

# Neurocryptococcosis and leptomeningeal carcinomatosis in metastatic prostate adenocarcinoma: differential diagnoses or overlapping symptoms?

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## Abstract

Acute headaches with red flags in patients with cancer may indicate metastasis or infection. This report describes a case of acute headache with red flags in a patient with metastatic prostate adenocarcinoma who presented a positive latex fixation test without pleocytosis in cerebrospinal fluid (CSF) analysis. Antifungal treatment was initiated based on the test's high accuracy combined with the patient's clinical condition and radiological impression of infectious meningitis, although we could not exclude associated secondary neoplastic involvement. Clinical improvement was first observed on D4 of treatment. On D14, CSF examination revealed therapeutic efficacy but positive oncotic cytology. The patient subsequently had new episodes of headache with warning signs and magnetic resonance imaging showed leptomeningeal carcinomatosis. Although neurocryptococcosis and leptomeningeal carcinomatosis are rare neurological complications, they may coexist with overlapping symptoms.

**Keywords:** Cryptococcosis; Meningitis, Cryptococcal; Meningeal Carcinomatosis; Neoplasm Metastasis; Prostatic Neoplasms.

## Introduction

Cancer patients presenting with acute headaches with red flags on admission should undergo further investigation to identify the etiology and prevent additional neurological damage. The differential diagnoses include infections and central nervous system metastases [1-3].

This report describes a case of acute headache with red flags in a patient with metastatic prostate adenocarcinoma who tested positive for latex fixation despite the absence of pleocytosis in the cerebrospinal fluid (CSF). This report also addresses the clinical reasoning involved in the investigation of neurological conditions and discusses the possibility of neurocryptococcosis and leptomeningeal carcinomatosis presenting with overlapping symptoms.

## Case report

In July 2019, a 37-year-old man with a history of smoking (<5 years/pack) was admitted to our clinical oncology service linked to the Brazilian public health system for the investigation of a wasting syndrome associated with bicytopenia and leukoerythroblastosis. Bone marrow anatomopathological diagnosis revealed infiltration by poorly differentiated

epithelial neoplasia; immunophenotypic analysis did not identify any changes.

Staging examinations were performed to confirm the diagnoses. Magnetic resonance imaging (MRI) of the pelvis revealed a lesion centered on the left side of the prostate, with signs of ipsilateral seminal vesicle extension, suggesting malignancy. A prostate biopsy was performed. The remainder of the staging demonstrated high-volume metastatic bone disease.

The biopsy (performed on August 8, 2019) revealed prostatic adenocarcinoma, with usual acinar pattern, Gleason 9 (score 4+5), and Group 5 of the International Society of Urological Pathology classification, compromising 80% of the fragments examined. The initial prostatic specific antigen (PSA) concentration was 384 ng/mL. A small-cell component was not observed after discussion with a pathologist.

Ten days after the biopsy, the patient complained of severe acute lower back pain, which limited his ambulation and movement. The low back pain had a burning character, with irradiation to the posterior region of the bilateral lower limbs associated with paresthesia and paresis. Lumbosacral MRI showed diffuse bone infiltrations. For symptom relief, palliative lumbar spine radiotherapy was performed (20 Gy for 7 days).

On August 20, 2019, antiandrogen therapy with bicalutamide was initiated due to flare risk. On the day before hospital discharge (August 27, 2019), hormonal blockade with leuporelin was performed. The patient was discharged with a 15-day systemic treatment reassessment plan in the outpatient clinic, where resistance to chemical castration was observed (PSA 526 ng/mL). Since the patient was undergoing treatment by the Brazilian public health system, bilateral orchiectomy was scheduled to allow palliative chemotherapy administration in a castration-resistant scenario.

The surgery was performed on October 17, 2019. The anatomopathological study showed testicular atrophy with poorly differentiated neoplasia infiltration. One week later, the patient started palliative treatment of docetaxel every 3 weeks with concurrent prednisone. The initial dose was reduced by 30% due to bicytopenia secondary to bone marrow infiltration.

In the second cycle, starting on November 14, 2019, the patient showed a reduced PSA level (170 ng/mL), but significant fluid retention and chemotherapy-induced peripheral neuropathy. Therefore, the suspension of docetaxel was programmed, and furosemide was introduced to control the edema.

One month after docetaxel discontinuation (December 14, 2019), the patient showed a significant PSA increase (624 ng/mL). A germline BRCA mutation test revealed that the patient was a BRCA2 carrier. In view of Pomerantz (2017), who demonstrated the benefits of platinum derivatives when associated with docetaxel in BRCA2 castration-resistant prostate cancer, we resumed docetaxel with carboplatin [4]. The patient showed significant clinical improvement after two treatment cycles (PSA 4 ng/mL).

However, coinciding with the chemotherapy nadir period in the second cycle, the patient experienced several episodes of diarrhea and vomiting associated with anorexia, abdominal pain, fever (38.8°C), and hypotension (84/52 mmHg). Owing to the suspicion of infectious gastroenteritis, a loading dose of ceftriaxone and metronidazole was prescribed.

For the next cycle, due to the toxicity presented, carboplatin was changed to cisplatin and the docetaxel dose was reduced by 50%. After cycle completion, the patient experienced great evolution, denying related toxicities.

Maintaining the regimen, the patient completed three further cycles of docetaxel and cisplatin. Subsequently, his PSA concentration was 0.82 ng/mL

and he showed significant clinical improvement: he was pain-free, no longer required opioids, and was able to walk again. Chemotherapy was paused on March 30, 2020, and the patient opted for outpatient follow-up.

