Leptomeningeal carcinomatosis, an emerging disease in internal medicine departments with a generally poor prognosis: two case reports

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ABSTRACT

As a result of improved diagnostic methods and higher cancer patient survival rates, leptomeningeal carcinomatosis is being found in internal medicine departments more frequently. Melanoma, lung cancer, and breast adenocarcinoma are the three cancers that are most commonly associated. When the main tumor diffuses through the bloodstream, cerebrospinal fluid, or direct diffusion and causes multiple focal neurological symptoms, it is known as leptomeningeal involvement; the prognosis is usually not good. Despite multimodal treatment, leptomeningeal carcinomatosis is an advanced form of cancer that frequently results in rapid death. Treatment is typically palliative and consists primarily of intrathecal or systemic radiation and/or chemotherapy. New experimental therapies and immunotherapy are promising means of lowering morbidity and mortality. Clinical cases of leptomeningeal carcinomatosis are reported; both cases were identified at the Ospedale dei Castelli's Department of Internal Medicine and resulted from primary breast pathology.

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Introduction

Leptomeningeal carcinomatosis develops when some cells of the primary tumor, be it a solid or hematologic neoplasm, reach the cerebrospinal fluid (CSF) and localize at the level of the leptomeninges in the central nervous system.[1] The solid neoplasms in which it is most frequently found are small-cell lung cancer, breast cancer, and melanoma. Neoplastic cells reach the meningeal via the bloodstream, lymphatic stream, or by direct extension from a pre-existing lesion in the brain, either primary or secondary. It becomes clinically manifest when there is an obstruction of the normal flow of CSF or a direct infiltration of the tumor at the level of the meningeal membranes. Signs and symptoms are due to increased intracranial pressure (ICP) (resulting in headache, seizures, nausea and vomiting) or they may be caused by the infiltration of nerve roots with focal neurological deficits. Diagnosis is based on the appearance of neurological symptoms and requires the identification of malignant cells in the CSF (lumbar puncture for CSF cytology is the standard diagnostic procedure) or the detection of frank disease on magnetic resonance imaging (MRI) which favors early detection of meningeal metastases and allows them to be located precisely. These can appear as subarachnoid and parenchymal nodules, volume loss in the parenchymal region, and dural enhancement images.[2]

Case reports

First case report

A 61-year-old female arrived at the ward after a day of observation in the emergency room (ED) where she was admitted for dyspnoea and asthenia. She had a history of dia-

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betes mellitus type 2, obstructive sleep apnea syndrome, overweight, arterial hypertension, gastroesophageal reflux (GERD), recent right lumbosciatica, asthenia of the lower limbs (AAII) neuropathy (already performed electromyography (EMG)/electroneurography (ENG), recent access to the ED for dysarthria and AAII without hospitalization [negative brain computed tomography (CT) and chest X-ray].

Upon access to the ED, the patient was apyretic, dyspnoeic in ambient air (a/a), with a referred AAII weakness, recent episodes of dysphonia, and dysphagia due to fluids. Investigations were carried out (Table 1), antibiotic therapy with Levofloxacin and Ceftriaxone was set and chest CT (cCT) with contrast was requested. The patient was diagnosed with acute respiratory failure in community-acquired pneumonia and referred to Internal Medicine.

At the onward admittance, the patient was alert, oriented, and collaborative but her general condition was poor. The physical examination was within the limits of the norm, except for the presence of rhonchi spread over the entire pulmonary area and AAII weakness. No upper limb strength deficit (AASS) nor sensitivity deficit was present, and parameters were within physiologic limits. A new series of investigations was carried out (Table 1) and the anamnestic collection was integrated, understanding that the patient met the criteria for healthcare practices-related pneumonia, with an increased risk for infections with multiple drug resistance pathogens.

Table 1. Patient assessments of the first case report.

