Case Report

A Rare Case of Leptomeningeal Signet-Ring Cell Melanomatosis with Unknown Primary Mimicking Leptomeningeal Carcinomatosis

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We present a first case of a 63-year-old man clinically diagnosed with leptomeningeal carcinomatosis, who upon postmortem examination was found instead to have leptomeningeal melanomatosis with signet-ring cell features and unknown primary. This patient presented with no known history of cancer or skin lesions and six months history of anorexia, weight loss and fatigue, followed by two weeks of confusion and difficulty with speaking and ambulating. Brain MRI showed multiple variably sized contrast-enhancing lesions and diffuse abnormal leptomeningeal contrast enhancement. Full body CT imaging revealed no detectable lesions elsewhere in the body.

Antemortem CSF cytology was diagnosed as metastatic adenocarcinoma on multiple occasions based upon the signet ring cell morphology. Immunohistochemical studies were not performed because of the scant cellularity. The patient expired despite treatment with Temazolamide, whole brain radiation, and intrathecal methotrexate. Postmortem examination of the brain revealed no gross abnormality. Microscopic examination showed a subdural collection of discohesive tumor cells with marked nuclear pleomorphism, hyperchromasia, and frequent signet-ring or rhabdoid morphology, as well as a striking, diffuse infiltration of tumor cells in the leptomeninges. Intraparenchymal deposits were also seen in many areas.

General autopsy also identified tumor metastases in the larynx and testes. Tumor cells were immunoreactive for melanoma markers (S100, Melan-A, Tyrosinase and HMB-45) and negative for cytokeratins and mucin. There is no evidence of primary melanocytic lesion or neurocutaneous melanosis. A diagnosis of leptomeningeal signet-ring cell melanomatosis with unknown primary was rendered.

While most patients with metastatic melanoma do have a known history, in a small percentage no primary site is ever identified. We discuss possible etiologies for this phenomenon and emphasize the potential pitfall of signet-ring melanoma clinically and cytologically mimicking adenocarcinoma. Melanoma with signet-ring cell features should be included in the differential diagnosis for cases of presumed adenocarcinoma with unknown primary.

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Key Words: *signet-ring cell melanoma, leptomeningeal melanomatosis, carcinomatosis, unknown primary*

INTRODUCTION

Malignant melanoma is notorious for the wide array of morphologies it may assume, including balloon cell, rhabdoid, small cell, myxoid, adenoid and clear cell types. One of the rarest variants is the signet-ring cell melanoma, first described in 1988 by Sheibani and Battifora.[1] Since the initial description, only 25 cases have been reported in the literature.[1-18] Ultrastructural studies have shown that the signet-ring appearance in these rare melanomas is due to the presence of abundant vimentin filaments in the cytoplasm, rather than accumulation of mucin.[7] Due to its striking similarity to signet-ring cells seen in mucin-producing adenocarcinoma, it may easily be confused with the latter, especially in cytologic specimens with limited material. Herein, we describe a patient with an antermortem diagnosis of leptomeningeal carcinomatosis based on signet-ring cells present in the cerebrospinal fluid (CSF). Autopsy findings, however, revealed leptomeningeal signet-ring cell melanomatosis. This is the first reported case of leptomeningeal signet-ring cell melanomatosis with unknown primary.

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CLINICAL PRESENTATION

The patient is a 63-year-old man with an extensive past medical history, including type I diabetes, hypertension, two prior strokes, myocardial infarction, chronic renal failure, alcoholism and marijuana use. He did not, however, have a personal history of cancer. He presented with a three to six month history of anorexia, 20-30 pound weight loss and fatigue, and two weeks of confusion, difficulty speaking and ambulating. Brain MRI (**Figure 1**) showed multiple variably sized enhancing lesions in the supra- and infra-tentorial brain. There was also abnormal leptomeningeal enhancement of the trigeminal nerves, internal auditory canals and cerebellar folia, as well as diffuse dural enhancement. MR spectroscopy was consistent with a neoplastic process. Full body positron-emission tomography (PET) scanning was negative for abnormal hypermetabolic activity. Antemortem CSF cytology was diagnosed as metastatic adenocarcinoma on multiple occasions based upon the signet-ring cell morphology (**Figure 2**). Immunohistochemical studies were not performed because of the scant cellularity. The patient unfortunately passed away only two months after presentation, despite treatment with Temazolamide, whole brain radiation, and intrathecal methotrexate. Autopsy was performed to determine the primary tumor site for his metastatic disease to the brain and leptomeningeal "carcinomatosis".

