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Role of CD56 In Diagnosing Small Cell Lung Carcinoma on A Limited Tissue Sample with Marked Crush Artifacts - A Case Report.

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ABSTRACT

Neuroendocrine tumors of lung comprise 20%–25% of all invasive lung malignancies, most common being Small cell lung carcinoma (SCLC). Immunohistochemistry is an extremely valuable diagnostic tool in the present era. SCLC are immune-reactive for chromogranin, synaptophysin and CD56, CD 56 being the most sensitive. Characteristically, CD56 shows a strong, diffuse cytoplasmic and membrane staining of tumor cells, even in areas of crush artefact. We describe a case of a 68 year old chronic smoker male, where CT guided biopsy showed tumor tissue with marked crush artifacts, andonly CD56 positivity in the tumor cells helped in achieving precise diagnosis.We emphasize the role of CD56 in diagnosing SCLC on limited tissue sample with crush artifacts.

Keywords: CD56, Crush artifact, Neuroendocrine, Small cell lung carcinoma

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INTRODUCTION

Neuroendocrine tumors (NETs) are rare tumors that develop in cells of the neuroendocrine system.Many are benign, while some are malignant. They most commonly occur in the intestine, pancreas, and the lung [1].NET lung comprise 20%–25% of all invasive lung malignancies. The 2015 WHO classification recognizes 4 major types of lung NETs: Typical carcinoid (TC), Atypical carcinoid (AC), Large cell neuroendocrine carcinoma (LCNEC) and Small cell lung cancer (SCLC). The most common NE lung tumor is SCLC, accounting for 15%–20% of all the invasive lung malignancies [2]. Immunohistochemistry (IHC)used for confirmation include chromogranin, synaptophysin, and CD56. CD56 is generally considered to be the most specific and sensitive marker because more than 90% of NEC cases show reactivity for this marker [3].

CASE REPORT

A 68-year-oldchronic smoker and alcoholic male presented with a5 day history of breathing difficulty and facial puffiness. On examination clubbing in all limbs, facial puffiness and conjunctival congestion were noted. Neck veins were engorged on raising both the hands suggesting superior venacaval(SVC) obstruction. All biochemical and hematological investigations were within normal limits.On computerized tomography, well-definedheterogeneously enhancing mass was noted in the anterior mediastinal region. Laterally the lesion was infiltrating the SVC. Right SVC was not visualized except for the distal 2.5 cm of the vein close to the right atrium. The possibility of thymoma/ lymphoma was suggested (Figure 1).

CT guided biopsy of the mass showed tumor with marked crush artifacts. Tumor was composed of dyscohesive clusters and sheets of small to medium sized cellswith scant cytoplasm and anindistinct cytoplasmic membrane. The nuclei were round to oval with stippled granular chromatin and inconspicuous nucleoli (Figure 2, 3).IHC showed the tumor cells positivity for CD56(Figure 4).Synaptophysin, chromogranin, cytokeratin, LCA, CD99, MPO, desmin and TTF-1 were negative (Figure 5). Ki-67 index was approximately 24% (Figure 6). Based on these findings, diagnosis of NEC- small cell variant (SCLC) was given. Bone marrow aspiration and biopsy was done and showed no infiltration. Patient was planned for external beam radiation therapy by 30Gy/10 fractions, received 24Gy/8 fractions and was being considered for chemotherapy with drugs like etoposide, cisplatin at the last follow up.

