Leptomeningeal Carcinomatosis as the Initial Manifestation of Metastatic Disease diagnosed in Postmortem Examination: A Case Series

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Leptomeningeal carcinomatosis (LMC) refers to the infiltration of malignant cells in the pia-arachnoids. LMC is undiagnosed until autopsy in about 20% of cases. A nonspecific neurologic symptomatology makes diagnosis challenging; especially in the scenario of unknown malignancy. Diagnosis is made by the identification of malignant cells in CSF; though studies have shown that serial examination may be required for acceptable accuracy. We report 3 cases with distinct neurological presentations, negative cerebrospinal fluid (CSF) examinations and neurological imaging. A 52 year old woman with history of breast cancer on remission, a 2 year old male with left ear rhabdomyosarcoma status post resection, and a 59 year old woman with communicating hydrocephalus of unknown etiology. LMC was diagnosed at autopsy and confirmed by immunohistochemistry. LMC is a complication requiring a high level of clinical suspicion. Postmortem examination is an invaluable tool to confirm LMC as part of the multidisciplinary approach aiming towards the improvement of clinical diagnosis. [*P R Health Sci J 2019;38:64-67*]

Key words: Leptomeningeal carcinomatosis, Metastasis, Postmortem examination

Leptomeningeal carcinomatosis (LMC) is a complication of advanced stage cancer in which malignant cells have metastasized to the pia-arachnoid. Metastases to the meninges is known to occur through several routes, including hematogenous spread, via the endoneural/perineural route, and cerebrospinal fluid (CSF) dissemination (1). The overall incidence of clinically diagnosed LMC in malignant solid tumors is currently at 5%, a value likely increasing due to advancements in neuroimaging, including the visualization of the subarachnoid space by MRI, and increased life expectancy in various malignant cancers (1-3). Despite diagnostic improvements, approximately 20% of cases of LMC remain undiagnosed until autopsy (1). This represents a detriment in prognosis evidenced by a decreased overall survival (1,5,8-10).

Carcinomas of the breast (12-25%) and lung (10-26%) are the solid tumors most often presenting with LMC (Chart 1) (1,7). However, several other malignancies have been shown to be prone to meningeal metastasis, including head-neck, cervical, ovarian, renal, bladder, relapsed leukemia, non-Hodgkin's lymphoma, and pediatric malignancies such as rhabdomyosarcoma and retinoblastoma (6,11).

Clinical features of LMC often include nonspecific neurologic symptoms such as headache and mental status change, or may mimic an inflammatory process like meningitis (Chart 2)(1,5-10). The lack of specific symptoms makes diagnosis challenging, especially in the scenario of no previous history if neoplastic process. CSF cytology revealing neoplastic cells is the gold standard for LMC diagnosis (1-3,5). However, CNS imaging is often the initial diagnostic tool utilized, due to the vagueness of the patient's symptomatology, with MRI proving to be the imaging modality with most sensitivity in the diagnosis of LMC (1,2).

Nonetheless, gross and histologic examination of the leptomeninges remains the most accurate technique in confirming LMC, making postmortem examination an invaluable tool in establishing this pathology.

We present three patients with leptomeningeal carcinomatosis as the initial manifestation of metastatic disease diagnosed in postmortem examination.

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The author/s has/have no conflict/s of interest to disclose.

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CASE 1

A 52 year old woman with history of breast cancer, diagnosed 4 years prior, status post chemotherapy and radiotherapy on remission developed headaches, generalized weakness, and difficulty walking one month before admission. Lumbar puncture was remarkable for increased opening pressure. Neurological imaging studies were unremarkable. Cerebrospinal fluid cytology revealed chronic inflammation. Patient was admitted under the clinical suspicion of a chronic inflammatory meningitis without a clear etiology. Postmortem examination showed metastatic carcinomatosis involving the lungs, and periaortic lymph nodes. Gross brain examination revealed opaque leptomeninges (Fig 1). Microscopic examination showed diffuse infiltration of malignant cells in the leptomeninges (Fig. 2A). Breast cancer etiology compatible with known primary was confirmed with immunohistochemistry studies (Fig. 2B and C). There was no evidence of residual breast disease.

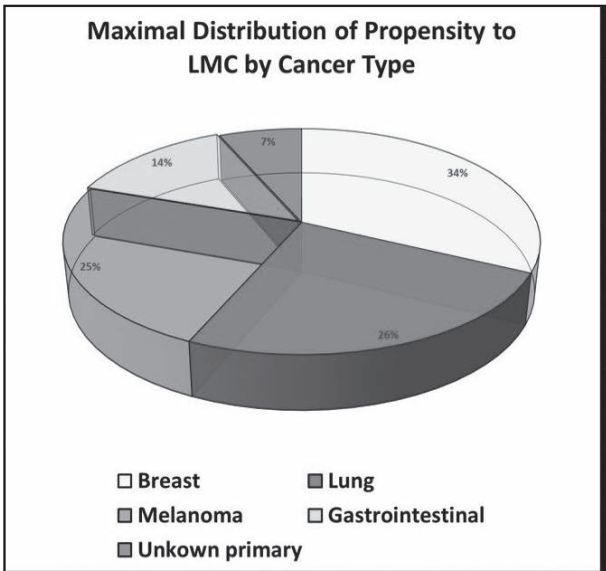

Chart 1: Maximal Distribution of Propensity to LMC by Cancer Type.[1]