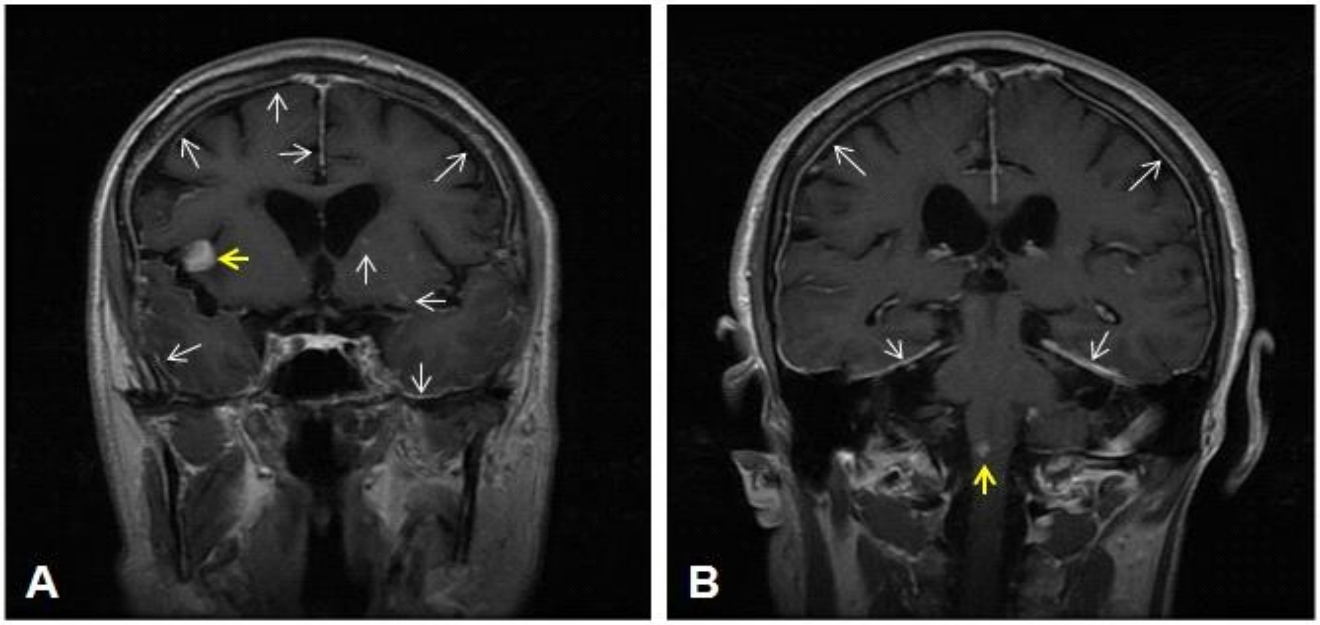

Figure 1. Brain MRI images (coronal T1 FLAIR with contrast) show an enhancing lesion in the right inferior Sylvian fissure (**A.** yellow arrow) and in the lower medulla (**B.** yellow arrow), as well as diffuse leptomeningeal enhancement (white arrows).

POSTMORTEM PATHOLOGIC FINDINGS

Gross autopsy findings did not reveal the primary site of leptomeningeal "carcinomatosis."

Gross examination of the brain was significant for a right subdural hemorrhage (**Figure 3A**), focal leptomeningeal thickening and pigmentation (**Figure 3B**), a pigmented lesion on the inferior bank of the right Sylvian fissure (**Figure 3C**), two areas of softening and discoloration in the distal medulla (not shown), and a remote infarct in the caudate nucleus (not shown). Microscopic examination showed a subdural collection of discohesive tumor cells with marked nuclear pleomorphism, hyperchromasia, prominent signet-ring or rhabdoid morphology with intraccytoplasmic vacuoles (**Figures 3D-E**), as well as a striking, diffuse infiltration of tumor cells in the leptomeninges (**Figures 3F-G**), focally infiltrating the underlying cortex (**Figure 3H**). Some clusters of tumor cells contain melanin pigments (**Figures 3G**). Intraparenchymal tumor deposits were identified in the hippocampus (**Figure 3I**), medulla (**Figure 3J**), and in the Sylvian fissure (not shown). Tumor cells are immunoreactive for S100 (**Figure 3K),** Melan-A (patchy) (**Figure 3L**) and Tyrosinase (not shown), negative for cytokeratins and mucin (not shown).

