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Case Report

Pathology Section

Hepatoid Adenocarcinoma of Lung Presenting as Soft-tissue Swelling: A Rare Case Report

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ABSTRACT

Hepatoid Adenocarcinoma of the Lung (HAL) is a rare type of Non-Small Cell Lung Cancer (NSCLC), histologically similar to Hepatocellular Carcinoma (HCC). Hepatoid adenocarcinoma presenting as soft-tissue swelling is extremely rare. Less than 40 well-documented cases in the literature have been added to date. Diagnostic work-up included clinical history, Alpha-Fetoprotein (AFP) serum marker level, imaging, histological uniqueness, immunohistochemical expression, and molecular testing. Hepatoid adenocarcinoma of the lung has high malignancy and poor prognosis and needs a better treatment plan. Hence, we report a case of a 73-year-old male presenting with a history of swelling on the right arm for three months. On Magnetic Resonance Imaging (MRI), the soft-tissue swelling radiological features were suggestive of sarcoma. An excisional biopsy was done. Histomorphological and immunohistochemical expression revealing features of metastatic deposits from hepatoid adenocarcinoma of the lung. Patient expired during follow-up. Hepatoid adenocarcinoma of the lung is a special type of NSCLC. The surgical treatment of HAL in the limited stage can achieve long-term survival, but most of them are in the advanced stage when they are found, and the prognosis is poor, which requires multidisciplinary comprehensive treatment.

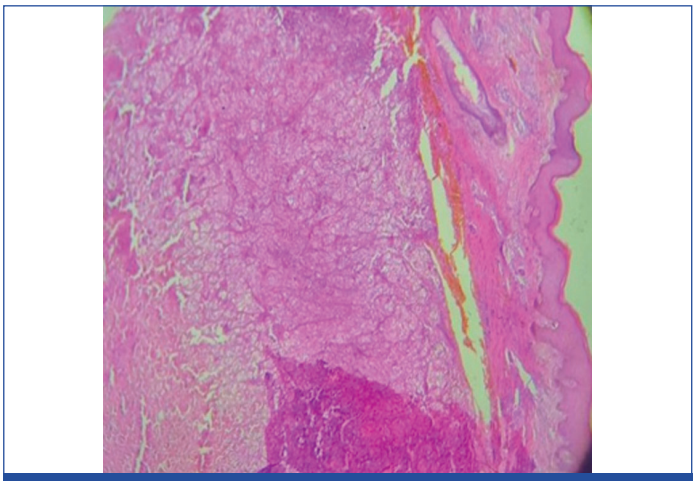
Keywords: Hepatoid adenocarcinoma of lung, Lobulated mass, Non-small cell lung cancer, Wheezing

