

Anterior mediastinal large cell neuroendocrine carcinoma with elevated AFP: A case report and review

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Received February 6, 2020; Accepted November 18, 2020

DOI: 10.3892/mco.2020.2196

Abstract. Large cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive cancer that typically presents in the lung. The current case report describes a 56 year old male who presented to Strong Memorial Hospital with progressive dyspnea and was revealed to have a large anterior mediastinal tumor with metastases to axillary, hilar and mediastinal lymph nodes. Tumor marker results revealed an elevated plasma level of α -fetoprotein (AFP), which initially pointed towards a diagnosis of teratoma, but the tumor stained positive for neuroendocrine markers CD56, chromogranin, and synaptophysin on biopsy, consistent with LCNEC. AFP-positive tumor cells were identified, and no alternate cause for the elevated AFP was identified. The patient underwent genetic testing revealing the tumor to be ALK, ROS1, KRAS, BRAF and EGFR wild type. The patient received 6 cycles of chemotherapy with cisplatin (80 mg/m²) and etoposide (100 mg/m²) and then radiation with an initial minor response. The patient's course was complicated by the development of superior vena cava syndrome requiring emergency stenting. The results of the current case suggest that AFP may be worthy of further exploration as a potential tumor marker in LCNEC.

Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a high-grade neoplasm most commonly presenting in the lung, although it has been noted in the literature to occasionally arise in other locations including the gastrointestinal tract, bladder, prostate, gallbladder, ovary, uterus and submandibular gland (1-7). LCNEC is a rare cancer, estimated to comprise between 2.1 and 3.5% of surgically resected lung tumors (8,9). It is morphologically different from small cell lung cancer (SCLC) and has a higher mitotic

count than low-grade neuroendocrine carcinoma (10-12). These tumors have unique histological features including large nuclei with prominent nucleoli, vesicular or open chromatin, rosette-like structures, and trabecular palisading patterns (13). When a diagnosis of LCNEC cannot be made on a morphological basis, immunohistochemical markers exist that can differentiate the disease from SCLC (14). A strong association between LCNEC and cigarette smoking has been documented (8,9,15). Unfortunately, prognosis for LCNEC is generally poor, with a 5-year all-stage survival rate of about 40% (16).

Investigations into the LCNEC genome via next-generation sequencing have found that the cancer clusters into two different groups, a SCLC-like subset and a NSCLC-like subset (17,18). There is no morphological difference between tumor cells belonging to either subset; however, the SCLC-like tumors tend to have higher proliferative activity (18). SCLC-like LCNEC tumors are characterized by inactivating mutations in TP53 and RB1, while NSCLC-like LCNEC has frequent mutations in STK11 (60%), KRAS (40%), and KEAP1 (36%) (18). Mutations in PIK3CA (3%), PTEN (4%), and FGFR (5%) are uncommon in LCNEC (19), and mutations for which targeted therapy exists, including EGFR, BRAF and ALK, are very unusual (<1%) (13,17,19).

Due to the relative rarity of LCNEC, no large-scale randomized controlled trials have been conducted and no standardized treatment regimen has been established as clearly superior. It is well-established that surgical resection is the only curative treatment modality and that adjuvant chemotherapy appears to confer a survival benefit (20). Thoracic radiotherapy (RT) also appears to show a survival benefit when combined with chemotherapy (21). Most patients are not surgical candidates (22), and typically are treated with chemotherapy regimens similar to those used for small cell lung carcinoma, most often platinum and etoposide. However, studies have not conclusively demonstrated the superiority of this regimen over platinum and gemcitabine chemotherapy regimens used for non-small cell lung cancer (23,24). Targeted therapy has been used against these tumors, but LCNEC rarely harbors targetable mutations (13,17,25). In the future, the incorporation of molecular data may ultimately impact treatment decisions and patient outcomes by identifying an optimal, personalized treatment regimen for a tumor's specific molecular makeup. In one study, patients found to be wild-type for RB1 had significantly longer survival when treated with gemcitabine and a

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Key words: large-cell neuroendocrine carcinoma, mediastinal tumor, anterior mediastinum, case report, α -fetoprotein, chemoradiation, small cell lung cancer