Investigations in the ED	Reports of investigations in the ED
Blood gas analysis	Normocapnic hypoxic respiratory failure; set oxygen therapy with VMK at 40%
Blood chemistry tests	In the normal except: WBC 18900, neutrophils 16400, PCT 0.51, CRP 277.35, blood glucose 154, BIL TOT 1.60 and DIR 0.70, ALT 80, LDH 293, albumin 3.3, fibrinogen 998
Electrocardiogram	Sinus tachycardia with ST-T non-specificity
Antigenic and molecular TNF for SARS-CoV-2 research	Negative
Chest X-ray	Marked and diffuse bilateral interstitial thickening with areas of parenchymal thickening at the level of both lower lobes
Investigations in the ward	**Reports of investigations in the ward**
Electrocardiogram	Sinus tachycardia
Blood chemistry tests	Increasing inflammation indices, total and fractionated bilirubin, and transaminases in range
Control EGA in ventimask at 40%	Within the limits of the norm
Molecular TNF for SARS-CoV-2 research	Negative
Serology for mycoplasma pneumoniae and chlamydia pneumoniae	Negative
Urinary antigenuria for legionella and pneumococcus	Negative
Respiratory virus panels	Negative
Chest CT scan with mdc	Multiple circumscribed pericentric ground-glass areas, pseudonodular morphology, modest areas of parenchymal consolidation in both lower lobes, slender pericardial effusion in the anterior site, some lymph nodes with a short subcentrimetic axis in the paratracheal site, subcarinal and hilar bilaterally, numerous lymphadenopathy in the left axillary area and at the level of the external quadrants of the left mammary gland hypodense nodular formation with blurred margins of about 15 mm
Neurological videat	Dysphonia, severe AAII right >left paraparesis, reported tingling in stocking bilaterally, ROT absent to 4 limbs, CPR in flexion bilaterally, cervicodorsal MRI with mdc and mediastinal CT with mdc is recommended if diagnostic doubts
MRI brain and marrow with MDC	Diffuse leptomeningeal thickening and enhancement in the supra- and subtentorial brain, along the emergence of the mixed and spinal nerves, medullary cord and cauda roots, no suspicious images for intra-axial lesions with developmental features nor signs of recent brain distress, sporadic millimeter gliotic areolas in the subcortical white matter of both cerebral hemispheres weakly hyperintense in T2 and FLAIR, fusiform thickening with signal hyperintensity in T2 and almost homogeneous strengthening of the extrinsic oculomotor muscles, some vertebral metameres affected by areas of enhancement of currently doubtful significance (13 mm D4, 9 mm D8, 6 mm D9) since the secondary origin cannot be excluded with certainty, thickening of the right lateral rectus and left medial oculomotor muscles and some areas of vertebral somatic enhancement of current unequivocal interpretation

ED, emergency department; VMK, Ventimask; WBC, white blood cells; PCT, procalcitonin; CRP, C-reactive protein; BIL TOT, total Bilirubin; DIR, death-inducing receptors; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; EGA, electrical control activity; TNF, Tumor necrosis factor; CT, computed tomography; ROT, xxxxxxxxxxxx; CPR, cardiopulmonary resuscitation; MRI, magnetic resonance image; MDC, major diagnostic category; FLAIR, fluid-attenuated inversion recovery.

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Further symptoms reported beside dyspnoea were investigated: i) dysphagia (for which she had already performed a negative brain and cervical spine MRI; still, she reports cough on fluid intake in the last week); ii) dysphonia (for which he had an otolaryngology examination with diagnosis of GERD and prescription of proton pump inhibitors and antacids; iii) AAII weakness (for which she performed EMG/ENG with a diagnosis of non-recent axonal suffering bilateral L5-S1 and L4-L5 right with evokable F waves in 100% of stimulations with motor worsening in the last 5-6 days with difficulty walking independently right>left).

On the second day of hospitalization, the patient had an episode of acute dyspnoea with dysphonia, SpO2 89% in Ventimask (VMK) at 40%, rhonchi from secretions mobilized with difficulty, bilateral harsh noises with inspiratory hissing. Aspiration, positioning of VMK at 60% with SpO2 98%, and electrical control activity (EGA) were performed. Therapy with piperacillin/tazobactam, enoxaparin in prophylaxis, insulin, methylprednisolone 40 mg/die ev, aerosol, and intravenous hydration were set up; anesthesia consultation was performed (continuation of ongoing therapy with clinical and multiparametric monitoring) and scheduled chest cCT was solicited, showing atypical pneumonia and suspected breast cancer. Inflammation indices were slightly reduced on re-evaluation. Neurological consultation posed an indication for cervico-dorsal MRI with contrast (cMRI) (Figure 1), and mediastinal cCT if diagnostic doubts. At this point, diagnostic hypotheses were: paraneoplastic myositis, paraneoplastic neurological syndromes, leptomeningeal carcinomatosis, brain metastases, primary brain tumor, central nervous system (CNS) infections, CNS cysts, and stroke.

