Leptomeningeal carcinomatosis as the initial manifestation of metastatic disease diagnosed in postmortem examination: a case series.

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Abstract

Leptomeningeal carcinomatosis (LMC) refers to the infiltration of malignant cells in the pia-arachnoid. It is commonly associated to solid tumors particularly carcinomas of the breast and lung. Lately, the incidence of undiagnosed LMC is increasing; currently about 20%. The usual presentation of non-specific neurologic symptoms makes diagnosis challenging; especially in the scenario of unknown malignancy. We report three cases with different clinical neurological presentations secondary to LMC. Cerebrospinal fluid (CSF) examinations were negative for malignant cells. Head CT-scans were non-suggestive. A 52 year old woman with history of breast cancer status post combined chemo/radiotherapy on remission who developed headaches and difficulty walking; a 2 year old boy recently diagnosed with left ear rhabdomyosarcoma status post resection on chemotherapy who suddenly developed vomiting, abdominal pain, and seizures followed by brain death; a 59 year old woman with history of chronic tobacco smoking and alcoholism just diagnosed with communicating hydrocephalus of unknown etiology that presented with rapidly deteriorating neurological status and death occurring less than a week after admission. LMC, consistent with primary, was diagnosed at autopsy by histologic examination and immunohistochemistry studies. Leptomeningeal carcinomatosis, currently increasing in incidence, is a complication that requires a high level of clinical suspicion. The presence of malignant cells in the CSF defines the diagnosis; although it has not been proven completely reliable. Studies have shown that serial CSF examinations enhance diagnostic accuracy. Postmortem examination is an invaluable tool to confirm LMC as part of the multidisciplinary approach aiming towards the improvement of clinical diagnosis.

Introduction

Malignant neoplasms have the capacity to metastasize to the central nervous system. There are different pathways of spread including, but not limited to, the hematogenous, endo/perineural, and cerebrospinal fluid (CSF) systems. Aggressive malignancies have a tendency to produce blood vessels (term known as neo-vascularization) that aid in the nourishment, growth, and subsequent spread to other organs.

Leptomeningeal carcinomatosis (LMC) is defined as focal or multifocal infiltration of malignant cells in the pia-arachnoids. The frequency of this diagnosis is increasing, currently at 5% in patients with solid tumors. On the other hand, undiagnosed leptomeningeal carcinomatosis occurrences are on the rise and now encompassing approximately 20% of cases. This etiology presents a detriment in prognostic evidence by the decreased overall survival.

The most common types of solid tumors associated with LMC are carcinomas of the breast and lung corresponding to around 12.25% and 20-26%, respectively (Chart 1). Patients with LMC often present with non-specific neurologic symptoms. Many of these could be remarkably subtle such as headache, while others may mimic an inflammatory process like meningitis (Chart 2). This is particularly challenging in terms of establishing diagnosis especially in the scenario where the patient has no previous history of a neoplastic process. The key diagnostic test for LMC is a CSF cytologic examination revealing the presence of neoplastic cells. CNS imaging studies are also standard in the process of determining the nature of the patient’s symptomatology. MRI has been proposed as imaging modality with the best sensitivity regarding the diagnosis of LMC.

Furthermore, the gross and histologic analysis of the leptomeninges is the most accurate in confirming LMC. Postmortem examination is an invaluable tool that has proven definitive in establishing this pathology.

Case Presentation

CASE 1: 52 year old female with history of breast cancer, diagnosed 4 years prior, status post chemotherapy and radiotherapy on remission developed headaches, general weakness, and difficulty walking one month before admission. Lumbar puncture was performed; remarkable for increased opening pressure. Neurological imaging studies were unremarkable. Cerebrospinal fluid cytology revealed chronic inflammation. Patient was admitted under the clinical suspicion of Cryptococcal meningitis without a clear etiology. Postmortem examination showed metastatic carcinomatosis involving the lungs, and periarticular 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.

CASE 2: 2 year old male recently diagnosed with left ear rhabdomyosarcoma. After 2 weeks of chemotherapy he developed 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 deterioration followed by brain death. Postmortem microscopic examination revealed diffuse meningeal infiltration of malignant cells consistent with Rhabdomyosarcoma (Fig.3). No evidence of residual disease was found in the primary's site.

CASE 3: 59 year old female patient with history of chronic tobacco smoking and alcoholism, just diagnosed with communicating hydrocephalus of unknown etiology. One week after discharge, she presented with headaches, vomiting, unsteadiness, 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 plassen formation involving the sigmoid, cecum and uterus in addition to a 2-cm peripheral lung mass. Metastatic lung adenocarcinoma involving the mesentry and leptomeninges was confirmed by microscopic analysis and immunohistochemistry studies (Fig.4).

Discussion

Leptomeningeal carcinomatosis, currently increasing in incidence, is a complication that requires a high level of clinical suspicion. The usual presentation of non-specific neurologic symptoms makes diagnosis challenging; especially in the scenario of unknown malignancy.

Since this signs and symptoms are associated to a wide range of differential diagnoses, the most common being meningitis. A high index of clinical suspicion must exist in order to avoid overlooking this deleterious entity. In our cases we were consistent with the already described most common symptomatology for LMC. Cerebrospinal fluid cytology is necessary to diagnose this entity, although its sensitivity and specificity have not been proven completely reliable. Studies have shown that serial CSF examinations are sometimes necessary to increase sensitivity and to enhance diagnostic accuracy. Almost 90% of cases have abnormalities in the CSF examination, most notably increased opening pressure, elevated leukocytes, elevated protein and decreased glucose.

Prognosis recognition and diagnosis is vital to ensure proper treatment due to the detrimental prognosis associated to leptomeningeal carcinomatosis. This diagnosis best utilizes all of the resources at hand. Post mortem examination is vital in the process of developing an understanding of this condition and in fine tuning the clinical suspicion necessary to consider it in the list of differential diagnoses. In addition, it is a necessary means to diagnose and confirm meningeal carcinomatosis as part of the multidisciplinary approach aiming towards the improvement of clinical diagnosis.

Conclusion

Leptomeningeal carcinomatosis is an unfavorable complication with an increasing incidence. Leptomeningeal carcinomatosis has a nonspecific clinical neurologic symptomatology making difficult its diagnosis; if suspected, serial CSF examinations are sometimes necessary to increase sensitivity and to enhance diagnostic accuracy. Postmortem examination is essential to confirm the diagnosis and improve clinical awareness.

References