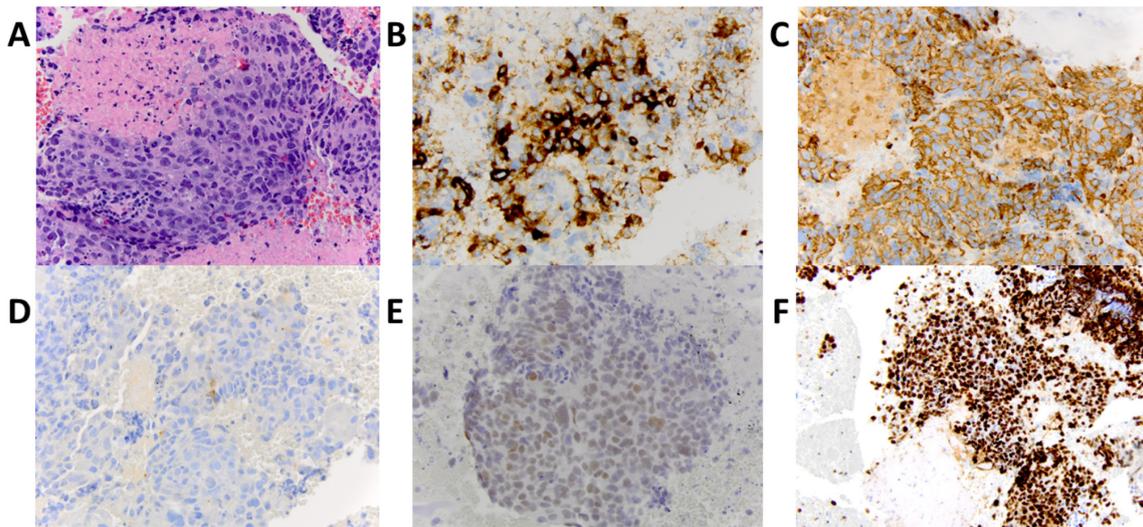


Figure 1. Immunohistochemical staining of tumor. (A) Chromogranin staining, magnification, x40. (B) Hematoxylin and Eosin staining, magnification, x40. (C) Pancytokeratin staining, magnification, x40. (D) AFP staining, magnification, x40. (E) SALL4 staining, magnification, x40. (F) Ki67 staining, magnification, x20. AFP, α -fetoprotein.

taxane than those treated with cisplatin/etoposide (26). Loss of P16 expression was also predictive of superior survival with gem/taxane chemotherapy (26).

Case report

A 56 year old male presented to the hospital after a month of progressive dyspnea. He attested to significant weight loss over the past 6 months and had also developed a cough with occasional hemoptysis. He was an active smoker, having smoked a pack of cigarettes a day for the past 20 years. He had been experiencing intermittent chest pain, but denied any fevers, chills, or night sweats. All initial laboratory data were unremarkable. A chest X-ray taken in the emergency department revealed a large perihilar opacity and follow-up chest computed tomography (CT) demonstrated a 7.9x8.5 cm right-sided anterior mediastinal mass with left tracheal deviation. The mass encased the superior vena cava (SVC) and right bronchus but both structures were patent. Tumor marker labs revealed an elevated lactate dehydrogenase (254 U/l) and an increased level (158 IU/ml) of α -fetoprotein (AFP), suggestive initially of teratoma. B-hCG was undetectable. The tumor was biopsied via endobronchial ultrasound (EBUS) guided bronchoscopy, which revealed sheets of large cells with eosinophilic cytoplasm, enlarged nuclei, and prominent nucleoli (Fig. 1A). Necrosis, apoptotic bodies and conspicuous mitotic activity was present. Immunohistochemical studies were performed on the Dako Omnis (Agilent) platform using a polymer detection method, utilizing horseradish peroxidase substrate 3,3'-diaminobenzidine tetrahydrochloride (DAB) for visualization. The tumor cells showed immunohistochemical positivity for pancytokeratin, chromogranin, synaptophysin and CD56. Rare cells showed cytoplasmic positivity for AFP (Fig. 1B-D). SALL4 showed patchy and weak nuclear positivity (Fig. 1E). Ki67 (MIB-1) showed an elevated proliferative index of over 95% (Fig. 1F). The tumor cells did not stain with TTF-1, napsin A, p40, CD30, OCT3/4 or PLAP. The findings were consistent with LCNEC. Follow-up staging with