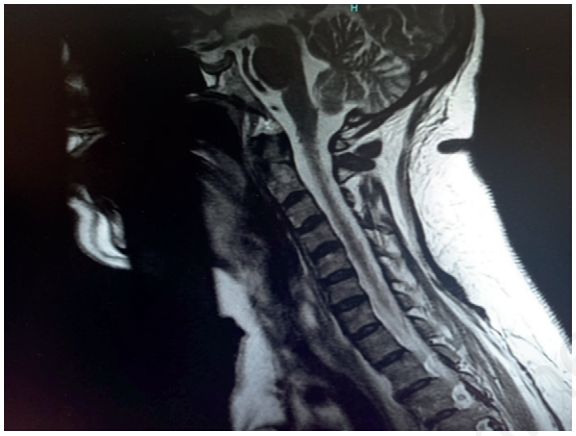

Figure 1. Magnetic resonance image of the brain and brainstem of the first clinical case.

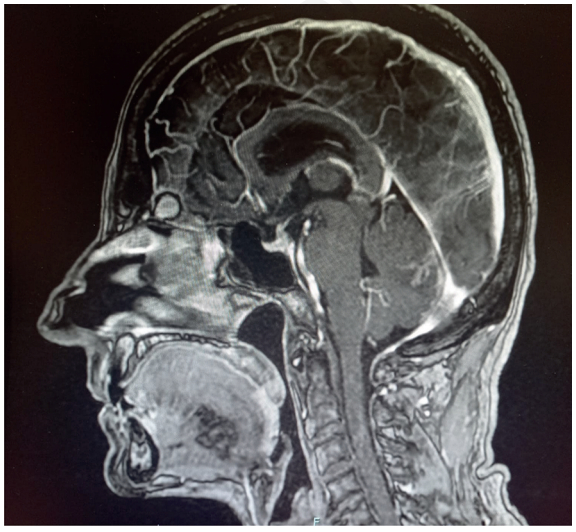

Figure 2. Magnetic resonance image of the brain and brainstem of the second clinical case.

Brain and marrow cMRI suggest leptomeningeal carcinomatosis due to suspected primary breast pathology. Oncologic consultation, breast biopsy with histological examination (adenocarcinoma), total body cCT, CSF examination and creatine kinase dosage were scheduled.

On the third day of hospitalization, there was a sudden worsening of the clinical condition: the patient was alert with sinus tachycardia, tachypnoic and very fatigued with productive cough, difficulty in expectorating, and worsening of gas exchanges at the EGA. Upon resuscitation consultation, support was given in the form of high-flow O2 (FIO2 40%-FLOW 40 LT) with close monitoring of parameters and EGA and a request for transfer in a sub-intensive setting.

In the evening, conditions worsened, with tachycardia, tachypnoea, agitation, and, at times, disorientation with worsening EGA. A new resuscitation consultation was obtained, with frank respiratory distress, non-invasive ventilation positioning (PS 10 CMH20, PEEPS 5, FIO2 50%), EGA improvement and request for transfer intensive environment. After 3 hours, still worsening with the insurgence of uncontrolled choreiform movements at AASS unresponsive to medical therapy, a new resuscitation consultation led to orotracheal intubation.

After 24 hours, the patient was finally transferred to the intensive care unit (ICU) for acute respiratory failure in aspiration pneumonia in a patient with leptomeningeal carcinomatosis due to primary metastatic breast disease. The patient died one week after being transferred to ICU.

Second case report

A 58-year-old female patient, in ED for positional vertigo associated with nausea, vomiting, and migraine of short duration, reported hearing loss and mild visual impairment in the left eye for about three months for which she was already admitted to other EDs, with brain CT and MRI she brought us. History of left breast neoplasm undergoing total mastectomy and cycles of radiotherapy and chemotherapy; other notable pathologies are denied. In ED, investigations are carried out (Table 2), and a neurological consultation with patient evaluation, objectivity, and the current and past (even before ED admission) examinations evaluation. The images of her brain CT scan were compared with MRI. In the MRI (Figure 2), the alteration of the leptomeningeal signal at the cerebellar level of the fluid-attenuated inversion recovery images was noted, also showing contrast capture. In light of these findings, hospitalization was requested to complete the investigations with brain cMRI and oncological consultation.

