CASE REPORT

AN UNORTHODOX PRESENTATION OF SCLC

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ABSTRACT

Small cell lung cancer (SCLC) is an aggressive, high-grade neuroendocrine neoplasm that possesses distinctive genetic features and clinical properties, has a highly reliable pathological diagnosis and responsiveness to specific chemotherapy. SCLC frequently presents with early metastasis, which confers a morbid prognosis. Herein we describe a 65-year-old male patient, whose preliminary investigations revealed primary SCLC with metastatic neuroendocrine carcinoma of the liver and anemia. Further analysis and a meticulous search for the unexplained anemia at diagnosis, revealed synchronous hepatic and skeletal metastases with primary small cell carcinoma of the lung. These conditions are uncommon and seldom described in the literature.

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1. Introduction

Neuroendocrine tumors (NETs) constitute 25% of primary neoplasms of the lung, while the remaining 75% include non–small cell lung cancer (NSCLC) and some rare tumors. The most common NET of the lung is small cell lung cancer (SCLC). SCLC is an aggressive, high-grade neuroendocrine tumor associated with a rapid doubling time, tremendous growth rate, and early widespread metastases, which leads to a grave prognosis. The lungs are the most common site of origin of small cell carcinoma in the body. Therefore, the lung should be included as one of the differentials for the primary site in metastatic small cell carcinoma with an unknown primary. The present case was unusual as initial investigations revealed primary SCLC with metastatic neuroendocrine carcinoma of the liver, however, further analysis unveiled synchronous hepatic and skeletal metastases with primary small cell carcinoma of the lung.

2. Case report

A 65-year-old male presented at the medicine OPD with multiple co-morbidities and gradually worsening breathlessness, dyspnea, and pleuritic chest pain. He was an active smoker who had smoked an average of one pack per day for the past 30 years. The physical examination noted decreased movement and absent breath sound on the left side, while the rest of the physical examination was unremarkable. A complete blood count revealed anemia, while other hematological and biochemical parameters were within normal limits. Exfoliative pulmonary cytology was negative for malignant cells. Evaluation of the thorax with plain and contrast-enhanced computed tomography (CT) revealed a heterogeneously enhancing lesion in the left upper lobe of lung, gross pleural effusion causing collapse of the underlying lung parenchyma, multiple pleural deposits, mediastinal lymphadenopathy and multiple hyperdense lesions in both lobes of the liver - likely metastasis. Fine needle aspiration cytology (FNAC) of the hepatic lesion revealed clusters and singly scattered tumor cells with scant cytoplasm, mildly pleomorphic nucleus with stippled chromatin, anisonucleosis and few with prominent nucleoli (Figure 1). Therefore, in accordance with the clinico-radiological investigations and morphology, provisional cytological diagnosis was in favor of metastatic carcinoma (neuroendocrine carcinoma). CT-guided core biopsy of the lung mass followed, and histopathological staining of the tissue revealed a tumor composed of discohesive sheets, nests, and singly dispersed hyperchromatic tumor cells with focal nuclear molding and crush artifact in a fibrocollagenous stroma (Figure 2). Immunohistochemical staining of the tumor cells revealed positive staining for TTF-1, synaptophysin, and chromogranin and a high Ki-67 proliferative index (up to 80%) (Figure 3).
Figure 1 - (A) Discohesive tumor cells arranged in clusters and singly scattered (Papanicolaou stain; X100). (B) Tumor cells with scant cytoplasm, mildly pleomorphic nucleus with stippled chromatin, anisonucleosis and few with prominent nucleoli (Papanicolaou stain; X200).

Figure 2 - (A) Discohesive tumor cells arranged in sheets, nests and singly dispersed (H&E; X100). (B) Hyperchromatic tumor cells showing focal nuclear moulding and crush artefact in a fibrocollagenous stroma (H&E; X200).

Figure 3 - Tumor cells demonstrating immunoreactivity for (A) TTF-1 (IHC; X200), (B) Synaptophysin (IHC; X200), (C) Chromogranin (IHC; X200), and (D) Ki-67 (IHC; X200).

Figure 4 - (A - left) Bone marrow infiltration by nests of tumor cells (H&E; X40). (B - right) Tumor cells show scant cytoplasm with stippled nuclear chromatin, focal nuclear moulding and inconspicuous nucleoli surrounded by normal marrow elements (H&E; X100).

A diagnosis was determined of primary small cell carcinoma of the lung with metastatic neuroendocrine carcinoma of the liver. To evaluate the unexplained cause of anemia, the patient underwent bone marrow aspiration and biopsy.

Bone marrow biopsy demonstrated the presence of metastatic neuroendocrine carcinoma (Figure 4), suggesting synchronous hepatic and skeletal metastases with primary SCLC. The patient was started on chemotherapy with Etoposide and Cisplatin and is currently on regular follow-up in the department of medical oncology.

3. Discussion

The 2004 World Health Organization (WHO) classification acknowledges four main types of neuroendocrine tumors of the lung: typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell lung cancer (SCLC). These NETs are further grouped into a three-tiered grading system as low grade (TC), intermediate grade (AC), and high grade (LCNEC and SCLC). SCLC is a distinct clinico-pathological entity, which was originally believed to arise from the lymphatic system because of its morphological similarities with lymphoma cells. In 1926, the term SCLC was coined, as it was recognized to possess epithelial origin.