CASE REPORT

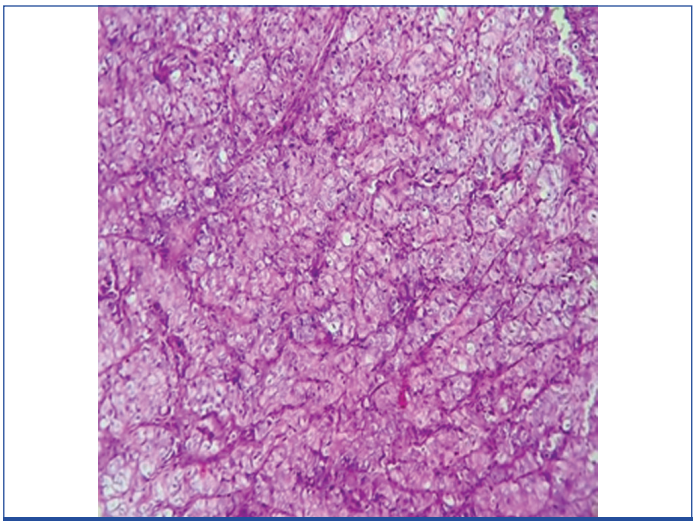
Here, we report a case of a 73-year-old Indian male with a history of Chronic Obstructive Pulmonary Disease (COPD) who presented with a chief complaint of cough, shortness of breath, decreased appetite, wheeze for two days and swelling in the right arm for three months with normal overlying skin. A history of weight loss, body ache and fatigue was also present. Blood investigations, including complete haemogram, liver and renal function test, and urea and creatinine levels, were all within normal limits. Serum AFP levels were not investigated. The Contrast-Enhanced Computed Tomography (CECT) chest showed a lobulated mass measuring 65×22 mm noted in the left-side lingula with obliteration of the left lingular bronchus. Features were suggestive of malignancy with mediastinal Lymphadenopathy (LAP). MRI showed a soft-tissue signal intensity mass lesion in subcutaneous tissue along the anterolateral aspect of the right distal arm, infiltrating the skin surface and measuring 47×40×37 mm. The mass lesion was abutting the anterolateral aspect of the right distal arm muscles; however, no obvious muscular infiltration was seen, suggesting features of either sarcoma or metastatic deposit. Diffuse subcutaneous oedema was seen in the mid and distal arm region. PET-CT scan revealed a left hilar consolidatory lesion in the lingular segment of level as suspicious for malignant aetiology (Primary). No cervical lymphadenopathy was noted.

Excisional biopsy of the right arm soft-tissue swelling was sent. Differential diagnosis included primary HCC with lung metastasis, conventional pulmonary adenocarcinoma, large cell carcinoma of the lung, and metastatic hepatoid adenocarcinoma from the stomach or pancreas. Histopathological examination revealed malignant tumour cells arranged in the form of diffuse sheets. Histological differential included NSCLC favouring adenocarcinoma or metastatic adenocarcinoma. The individual tumour cells were large, polygonal-shaped with centrally placed nuclei, prominent nucleoli and abundant granular eosinophilic cytoplasm [Table/Fig-1,2].

Further to rule out lung or other metastatic adenocarcinoma, an Immunohistochemical panel was decided and TTF cytoplasmic

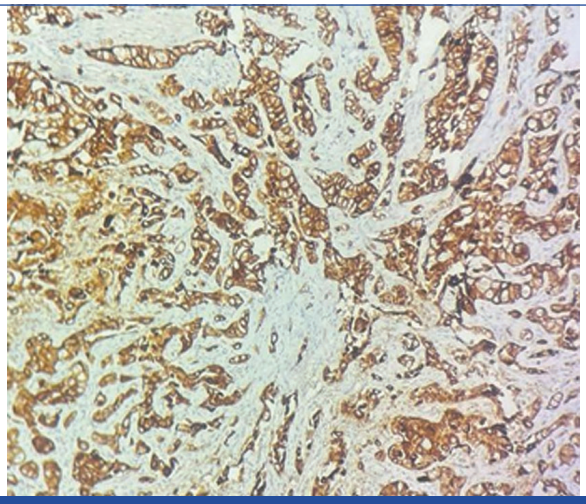


[Table/Fig-1]: Haematoxylin and Eosin (H&E)-stained section showing skin-covered soft-tissue with underlying malignant cells arranged in the form of diffused sheets (100x).

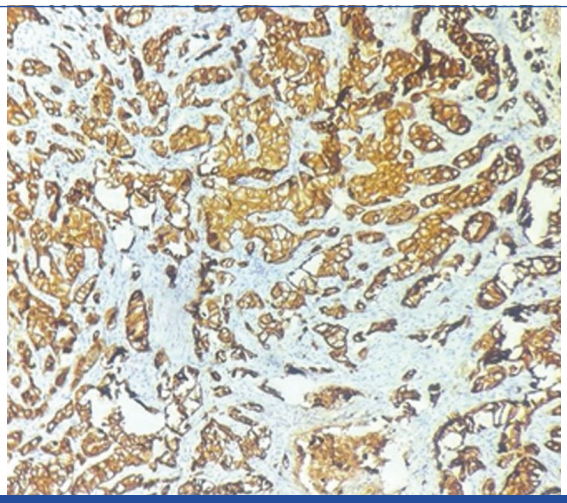


[Table/Fig-2]: Haematoxylin and Eosin (H&E)-stained section showing tumour cells polygonal shaped with centrally placed nuclei, prominent nucleoli and abundant granular eosinophilic cytoplasm (400x).