LMC: Leptomeningeal Carcinomatosis

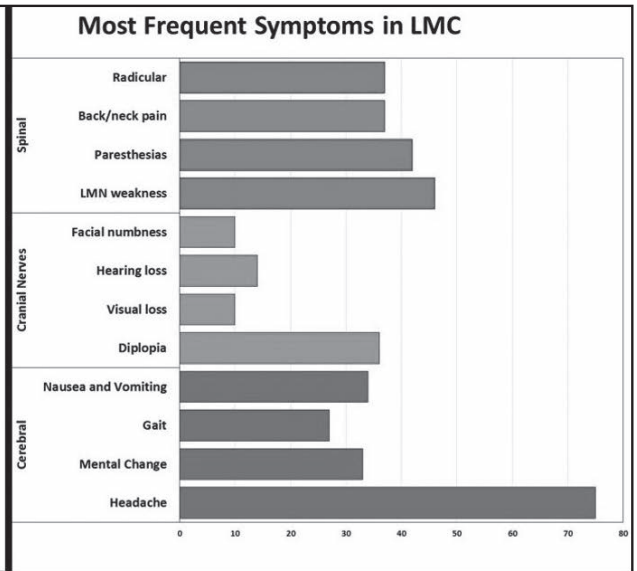

Chart 2: Most Frequent symptoms in LMC.[1]

LMC: Leptomeningeal Carcinomatosis . LMN: lower motor neuron

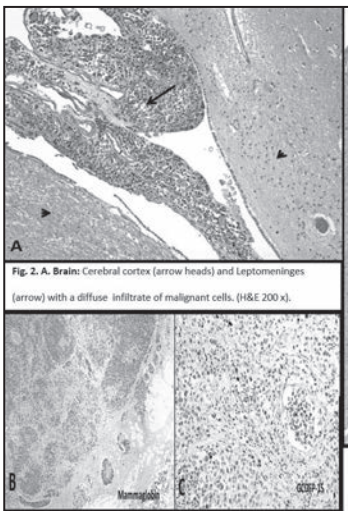

Fig. 2. A. Brain: Cerebral cortex (arrow heads) and Leptomeninges (arrow) with a diffuse infiltrate of malignant cells. (H&E 200 x).

Fig 2 .B and C: Lymph node: Tumor cells positive for Mammaglobin and GCDFP-15 (100X)

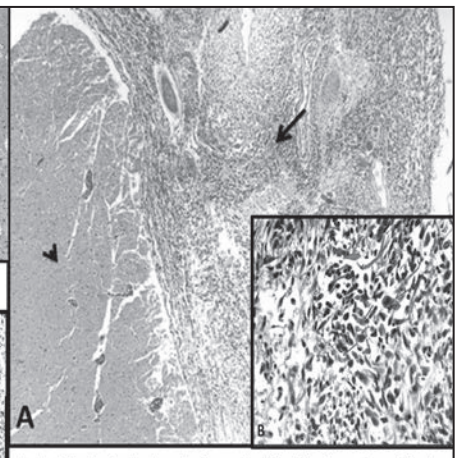

Fig. 3. A. Brain: Cerebral cortex (arrow head) and Leptomeninges (black arrow) with a diffuse infiltrate of malignant cells. (H&E 200 x). **Fig 3. B. Insert**: Rhabdomyoblasts : tumor cells with a spindle cell conformation and eosinophilic cytoplasm with striations (red arrows) (H&E 100X).

CASE 2

A 2 year old boy recently diagnosed with left ear rhabdomyosarcoma. After 2 weeks of chemotherapy, he presented with vomiting, abdominal pain, poor oral intake and seizures. Head computed tomography (CT) scan revealed marked edema, ventricular system dilation and changes suggestive of anoxic encephalopathy. CSF cytologic examination was unremarkable. The patient presented rapid clinical deterioration followed by brain death. Postmortem microscopic examination revealed diffuse meningeal infiltration of malignant cells consistent with rhabdomyosarcoma (Fig.3a-b). No evidence of residual disease was found in the primary's site.

CASE 3

A 59 year old woman with history of chronic tobacco smoking and alcoholism was just diagnosed with communicating hydrocephalus of unknown etiology. One week after discharge, she presented with headaches, vomiting, unsteady gait, and seizures. An abdominal CT scan revealed a mass effect in the colon. CSF cytology was negative for infection or malignancy. She developed a rapidly deteriorating clinical picture with death occurring less than a week after admission. Autopsy revealed perforated diverticular disease with plastron formation involving the sigmoid, cecum and uterus in addition to a 2-cm peripheral lung mass. Metastatic lung adenocarcinoma involving the mesentery and leptomeninges was confirmed by microscopic analysis and immunohistochemistry studies (Fig 4c-e).