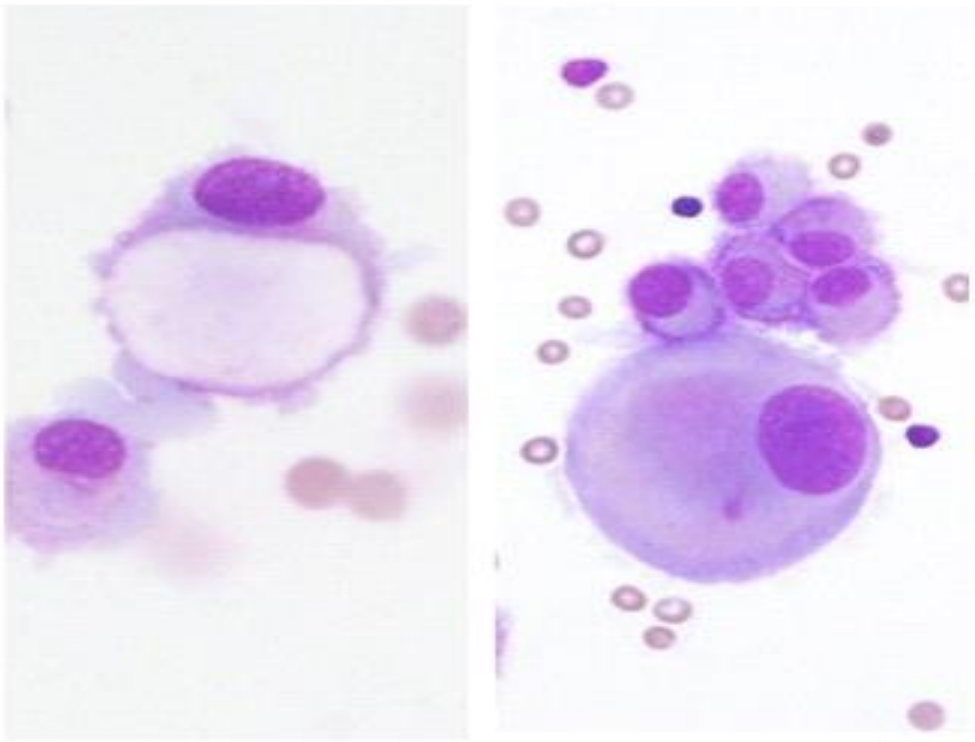

Figure 2. Antemortem CSF cytology diagnosed as adenocarcinoma shows striking signet-ring and plasmacytoid morphology (400x). Intraccytoplasmic vacuole is evident in tumor cell.

General autopsy also identified tumor metastases in the larynx and testis. Laryngeal metastasis shows that tumor cells are similar to those seen in the leptomeninges and brain, displaying marked pleomorphism and prominent signet-ring cell morphology (**Figure 4A**). Intraccytoplasmic vacuoles are evident in many tumor cells (**Figure 4A**). Tumor cells were completely negative for cytokeratin AE1/3 (**Figure 4B**), but strongly positive for S100 (**Figure 4C**) and Melan-A (**Figure 4D**). Tumor cells are also positive for Tyrosinase and HMB-45 (not shown);

Gross and microscopic autopsy findings reveal one benign blue nevus on the left arm. There was no evidence of large or multiple congenital melanocytic nevi or cutaneous malignant melanoma.

DISCUSSION

The differential diagnoses in this patient are metastatic melanoma versus primary melanocytic neoplasm of the central nervous system (CNS).

Primary melanocytic neoplasms of the CNS arise from leptomeningeal melanocytes, which include diffuse melanocytosis and melanomatosis, melanocytoma and malignant melanoma. The incidence of primary CNS melanoma is low: 0.005 cases per 100,000 population.[19,20] The diffuse leptomeningeal melanocytic lesions are rare and population based incidence is not available.[19,21] Diffuse leptomeningeal melanocytosis and melanomatosis are usually associated with neurocutaneous melanosis that typically present before age two and carry poor prognosis.[21,22] These patient usually have large or numerous congenital cutaneous nevi.[22] Our patient is a 63-year-old man with no prior history of skin lesions and no evidence of congenital cutaneous nevi at autopsy examination.