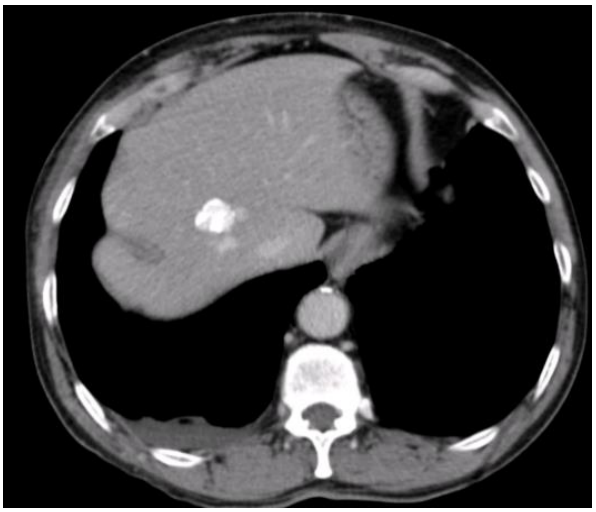

Figure 1: CT scan- Well-defined mass in the anterior mediastinal region

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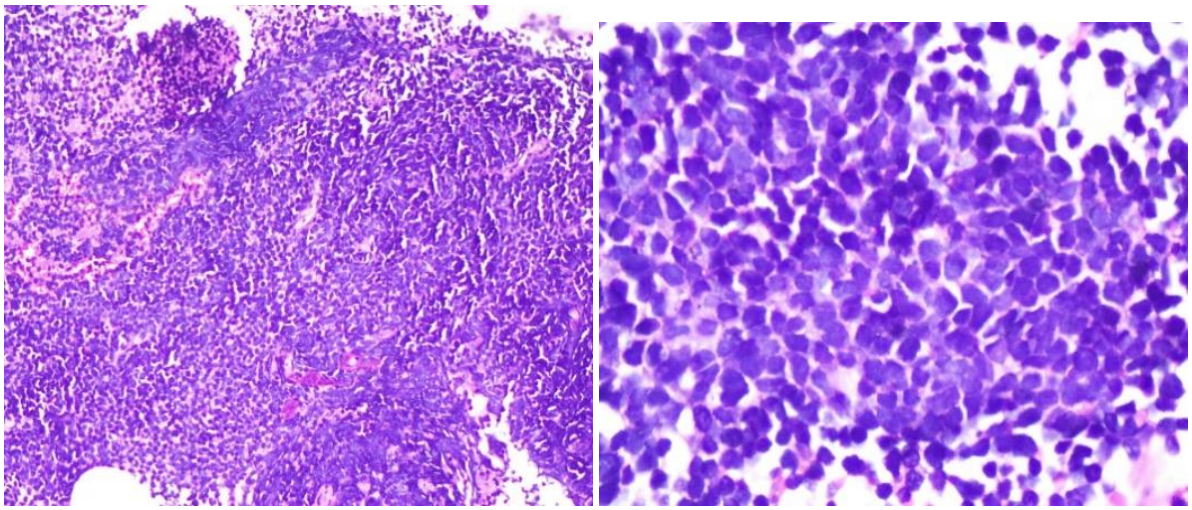

Figure2: Dyscohesive clusters with crush artifacts on biopsy H&E X40.
Figure 3: Cells with round nuclei, stippled granular chromatin H&E X400

