# Case Report Leptomeningeal carcinomatosis as initial presentation in adenocarcinoma of lung with signet ring cell features: an autopsy case report

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Abstract: Signet ring cell (SRC) features are rare but well-recognized cytological changes of pulmonary adenocarcinoma (PA). PA with SRC features (PA-SRC) is frequently associated with anaplastic lymphoma kinase (ALK) gene rearrangement, and recognition of PA-SRC may be important for the administration of targeted treatment. To the authors' knowledge, leptomeningeal carcinomatosis (LMC) as an initial presentation of PA-SRC has not yet been reported. We report an autopsy case from a 59-year-old female who presented with intractable headache for 6 weeks and died of LMC as a result of metastatic PA-SRC. Premortem brain MRI showed nonspecific leptomeningeal enhancement. At autopsy, a tan rubbery mass was found in the hilar area of the right lung, which also surrounded the lower trachea and carotid arteries. A right posteromedial middle lobe mass was also found. Leptomeninges were slightly thickened, without discrete masses. Microscopic examination of the lung mass and leptomeninges showed solid sheets and nests of malignant cells with pleomorphic nuclei and frequent SRC features which comprised 50% of the mass. Immunohistochemically, the tumor cells demonstrated strong diffuse expression of cytokeratin (CK)-7, TTF-1, and napsin-A. Immunostains for CK-20 and ALK were negative. These features were consistent with PA-SRC. It has been reported that approximately 70% of PAs demonstrate ALK gene rearrangement when SRCs comprised >10% of the tumor cells. The presence of SRCs can be indicative of a lung primary and, because of frequent ALK gene rearrangement in PA-SRC, proper recognition of PA-SRC may be important in determining whether further testing is advisable (e.g., ALK immunostaining and/or ALK gene rearrangement).

Keywords: Anaplastic lymphoma kinase, leptomeningeal carcinomatosis, pulmonary adenocarcinoma, signet ring cell

#### Introduction

Pulmonary adenocarcinoma with signet ring cell features (PA-SRC) has been studied in numerous case reports since it was initially described in 1989 [1]. The morphology of the SRC feature is characterized by cells containing abundant cytoplasmic mucin which displaces the nucleus to the periphery. In the 1999 and 2004 WHO classifications, primary SRC carcinoma (SRCC) of the lung was recognized as a rare variant of adenocarcinoma [2]. However, leptomeningeal carcinomatosis (LMC) from PA-SRC has not been described in the literature. In the most recent International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification of PA, SRCC was removed from the variant because the new classification is based on tumor growth patterns, not tumor cell morphology [3]. Although SRCC is not recognized as a histologic subtype, it is important to recognize SRC features because of the high association with anaplastic lymphoma kinase (*ALK*) gene rearrangement and the potential use of ALK inhibitors for treatment. Numerous reports have been published on *ALK* rearrangements in lung carcinoma, and therapeutic response to ALK tyrosine-kinase inhibitor therapies [4-6].

LMC is defined as malignant cells originating from a primary tumor elsewhere seeding to the leptomeninges (arachnoid and pia maters).



**Figure 1.** Gadolinium-enhanced MRI of axial T1. Leptomeningeal enhancement without a discrete mass is seen.

Clinically, patients develop signs and symptoms of increased intracranial pressure and high lumbar opening pressures. Headache, changes in mental status, cranial nerve palsies, back or radicular pain, incontinence, lower motor neuron weakness, and sensory abnormalities are common presenting findings. The most informative study in the evaluation of LMC is lumbar puncture; a finding of carcinoma cells in the cerebrospinal fluid (CSF) is diagnostic. In addition, gadolinium-enhanced MRI is able to detect leptomeningeal enhancement [7]. However, in cases with LMC as an initial manifestation, a correct diagnosis may be challenging.

