WF. Large cell neuroendocrine carcinoma of the endometrium: a case report and literature review. Taiwan J Obstet Gynecol 2018;57:144–149. doi: 10.1016/j.tjog.2017.12.025.
2. Hidaka T, Okuzumi S, Matsuhashi A, Takahashi H, Hata K, Shimizu S, *et al*. Large cell neuroendocrine carcinoma of the mediastinum successfully treated with systemic chemotherapy after palliative radiotherapy. Intern Med 2018. doi: 10.2169/internalmedicine.0437-17.
3. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, *et al*. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10:1243–1260. doi: 10.1097/JTO.0000000000000630.
4. Hiroshima K, Mino-Kenudson M. Update on large cell neuroendocrine carcinoma. Transl Lung Cancer Res 2017;6:530–539. doi: 10.21037/tlcr.2017.06.12.
5. Derks JL, Hendriks LE, Buikhuisen WA, Groen HJ, Thunnissen E, van Suylen RJ, *et al*. Clinical features of large cell neuroendocrine carcinoma: a population-based overview. Eur Respir J 2016;47:615–624. doi: 10.1183/13993003.00618-2015.

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