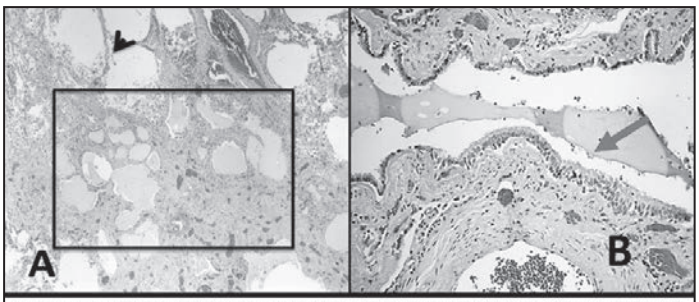

Fig. 4. A. Lung: Distended alveoli (arrow head) and peripheral mass with glandular formation and extensive mucin production (box) (H&E 20x) **B:** Malignant glands composed of tall columnar epithelial cells lining the alveolar septa. (Red arrow) (H&E 100X)

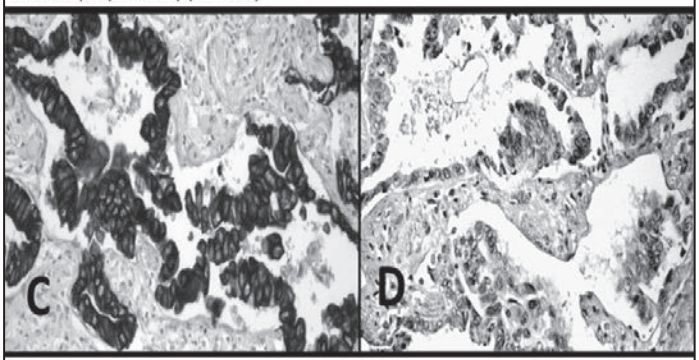

Fig 4. C and D. Tumor cells positive for CK7 and TTF-1, respectively (200x) .

Discussion

The incidence of Leptomeningeal carcinomatosis has shown to be increasing, likely due to a combination of factors, including improved diagnostic imaging, prolonged life-expectancy in several carcinomas, and limited CNS penetration of most chemotherapeutic agents (1-3). A concurrent increase in undiagnosed cases of LMC, however, shows that this diagnosis requires a high level of clinical suspicion. The usual presentation of vague, nonspecific neurologic symptoms makes diagnosis of LMC challenging, especially in the scenario of unknown malignancy.1,5-10 Signs and symptoms of LMC are associated to a wide range of diseases, including meningitis, with which many cases of LMC are confused (1,5,7). Our cases were consistent with the already described most common symptomatology for LMC.

Cerebrospinal fluid cytology has proven to be an important tool in the diagnosis of LMC, but is limited by a sensitivity of <50%, often yielding false negative results (13). Several studies have shown that serial testing can greatly improve the diagnostic accuracy of CSF cytology, and should be considered if clinical suspicion exists (1,12,13). Negative CSF cytology was found in our cases.

Almost 90% of cases have abnormalities in the CSF examination; most notably increased opening pressure, elevated leukocytes, elevated protein and decreased glucose (1,12,14,15). Case number 1 exhibited the first two abnormalities.

Post mortem examination is essential to develop an understanding of LMC and in fine-tuning the clinical suspicion necessary to avoid undiagnosed cases, especially considering its detrimental prognosis.1,8 It is also a necessary means to diagnose and/or confirm meningeal carcinomatosis as part of the multidisciplinary approach aiming towards the improvement of clinical diagnosis (8).

Conclusion

Leptomeningeal carcinomatosis is an unfavorable complication with an increasing incidence. The nonspecific clinical neurologic symptoms that characterize its clinical picture, however, denote a diagnostic challenge. Cerebrospinal fluid cytology has proven a valuable tool to aid in the diagnosis, yet an acceptable level of sensitivity is only achieved when performed in a serial manner. Postmortem examination is an essential tool to rule-out or confirm the diagnosis and improve overall clinical awareness.

Resumen

Carcinomatosis leptomeníngea (CLM) es la infiltración de células malignas en la pia-aracnoides. La incidencia de CLM no diagnosticada está alrededor de 20%. La sintomatología neurológica inespecífica hace el diagnóstico difícil; especialmente secundario a malignidad desconocida. Reportamos 3 casos con cuadros neurológicos distintos, exámenes de líquido cefalorraquídeo (LCF) y radiologías negativos. Una mujer de 52 años con historial de cáncer de mama en remisión, un varón de 2 años con diagnóstico de rabdomiosarcoma del oído izquierdo post-resección, y una mujer de 59 años con hidrocefalia comunicante de etiología desconocida. CLM se diagnosticó en autopsia confirmado por inmunohistoquímica. CLM es una complicación que requiere

un alto nivel de sospecha clínica. La identificación de células malignas en el LCF define el diagnóstico; aunque estudios han demostrado que exámenes seriados aumentan la sensitividad. El examen post-mortem es una herramienta invaluable para confirmar CLM como parte del esfuerzo multidisciplinario para el mejoramiento del diagnóstico clínico.

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