On the second day of ED observation, due to an insurgence of paraesthesia to the left hemiface of the II and III

trigeminal branches associated with deviation of the buccal rim and approximation of headache crises, the patient had an urgent brain cCT and subsequent neurological re-evaluation that recommended cortisone therapy (Prednison 25 mg/die) while waiting for cMRI.

The patient stayed 3 days in the emergency room for observation and the following day was admitted to Internal Medicine with an ED diagnosis of headache in a patient with breast neoplasia and suspected cerebral secondaries. Upon admittance, clinical parameters were within the limits of the norm, general conditions expired, patient alert, oriented, reactive, collaborating, eupneic in a/a, apyretic. On physical examination, we observed normal cranial nerve behavior, dysphonia, unreported dysphagia, negative antigravity tests, mild left upper limbs dysmetria, normoelicitable deep reflexes, and flexion orthotics. A series of tests were carried out (Table 2) with an in-depth anamnestic analysis. The patient reported suffering from left breast cancer, treated at another hospital, for which she underwent neoadjuvant chemotherapy treatment for proliferative index triple-negative breast cancer Ki-67 60% the year before, subsequent surgery and radiotherapy, and adjuvant capecitabine until two months before admission when she also performed a negative positron emission tomography scan for sure signs of disease recurrence. Due to the

Table 2. Assessment of the patient of the second clinical case.

Investigations in the ED	Reports of investigations in the ED
Blood gas analysis	Within the limits of the norm
Blood chemistry tests	Within the limits of the norm
Electrocardiogram	Within the limits of the norm
Antigenic TNF for SARS-CoV-2 detection	Negative
Chest X-ray	Negative for alterations with a bilateral phlogistic character
CT scan of the brain	Tenuously hyperdense appearance of the cortex of both cerebellar hemispheres with hyporepresentation of the CSF spaces between the cerebellar folia
Brain CT scan with MDC in urgency	The faintly hyperdense appearance of the cortex remains recognizable in the cerebellar site bilaterally, more evident in the right lateral hemispheric site and at the level of the vermis where subtle enhancement is recognized in the post-contrastographic phase, hyporepresentation of the cerebellar folia is associated
Investigations in the ward	**Reports of investigations in the ward**
Electrocardiogram	Within the limits of the norm
Blood chemistry tests	Within normal limits, with the exception of mild hypokalemia, which is corrected
Control blood gas analysis in ambient air	Within the limits of the norm
Brain and marrow MRI (with acquisition of T1 and T2 dependent sequences, also with FLAIR technique, on multiple planes, diffusion sequences and T1 dependent sequences after IV administration of MDC and study of the intracranial circulation with TOF technique)	Diffuse leptomeningeal thickening both in the supra- and subtentorial sites, more evident in the subtentorial site, in the posterior cranial fossa, where after IV administration of MDC, a micro-pseudonodulaform appearance is observed both in the hemispheric site and along the tentorium where some areas of larger post-contrastographic enhancement are observed (in the right cerebellar hemispheric region, close to the ipsilateral sigmoid sinus, in the left cerebellar hemispheric site, in the anterior and posterior sites), which seems to be associated with a modest amount of perilesional edema. A further area of altered signal intensity, characterized by signal hyperintensity in T2-dependent sequences and post-mdc enhancement, is observed in the cranial vermian site, close to the tentorial veil. Thickened appearance and altered signal intensity of the intracisternal portion of the V cranial nerve on the left, and of the VII and VIII nerves bilaterally, characterized by signal hyperintensity in the FLAIR sequences and increased post-contrast enhancement
Neurological re-evaluation	At EON the patient appears to be in great pain, intensely asthenic, alert, oriented and collaborative. Pertipheric deficit of the right VII nc. Concomitant ipsilateral hypoesthesia and paresthesias of the trigeminal territory. NY in the laterality of the view to the right (wide and slow tremors, not exhaustible). Reports blurry vision. On manual assessment of the visual field, reduction of the right hemifield. He reports neck pain in the absence of frank meningeal signs and widespread pain in the left hemisome. No disturbance of superficial sensitivities to the body and limbs. No strength deficit at outbreak. Dysmetria on the left AS segmental coordination test. Balance and standing/sitting cannot be assessed due to profound asthenia. The patient reports intense headache predominantly nuchal with poussets characterized by electric shock-like pain in the left hemiface
Electroencephalogram	Absence of epileptiform or irritative changes
Pain therapy counseling	Morphine elastomer, cortisone enhancement and NSAIDs are recommended as needed

ED, emergency department; TNF, Tumor necrosis factor; CT, computed tomography; CSF, cerebrospinal fluid; MDC, major diagnostic category; MRI, magnetic resonance image; FLAIR, fluid-attenuated inversion recovery; TOF, tetralogy of Fallot; EON, xxxxxxx; NY, xxxxxxxxx; AS, xxxxxxxx; NSAIDs, nonsteroidal anti-inflammatory drugs.