The most common primary tumors to involve the leptomeninges have been breast (35%), lung (25%), lymphoma (11%), leukemia (8%), and melanoma (5%). Among the primary lung tumors, 92% were non-small cell carcinoma with a predominance of adenocarcinoma, and 8% were small cell lung carcinoma [8]. However, LMC in PA-SRC has not been described in the literature. Most patients with LMC present at a late stage of their disease, usually in the setting of widespread metastases. We present a case



**Figure 2.** MRI of axial T2. A 2.6 cm area of nodular enhancement is seen in the posteromedial aspect of the right mid lung.

of LMC, from PA-SRC as an initial manifestation, who died of LMC before the detection of lung cancer.

## Report of a case

# Clinical and radiologic findings

A 59 year-old female non-smoker was admitted to an outside hospital for a 6-week history of intractable daily headaches, nausea, and vomiting. During this hospitalization, a brain MRI, with and without contrast, was performed. Chest CT or other imaging was not performed. Brain MRI showed nonspecific findings. The outside records of treatment were not available for review. After three weeks of hospitalization, the patient's headache did not resolve, and she was transferred to our institution.

On admission to our institution, another brain MRI was performed and it again showed nonspecific leptomeningeal enhancement (**Figure 1**). Two days before the patient died, an MRI of the thoracic/lumbar spine was performed and showed multifocal areas of abnormal enhancement in the thoracic and lumbar vertebrae, and an increased short TI inversion recovery signal, indicating metastatic disease. MRI also revealed a 2.6 cm nodular enhancement within the posteromedial aspect of the right mid lung (**Figure 2**). A CSF cytologic exam was then per-



**Figure 3.** Histologic features of pulmonary adenocarcinoma with signet ring cell features. Solid sheets and nests of tumor cells and isolated cells with abundant intracytoplasmic vacuoles and peripherally displaced nuclei (arrows). A. Hematoxylin and eosin (H&E) stain. Original magnification x200); B. A higher magnification of signet ring cells (arrows) H&E stain. Original magnification x600.



**Figure 4.** Pulmonary adenocarcinoma with signet ring cell features shows tumor cells including signet ring cells (arrow) with nuclear positivity for TTF-1. Original magnification x100.

formed. The patient expired 11 weeks after presentation of the initial symptom of intractable headache, and an autopsy was performed.

#### Cytologic findings

During the hospitalization at our institution, a lumbar puncture for cytologic examination of the CSF was performed. The Papanicolaou and Giemsa stains of CSF cytology showed a few cells with plasmacytoid appearance and minimal cytologic atypia. The cytology was interpreted as negative for malignancy, favoring ependymal cells.

## Gross, histopathologic, histochemical, and immunohistochemical findings on autopsy

Significant pathology was limited to the thoracic cavity and leptomeninges. On gross examination, a tan, rubbery mass in the right hilum surrounded the trachea and extended almost completely around the carotid arteries. A 2.6 cm nodule was also found in the posteromedial aspect of the right mid lung. Microscopic examination of the lung mass showed solid sheets and nests of malignant cells with pleomorphic nuclei and SRC features (Figure 3), metastatic to the hilar and paratracheal lymph nodes. Histochemical and immunohistochemical stains were performed under the presumptive diagnosis of a primary lung cancer. The primary antibodies used were monoclonal antibody directed against cytokeratin (CK)-7 (OV-TL 12/30, DAKO, Carpinteria, CA, USA, 1:100), CK-20 (Ks20.8, DAKO, 1:40), and TTF-1 (8G7G3/1, DAKO, 1:50), and polyclonal antibodies against napsin-A (Ventana Systems Inc., Tucson, Arizona, USA). In addition, periodic acid Schiff with diastase treatment (DPAS, Ventana Systems Inc.) and mucicarmine (Ventana Systems Inc.) were performed. Immunohistochemically, the tumor cells demonstrated strong and diffuse expression of CK-7, TTF-1 (Figure 4), and napsin-A. The cells were negative for CK-20. The DPAS stain, which stains neutral mucin, showed intracytoplasmic mucin positivity whereas mucicarmine, which stains acid mucin, did not. These morphologic,

histochemical, and immunohistochemical features were consistent with PA-SRC.