Most patients with metastatic melanoma have a known site of origin, although in approximately 2-6% of cases, a primary lesion cannot be identified (Melanoma of unknown primary, MUP).[23,24] Certain groups of patients are excluded from this classification, which include: patients with previous orbital enucleation or exenteration; patients with a history of excision, electrodessication, or cauterization of a mole, birthmark, freckle, chronic paronychia, or skin blemish; patients who didn't have a thorough exam including ophthalmoscopy and adequate exam of anus and genitalia; and patients presenting with nodal melanoma who have a scar of previous local treatment in the skin area drained by the lymphatic basin.[23,24]

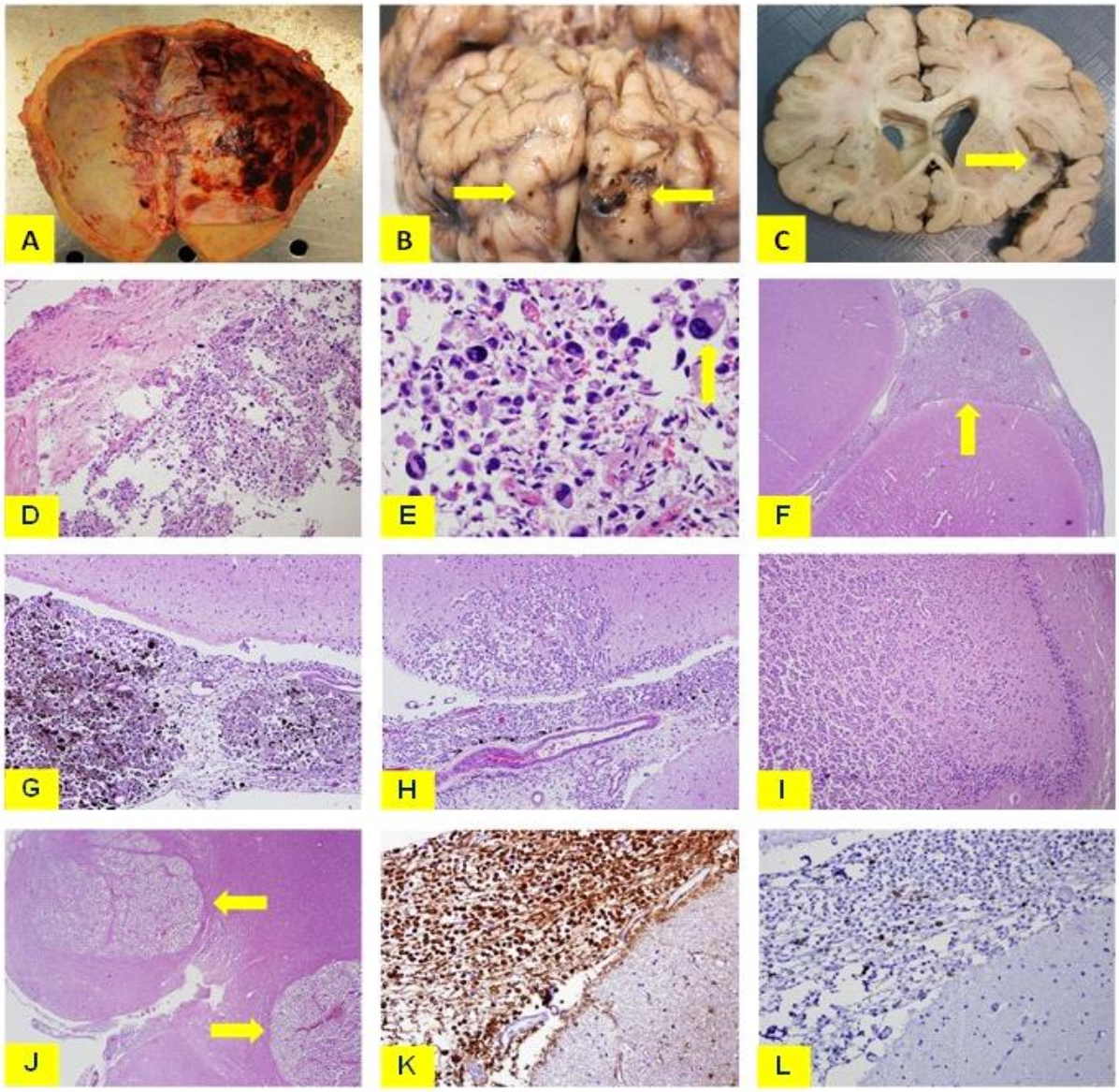

Figure 3. Gross examination of the brain shows right subdural hemorrhage (**A**), focal leptomeningeal thickening and pigmentation (**B.** yellow arrow), a pigmented lesion on the right Sylvian fissure (**C.** yellow arrow). Microscopic examination showed a subdural collection of tumor cells with signet-ring or rhabdoid morphology (**D.** 100x) and (**E.** 400x), diffuse infiltration of tumor cells in the leptomeninges (**F.** 20x. yellow arrow) and (**G.** 100x), the underlying cortex (**H.** 100x), the hippocampus (**I.** 40x) and medulla (**J.** 20x. yellow arrow). Tumor cells are immunoreactive for S100 (**K.** 100x) and Melan-A (**L.** 100x). Intraccytoplasmic vacuoles are evident in tumor cells (**E.** 400x. yellow arrow).