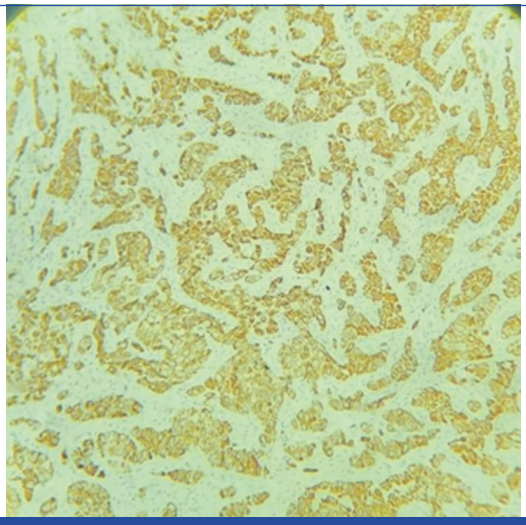
positivity instead of nuclear positivity raised a doubt of HCC mets or hepatoid adenocarcinoma of the lung. On IHC, these tumour cells were: CK-positive, CK7-positive, CK8/18 positive, TTF-1-cytoplasmic positive, Hep-Par-positive, Glypican-negative, Napsin-negative, Vimentin- negative, SOX10- negative [Table/Fig-3-6]. Brown colour staining was observed for the positive marker. No colour observed in the negative IHC expression. Histomorphological and immunohistochemical features were suggestive of metastatic deposits of hepatoid adenocarcinoma of the lung. So the final diagnosis of metastatic deposit from hepatoid adenocarcinoma of the lung was made. During follow-up, the patient expired and no further treatment was possible .



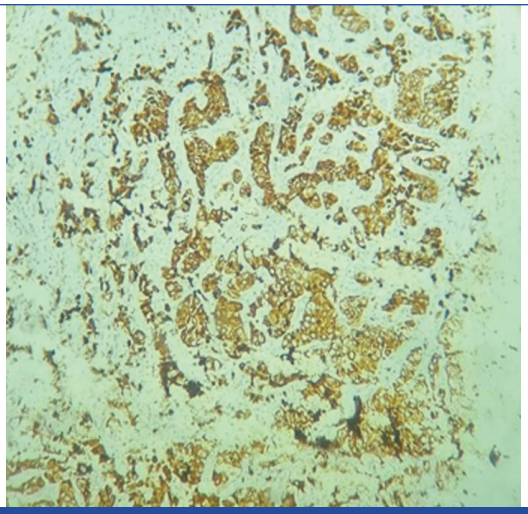
[Table/Fig-3]: Tumour cells showing CK7 cytoplasmic positivity (IHC stained, 100x).



[Table/Fig-4]: Tumour cells showing CK8/18 diffuse cytoplasmic positivity (IHC stained, 100x).



[Table/Fig-5]: IHC Stained section showing Hep-Par cytoplsmic positivty (100x).



[Table/Fig-6]: IHC stained section showing TTF-1 cytoplasmic positivity (100x).