The leptomeninges were slightly thickened with no discrete masses. Microscopic examination showed leptomeninges that were diffusely infiltrated by the same tumor cells as seen in the lung with round, eccentrically placed nuclei and relatively abundant granular cytoplasm; some cells had SRC features. Focal invasion into the superficial cerebral cortex (molecular layer) was also noted in the left parietal lobe. The tumor cells showed the same histochemical and immunohistochemical findings as those seen in the lung tumor, except they were negative for TTF-1 staining. Other organs were grossly and microscopically unremarkable. There were no other sites of lung cancer metastasis.

# Discussion

Before the most recent IASLC/ATS/ERS classification of lung adenocarcinoma, a previous report describing SRCC stated that the incidence of SRCC of the lung was rare (0.14% of all adenocarcinoma of the lung) [1]. Because PA-SRC is rare, when SRCs are identified in lung specimens, it becomes important to distinguish PA-SRC from metastatic SRCC with secondary lung involvement. In our case, immunohistochemical stains for TTF-1, napsin-A, CK-7, and CK-20 were performed to distinguish between these two diagnoses. Merchant et al. [9] reported that TTF-1 is a specific marker for PA-SRC since 82.4% of PA-SRC showed TTF-1 positivity in comparison to none of SRCC of other organs. The tumor was determined to be that of a PA-SRC because its cells stained positive for TTF-1, napsin-A, and CK-7.

Due to the rare incidence of *ALK* gene rearrangement in unselected populations of lung cancer (3.8%) [6], it would be helpful if a subgroup of patients with higher likelihood of ALK positivity could be identified as good candidates for gene testing [5]. It has been reported that approximately 70% of PAs demonstrate *ALK* rearrangement when SRCs comprised >10% of the tumor cells [10]. An additional study also demonstrated an association between PA-SRC and *ALK* gene rearrangement [11]. For this reason, identifying PA-SRC will help pathologists to preselect a patient population for ALK testing. In a recent analysis, an ALK tyrosine kinase inhibitor (crizotinib) therapy was associated with improved survival, when compared to that of crizotinib-naive controls [4]. As PA-SRC indicates a poor prognosis, and crizotinib has been shown to be effective in treating ALK-fusion-positive lung cancers [12], it is crucial to recognize SRC features so as to alert clinicians to the potential presence of *ALK* gene rearrangement in the tumor.

However, in our case, although the tumor was predominantly composed of SRCs, it did not show ALK positivity in immunohistochemistry. A FISH study was not performed. Our case was a unique example because LMC was the presenting finding. To the best of our knowledge, PA-SRC with LMC, as seen in this case, has not yet been reported. Due to its rapid progression and poor prognosis, prompt recognition and diagnosis of LMC is crucial. As in this case report, the initial presentation of diffuse LMC includes headache and vomiting. With or without treatment, the median survival of patients with LMC is reported to be 4-6 weeks [7].

Cytological examination of CSF is often considered the gold standard test for diagnosis of LMC [13]. However, one study found that the diagnosis of LMC was accurately reported in only 54% (49/90) of cases upon initial CSF specimen examination, and 91% (82/90) in the subsequent specimen [13]. Cytologic specimens with sparse cellularity and minimal cytologic atypia can be misleading. In addition, the SRCs in bronchial brushings also lend to erroneous interpretations due to the often bland and monotonous appearance of the nuclei that lack a typical malignant cytologic appearance normally seen in non-small cell lung carcinomas [14]. In our case, the cytologic diagnosis of CSF was interpreted as negative.

In conclusion, although PA-SRC is not a histologic subtype in the most recent IASLC/ATS/ ERS classification of lung adenocarcinoma, it is important to recognize it given that this morphological subtype is reported to be more significantly associated with *ALK* gene rearrangement and targeted treatment may be effective. The present case highlights an ominous prognosis of LMC. The patient expired within an 11-week period since the initial presentation of symptoms (Six (6) weeks of symptoms before hospitalization, three (3) weeks at an outside institution, and two (2) weeks at our institution). To the authors' knowledge, this is the first report of a PA-SRC initially presenting with LMC. LMC should be included in the differential diagnosis when patients present with intractable headache and are not responding with proper symptomatic management.

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