Several theories have been proposed as to the etiology of MUPs. It has been suggested that they may arise from a regressed melanoma, from malignant transformation of a nevus cell in a lymph node or other non-skin tissue, or from a melanoma that was excised and misdiagnosed or not further investigated histopathologically.[23,24] The literature on survival of MUP patients versus melanoma of known primary (MKP) patients is not consistent. Some studies have shown better survival in MUP patients, arguing that MUP patients may have a better prognosis than MKP patients due to the same immunological mechanisms responsible for the regression of their primary tumor.[23,24] In this patient, there was no known history of melanoma and no cutaneous melanocytic lesion was discovered at autopsy. Unfortunately, eye examination was not performed at premortem or at autopsy.

Along with the autopsy findings of metastatic signet ring cell melanoma at larynx and testes, a diagnosis of metastatic leptomeningeal melanomatosis of unknown primary is favored. It is interesting to note that about 30% of the reported signet-ring cell melanomas also had unknown primaries.[1-18] This rare case of leptomeningeal signet-ring cell melanomatosis emphasizes the importance of considering melanoma in the differential diagnosis of tumors with signet-ring cell morphology when there is no primary

site identified after thorough systemic examination. Furthermore, in patients presenting with a presumptive diagnosis of leptomeningeal carcinomatosis of unknown primary, MUP should remain in the differential diagnosis and eye examination should be included in the clinical examination and at autopsy until a site of primary disease is identified.

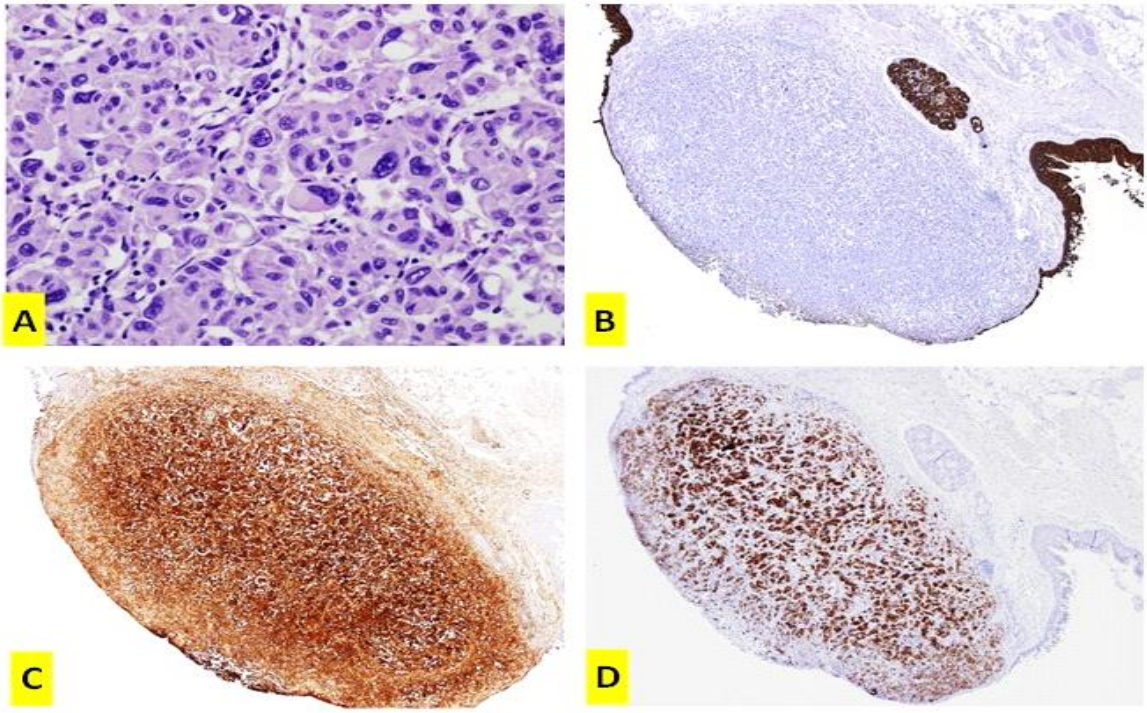

Figure 4. Tumor metastases in the larynx. Tumor cells have prominent signet-ring or rhabdoid morphology and intraccytoplasmic vacuoles are evident in many tumor cells (**A.** 200x). Tumor cells are negative for AE1/3 (**B.** 40x). Tumor cells are immunoreactive for S100 (**C.** 40x) and Melan-A (**D.** 40x).

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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