DISCUSSION

Hepatoid adenocarcinoma is a rare extrahepatic tumour with morphologic features like HCC with both adenoid and hepatocyte-like differentiated structures, usually occurring in tumours of the digestive tract. The most common site of origin for hepatoid adenocarcinoma is the stomach (63%). Other sites of origin include ovary (10%), lung (5%), gallbladder (4%), pancreas (4%) and uterus (4%) [1]. Males with a smoking history have a higher risk than females and a poorer prognosis. Earlier, there was an association of primary pulmonary adenocarcinoma with AFP expression. The term hepatoid adenocarcinoma of the lung was coined and two criteria for diagnosis were adopted: 1) Typical acinar or papillary adenocarcinoma; and 2) a component of carcinoma that resembles HCC and produces AFP [2]. Later in 2014, diagnostic criteria for HAL were modified and the presence of hepatoid adenocarcinoma of the lung without AFP expression and defined as AFP-negative HAL [3]. Similar to the present Haninger M et al., which included five patients, all had a history of smoking and presented with respiratory symptoms along with mediastinal lymphadenopathy in some [3]. Yang K et al., studied a patient who had a history of smoking as well as alcohol intake and the patient presented at a later stage of disease progression with brain mets [4]. The study by Miyama Y et al., revealed a history of smoking and revealed bony and brain metastases [5].

Due to its rarity and overlapping morphological features with other cancers, careful differential diagnosis is crucial. Clinicians must exclude other possibilities such as large cell NSCLC, pulmonary Adenocarcinomas (ADCs), and metastatic tumours- particularly those originating from the liver, stomach, and ovary. This is essential because the stomach and ovary are the most frequent sites of hepatoid adenocarcinomas, and HCC is known to metastasise to the lung. IHC is an important tool to distinguish HAL from metastatic HCC. Thyroid Transcription Factor-1 (TTF-1) (cytoplasmic) and Hep-Par (cytoplasmic granular) immunoexpression is seen in both HAL and HCC, which is reminiscent of hepatoid differentiation. However, CK7 (positive in HAL, negative in HCC), Epithelial Membrane Antigen (EMA) (often positive in HAL, usually negative or weak focal positive in HCC), and glypican-3 (often negative in HAL, mostly positive in HCC) will help to differentiate between them [2,3,6].

The HAL most commonly affects middle-aged men, with over 80% of reported cases occurring in male patients who have a history of heavy tobacco smoking. The right upper lobe of the lung is the most commonly affected site. Unfortunately, HAL is typically diagnosed at an advanced stage, often presenting as a bulky mass. Pain is a well-documented and alarming symptom that frequently prompts clinical investigation [1,7].

Histologically, HAL exhibits characteristic hepatoid morphology, often alongside features typical of acinar or papillary adenocarcinoma.

In a few cases, the tumour may include components of signet ring cells or even neuroendocrine carcinoma, indicating a degree of histologic heterogeneity and complexity in tumour differentiation. A notable hallmark of many HAL cases is the expression of Alpha-Fetoprotein (AFP), a major foetal serum protein. While AFP is not a definitive requirement for diagnosis, its expression supports the hepatoid nature of the tumour [1]. AFP is typically reactivated during liver regeneration and in HCC, further linking HAL to hepatocellular-like characteristics at the molecular and immunohistochemical level.

In terms of treatment, surgical resection is looked out in approximately half of the reported HAL cases and is considered a viable option when detected early. However, due to the aggressive and advanced nature at diagnosis, systemic therapy is often necessary. The current medical standard includes platinum-based chemotherapy, typically administered in double or triple drug regimens [8]. This approach aligns with treatment protocols for NSCLC. Nevertheless, resistance to chemotherapy has been observed in some cases, highlighting the need for continued research into more effective, individualised treatment strategies for HAL.

CONCLUSION(S)

The HAL is an extremely rare tumour with an aggressive nature and morphologically overlapping with other cancers, so early diagnosis and treatment are essential for the betterment of the patient. HCC may require radiologic, morphologic, and immunophenotypic correlation. AFP expression is not a requisite for the clinical diagnosis of HAL, but elevated serum levels may indicate an increased risk of hepatoid adenocarcinoma among elderly male smokers with lung mass. A judicious and decisive IHC panel is warranted for accurate diagnosis and to conserve the tissue for further molecular studies.

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