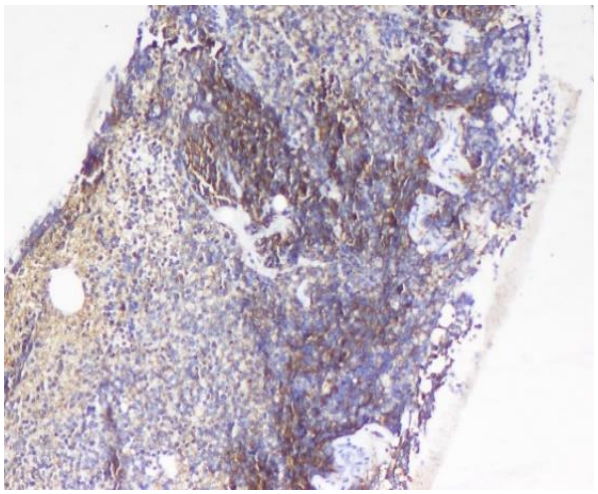

Figure 4: CD 56 positive in tumorcells X100

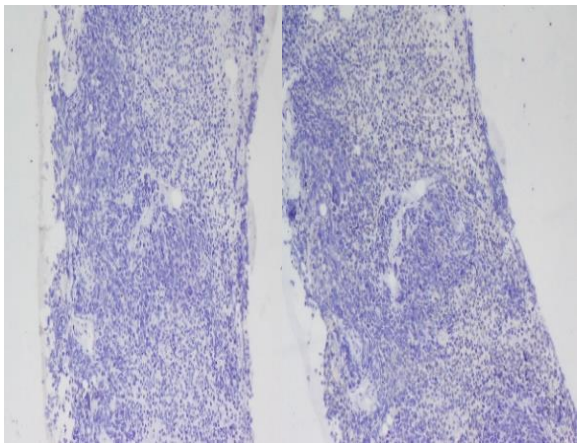

Figure 5: Synaptophysin & chromogranin-Negative X100

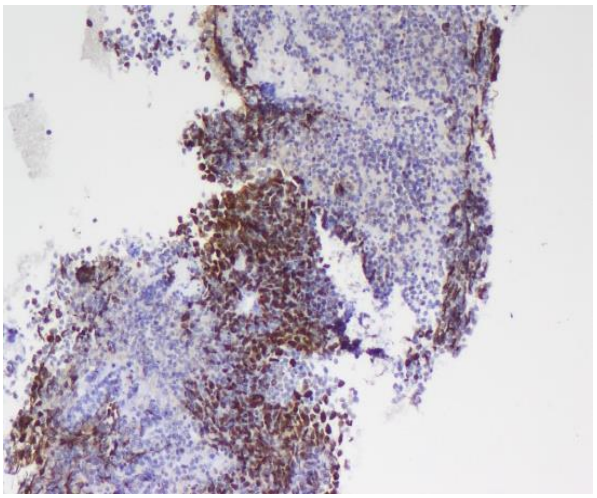

Figure 6: Ki67 – Approx.24% X100

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DISCUSSION

SCLC accounts for approximately 13% of all newly diagnosed lung cancers worldwide [4].Predominantly the central location of these tumors (nealy in 95% cases) gives rise to the common clinical manifestations of cough, dyspnea, and hemoptysis. Invasion of mediastinal structures may result in dysphagia, hoarseness and SVC syndrome. Metastasis to hilar lymph nodes and mediastinal involvement secondary to metastases to mediastinal lymph nodes and/or direct invasion from a contiguous mass are invariably present. SCLC has strong association with smoking and old age [4].

Pre-malignant lesions/conditions have not been identified in SCLC, but genetic factors includingincreasing evidence of EFGR mutations, insulin-like growth factor-1 receptor protein expression has been proven. SCLC and LCNEC show a high frequency of loss of heterozygosity (LOH) for 3p, RB, 5q21, 9p and p53 compared with TC and AC [5].

Grossly, SCLC presents as a central/ hilar mass showing white-tan, soft and friable areas with extensive necrosis. They characteristically spread along airway submucosa andperibronchovascular connective tissue. Endobronchial growth is uncommon in SCLC whereas it is frequently seen in squamous cell carcinoma [2].

Histologically, SCLCs are composed of small cells, with size less than three small resting lymphocytes, with scant cytoplasm, round, ovoid or spindled nuclei, fine granular nuclear chromatin, and inconspicuous or absent nucleoli [3].Nuclear molding is frequent. Cell borders are indistinct. Mitotic rates are high, with an average of 60 mitoses per 2-mm^2 area [5].Necrosis is often extensive. Crush artifact is typically associated with SCLC. However, it can also be seen in some NSCLCs and carcinoid tumors. Up to two-thirds of SCLC are negative for chromogranin and synaptophysin whereas CD56 stains approximately 90–100% of the cases [5]. While CD56 is considered to be the least specific NE marker at other sites, it is the most sensitive NE marker for SCLC [6].It is documented that anti-CD56 show a strong pattern of diffuse cytoplasmic ansmembrane staining in tumor cells, even in areas of crush artifact [5].In small biopsy specimens, when NE nature of the tumor is confirmed, the presence of crush artifact may lead to over-interpretation of a carcinoid tumor as SCLC. In this setting, IHC for Ki-67 can serve as an important ancillary tool, particularly in small biopsy and cytology specimens [3].Based on the data available in several recent studies, theKi-67 proliferation rate of TC is less than 2%, AC is less than 20% (typical rate 10%), while SCLC and LCNEC have Ki-67 proliferation rates significantly higher than 20% (typical rate for SCLC is 60%–100%) [4].

Differential diagnosis of SCLC include NSCLC (including large cell carcinoma or basaloidsquamous cell carcinoma), malignant lymphoma, chronic inflammation, other neuroendocrine lung tumors (including carcinoids and large cell neuroendocrinecarcinoma) [5]. Based on the clinical details, characteristic morphology and IHCthese can be excluded as in our case.

SCLC is an aggressive tumor invariably presenting in advanced stages. Even if localized, it is rarely curable by surgery [4].SCLC is more responsive to chemotherapy and radiation therapy than any other cell types of lung cancer, however, unfortunately a cure is difficult to achieve because of its tendency to be widely disseminated by the time of diagnosis [6-8]. Regardless of the stage, prognosis for patients with SCLC is unsatisfactory despite improvements in diagnosis and therapy made during the past two decades. The median survival from diagnosis of only about 2 to 4 months [7-9].

CONCLUSION

SCLC are aggressive tumors, usually presenting in advanced stages. However, they are more responsive to chemotherapy and radiation therapy. Usually, the diagnosis has to be made on small biopsies received with extensive crush artifacts obscuring the cell morphology. In such circumstances, IHC especially CD56 as in our case serves as an immensely valuable tool in the surgical pathologists' armamentarium and helps in making a precisehistological diagnosis.

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