positron emission tomography (PET) revealed hypermetabolic mediastinal, right hilar, and left axillary lymph nodes (non-regional lymphadenopathy) suggestive of metastasis, making this stage IV (Fig. 2). Molecular studies performed on the biopsy tissue revealed the tumor to be ALK, ROS1, KRAS, BRAF and EGFR wild type. PD-L1 (clone 22C3) expression was 3%. The biopsy tissue stained negative for AFP. The patient was not a surgical candidate and was started on a palliative chemotherapy regimen of cisplatin (80 mg/m²) and etoposide (100 mg/m²). He completed five cycles of cisplatin/etoposide, with a dose reduction on the fifth cycle due to anemia. A follow-up CT scan after the second cycle of chemotherapy revealed interval decrease in size of the mediastinal mass to 7.0x7.6 cm, however AFP had almost doubled in this time to 267 IU/ml (Fig. 3). Another follow-up CT scan at the time of his last cycle revealed interval development of a 3.2 cm right upper lobe mass. AFP was now 392 IU/ml. He was recommended to undergo palliative radiotherapy. No concomitant chemotherapy was administered during this period. He received 15 fractions of external beam RT to the mediastinal mass totaling 37.5 Gy. AFP measured at the conclusion of radiotherapy was 161 IU/ml. Follow-up CT scan 2 months after conclusion of radiotherapy revealed the mediastinal mass to be roughly unchanged in size at 6.8x8.2 cm. A moderate size right pulmonary effusion was noted and the SVC was also noted to be completely occluded. The patient underwent thoracentesis and no malignant cells were detected within the thoracentesis sample. The SVC was recanalized and stented successfully by interventional radiology (Fig. 4). Several months after this incident he experienced a rapid decline in functional status and passed away.

Discussion

LCNEC is a rare form of cancer most frequently seen in the lung. Here, we report a case of LCNEC presenting in the anterior mediastinum associated with elevated AFP, which has only been reported in the literature once before (27). The

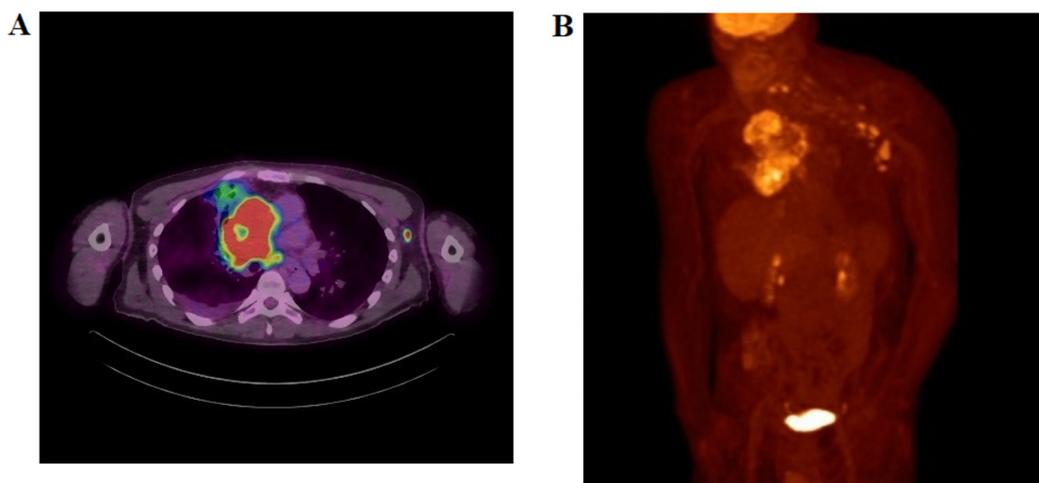


Figure 2. Initial staging of anterior mediastinal mass, PET/CT. (A) Axial view. Hypermetabolic left axillary lymph node is also visible. (B) Transverse view. Multiple subcarinal and left axillary hypermetabolic lymph nodes are visible.