SCLC accounts for 20% of lung NETs. The lungs are reported to be the most common site of origin of small cell carcinoma in the body, accounting for more than 95% cases. Therefore, lungs should be given top priority while evaluating for metastatic small cell carcinoma with an unknown primary site. Molecular biology of SCLC encompasses numerous unique cytogenetic characteristics. The most commonly encountered cytogenetic alterations in SCLC include inactivation of the TP53 and RB1 tumor suppressor genes and copy number gains of the genes encoding for MYC family members. These mutations reduce pro-apoptotic activity during tumorigenesis, which promotes growth and enhances the survival of the carcinogenic cells. On the other hand, oncogenes involving tyrosine kinase signaling pathway such as KRAS and EGFR, remain unaltered in SCLC. In addition, tobacco carcinogens also act as an initiator for SCLC and facilitate the accumulation of somatic mutation.

SCLC generally affects elderly men who are primarily current or ex-smokers and have multiple cardiovascular, pulmonary, or metabolic co-morbidities. Most patients are symptomatic with cough, wheeze, dyspnea,
hemoptysis, and less frequently present with paraneoplastic syndromes such as the syndrome of inappropriate antidiuretic hormone secretion, Cushing’s syndrome, Lambert-Eaton syndrome, etc. SCLC often exhibits isolated metastasis to the brain, liver, adrenal glands, bone, and bone marrow, however, synchronous metastases are relatively uncommon. Among these, skeletal metastasis is associated with significant morbidity and mortality. The most common site for bone metastasis is the spine followed by the ribs, ilium, sacrum, femur, and humerus. Metastasis to the appendicular bones confers a grave prognosis with respect to axial bone metastasis. The pathobiology of bone metastasis primarily revolves around the concept of reciprocal signaling between the bone microenvironment and the tumor. According to this theory, bone resorption is drastically increased in patients with bone metastasis by secretion of various factors such as interleukin (IL-1, IL-6), parathyroid hormone related protein (PTHrP), receptor activator of NF-kB ligand and macrophage inflammatory protein-1α (MIP-1α) from the malignant cells. These factors upregulate osteoclastic and osteoblastic activity and stimulate the osteoclasts to release growth factors such as transforming growth factor-β (TGF-β) and insulin-like growth factor-1 (IGF-1) from the bone matrix, which amplifies PTHrP production and promotes tumor growth.\(^5\)

SCLC is primarily diagnosed on the basis of histological appearance by light microscopy. Histological features include sheets of small cells with neuroendocrine differentiation (characterized by scant cytoplasm; poorly defined cell borders; dispersed, finely granular nuclear chromatin; absent or inconspicuous nucleoli; and prominent nuclear moulding). Additionally, crush artifact with nuclear streaming and incrustation of vessels (Azzopardi phenomenon), and extensive necrosis and exceptionally high mitotic count (>10 mitoses per 10 high-power fields) also favor the diagnosis of SCLC. Often, in challenging biopsies, immunohistochemical markers such as TTF-1, synaptophysin, chromogranin, CD56, and Ki-67 can assist in confirming the diagnosis of SCLC. The Ki-67 index is typically high (around 90-100%) in SCLC, indicating rapid cell proliferation.\(^1,2\)

Investigations pertaining to the staging of SCLC should at least include: a full patient history, physical examination, complete blood count, hepatic and renal function tests, serum electrolyte assay, assay of lactate dehydrogenase, chest radiography, and contrast-enhanced computed tomography (CT) of the chest and upper abdomen.\(^4\) Other imaging modalities such as magnetic resonance imaging (MRI), bone scanning, and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) help in detecting distant metastases.\(^3\) A review of the literature, authored by van Meerbeeck et al., emphasized that a suspicion of bone marrow infiltration should arise if an isolated increase in lactate dehydrogenase concentration appears, or if blood counts indicate otherwise unexplained anemia, or a leucoerythroblastic response is identified.\(^4\) In the present case, initial clinical and laboratory work-up favored the diagnosis of primary SCLC with metastatic neuroendocrine carcinoma of the liver. However, a diligent search for the cause of unexplained anemia revealed bone marrow infiltration. Therefore, deferring the initial diagnosis, the final diagnosis of primary SCLC with synchronous hepatic and skeletal metastases was made. To the best of the authors’ knowledge, this is the first case of primary small cell carcinoma of the lung simultaneously metastasizing to both the liver and bone. This has also been substantiated by Kagohashi et al., who claimed a high incidence of liver metastasis in SCLC patients, in contrast only a meager percentage of cases presented with synchronous spread to the liver and one other organ; thereby making it pertinent for us to report this unusual case.\(^6\)

SCLC is commonly staged as limited-stage or extensive stage. Both these stages have different prognostic implications and therapeutic protocol. Nonetheless, staging ultimately aims to identify the disease as non-metastatic or metastatic. The mainstay of treatment of metastatic SCLC is combination chemotherapy, usually platinum-based plus Etoposide or Irinotecan. On the other hand, early concurrent thoracic radiotherapy is preferred for the non-metastatic disease. SCLC confers a poor prognosis and median survival in the absence of treatment is merely 2–4 months.\(^4\)

### 4. Conclusion

SCLC is an aggressive neoplasm of neuroendocrine origin characterized by a high proliferation index, early metastatic spread, and responsiveness to cytotoxic therapy. This case is unique as it underscores the diagnostic implication of unexplained anemia in a case of primary SCLC. Isolated unexplained anemia at diagnosis should prompt the pathologist towards bone metastasis. Therefore, it is essential for a vigilant search of metastatic sites in SCLC, as it might show synchronous spread involving more than one organ. An early detection of skeletal metastasis might improve clinical outcome and prolong overall survival.

### References