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onset of neurological symptoms, the treating oncologist had prescribed a brain MRI, which was reported negative, with subsequent visits to the ED for neurological worsening until current admission.

Brain cMRI was performed confirming the suspicion of meningeal carcinomatosis secondary to her known breast neoplasm. A neurological re-evaluation, in consideration of the worsening clinical picture, recommended an increase in cortisone therapy (Desametasone mg/die bis *in diem*), Carbamazepine therapy up to 800 mg/day, electroencephalogram, evaluation of pain therapy and oncology for a therapeutic update. Oncology consultation only indicated treatments with palliative purposes. In agreement with the family members and the patient, a residential hospice was activated, where the patient was transferred with the diagnosis of leptomeningeal carcinomatosis secondary to left breast cancer, known in anamnesis, undergoing neoadjuvant chemotherapy treatment and subsequent surgical and radiotherapy treatment. The patient died 20 days after being transferred to hospice.

Discussion

We described two cases of frank leptomeningeal carcinomatosis on brain MRI coming from primary breast neoplasm, in the first case of newly diagnosed, in the second case already known in anamnesis; both cases had a rapidly poor prognosis as no therapeutic approach was possible due to a low-performance status. The analysis of these cases gave several insights into a pathology of growing interest.

The first fundamental aspect is the difficulty of diagnosis. Signs and symptoms depend on the site of involvement; however, due to the frequent multifocality, the clinical presentation may be non-specific, and therefore the index of suspicion should be high. Common clinical signs are often attributable to cranial and spinal nerve dysfunction, ICP, or meningeal irritation with broad presenting features that do not rule out alternative diagnoses, including chronic infections, infectious meningitis, encephalitis, autoimmune diseases (*e.g.*, sarcoidosis), meningeal reaction to brain abscess, side effects of chemotherapy or radiation, paraneoplastic syndromes and toxic-metabolic encephalopathy.

The second important aspect is treatment difficulty. Treatment has traditionally been directed toward palliation, although new therapies show promising response rates.[3] Systemic chemotherapies have been limited in their ability to cross the blood-brain barrier (BBB) but are often combined with radiation and other palliative surgeries to prevent neurological deterioration, maintain quality of life, and prolong survival. Intrathecal chemotherapy is often considered as it bypasses the BBB and minimizes side effects; commonly used agents include methotrexate, thiotepa, cytarabine, and liposomal extended-release cytarabine. Several retrospective studies demonstrated a survival benefit for intrathecal therapy but there is little data on quality-of-life improvement, while many studies have shown increased rates of treatment-related neurotoxicity.[4,5] Finally, in subgroups of solid tumors, targeted therapies have shown promise, but there is still little available evidence.[6,7] Lastly, comes the prognosis. Despite advances in treatment, prognosis remains poor with an overall survival of about 4-6 months from the time of diagnosis, if treated. If left untreated, death occurs due to progression to neurological deterioration in 4 to 6 weeks. Favorable prognostic factors have been identified as Karnofsky performance score >70, cancer chemosensitivity, impaired CSF flow, CSF protein less than 50 mg/dL, and active treatment. The type of primary tumor also plays an important role; patients with hematologic malignancies slightly improved survival by 4.7 months compared to 2.3 months for those with solid malignancies, while among solid tumors, breast cancer has a higher prognosis than other tumor types with a median survival of 5-7 months.[8]

Conclusions

Despite diagnostic improvements, leptomeningeal carcinomatosis has yet a poor prognosis; due to the low-performance status of patients, it is often impossible to implement a meaningful therapeutic attempt. Clinical trial data on the topic is still limited. Therefore, due to the paucity of prospective randomized trials, optimal therapy is not well-defined, and treatment is mostly guided by expert opinions.

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