Figure 3. Response to initial chemoradiation, CT chest. Tumor dimensions diminished to 7.0x7.6 cm.

differential for this tumor included lung adenocarcinoma extending into the mediastinum, SCLC, and other tumors of the anterior mediastinum: Thymoma, thymic carcinoma, lymphoma, and teratoma (28,29). Our patient was initially suspected to have a teratoma as these tumors have been known to present as a large mediastinal tumor with elevated AFP (30). His tumor was initially marginally responsive to standard SCLC cisplatin/etoposide chemotherapy, but then the disease quickly progressed on this regimen with development of a new lung mass. In a previous study, 73% of LCNEC patients treated with cisplatin/etoposide achieved at least a partial response, defined as a 30% reduction in the sum of tumor diameters (23). Our patient unfortunately did not achieve even this partial response, which could have been due to the size of the tumor at the onset of therapy, or the inability of the patient to complete the full course of chemotherapy.

AFP is known to be a valuable tumor marker in hepatocellular carcinoma (HCC) to evaluate response to chemotherapy and radiotherapy (31). In this case, the patient's disease progressed while on chemotherapy, associated with a

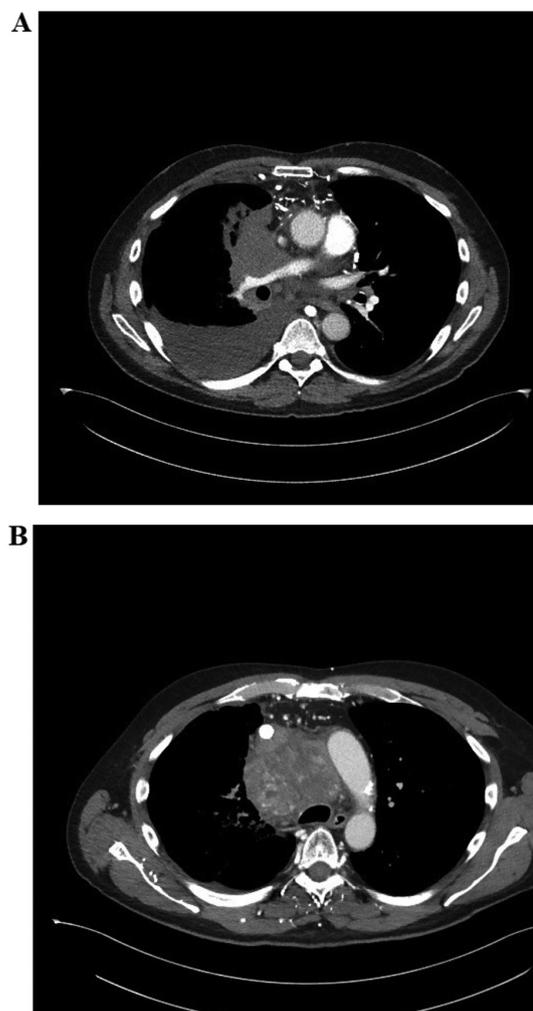


Figure 4. SVC occlusion and stenting, CT chest. (A) Complete occlusion of the SVC. (B) Successful stenting of the SVC with clinical improvement in SVC syndrome. SVC, superior vena cava.

significant rise in AFP. After receiving palliative radiotherapy to the mediastinal mass, AFP decreased and the patient's disease was stable for some time. While the biopsy sample

did not stain positive for AFP, these tumors are known to be heterogenous and this does not rule out the possibility that a portion of the mass that was not captured by biopsy was producing AFP. The patient did not have HCC or a germ-cell tumor that could have been responsible for this elevated AFP. These findings suggest that the use of AFP as a tumor marker for some LCNECs may be worthy of future exploration.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

JK and DM wrote the manuscript. DM was the patient's primary medical oncologist. MJV performed immunohistochemical staining. HQ was the patient's primary radiation oncologist and helped generate figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent was unobtainable as the patient passed away prior to publication and it was not possible to contact next of kin. The IRB of the University of Rochester reviewed this work and confirmed that there is no identifying information and that there are significant public interest considerations in the publication of this work.

Competing interests

The authors declare that they have no competing interests.

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