Approximately 6 months after the chemotherapy break, on October 14, 2020, the patient experienced an abrupt return of bone pain, characterizing neoplasm progression (PSA 13.6 ng/mL). Because the patient was not eligible for clinical trials of poly-ADP ribose polymerase inhibitors and the non-release of the medication by judicialization (based on the clinical response in previous treatment cycles), cytotoxic chemotherapy (docetaxel and cisplatin) was restarted. After completing six new cycles, on March 8, 2021, the patient showed clinical improvement and reduced PSA values (5.2 ng/mL).

However, in the following month, on April 6, 2021, the patient presented to the hospital emergency department complaining of a sudden-onset severe headache (refractory to symptomatic medication) associated with nausea and vomiting. Physical examination revealed no meningeal irritation or focal deficits. His PSA level was 4.2 ng/mL.

Due to the red flags on admission, the patient was hospitalized for further investigation of the etiology

of his condition. A brain computed tomography scan (with contrast) did not show central nervous system (CNS) lesions nor an expansive process. For symptom relief, the analgesia was optimized and antiemetics were prescribed. The patient reported significant improvement in his headache and subsequent complaints of nausea and vomiting.

On April 14, 2021, the patient showed significant worsening of his neurological condition, evolving with new episodes of headaches and mental confusion. MRI revealed diffuse leptomeningeal enhancement. The radiological impression was infectious meningitis, which could not rule out associated secondary neoplastic involvement.

Thus, owing to suspected infection, lumbar puncture and CSF analysis were performed. The CSF revealed five red blood cells/mm<sup>3</sup>, one leukocyte/mm<sup>3</sup>, a glucose concentration of 29.2 mg/dL, and a total protein concentration of 234.7 mg/dL, with an opening CSF pressure of 20.5 cmH<sub>2</sub>O. Although tuberculosis polymerase chain reaction, microbiological cultures, and a panel for detection of viral meningitis were not detectable, the latex agglutination test was positive in the CSF sample. The oncotic cytology results were negative (Table 1).

Despite the atypical finding of only one leukocyte in the CSF, the infectious disease team recommended the initiation of intravenous fluconazole (400 mg every 12 hours) and amphotericin B (0.7 mg/kg every 24 hours), supported by the association of clinical and imaging findings and positive latex agglutination test. The patient began to show clinical improvement in headache and mental confusion four days after the initiation of antifungal therapy (D4).

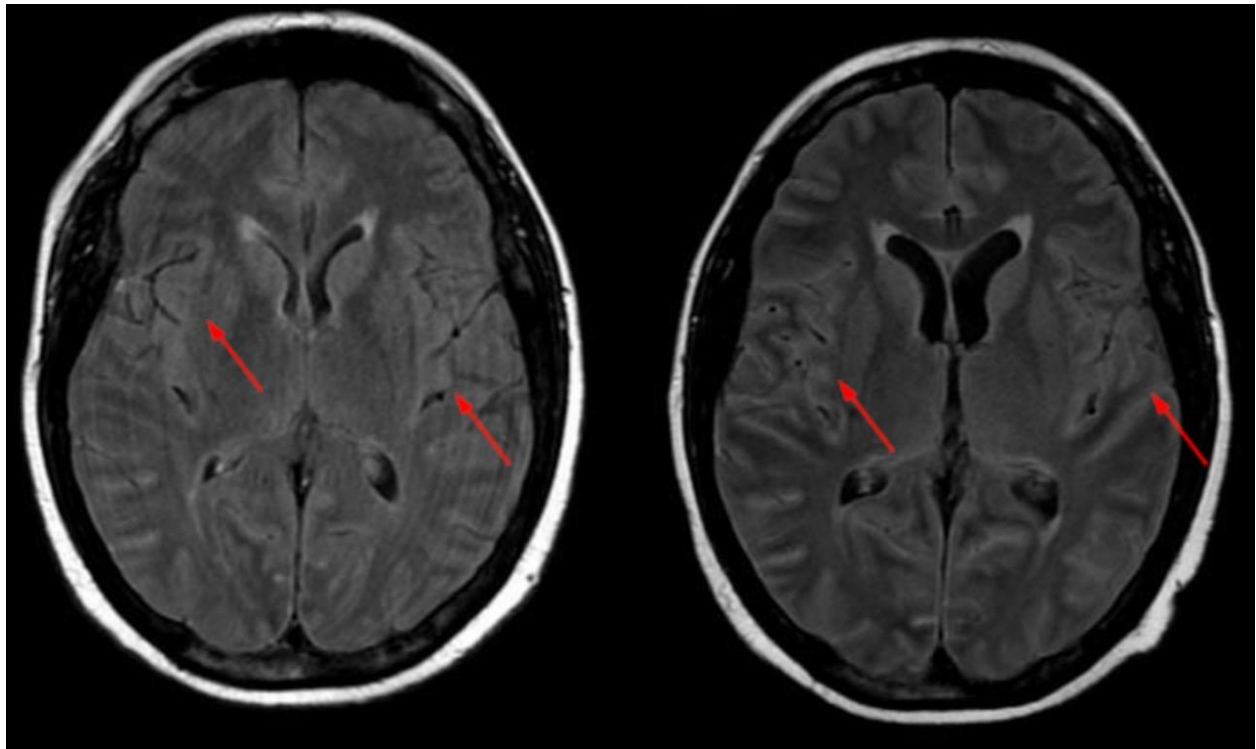
On D14 of fluconazole and amphotericin B (April 28, 2021), a new CSF sample was collected for oncotic cytology, latex fixation test, and direct mycological examination. The plan was to maintain amphotericin B until negative laboratory data and transition to oral fluconazole at the same dosage as used intravenously for 6 weeks. CSF analysis revealed negative results for the latex agglutination test and direct mycological examination, indicating therapy effectiveness; however, the oncotic cytology was positive for malignancies. At this time, the patient's PSA level was 14.7 ng/mL.

On the day following data availability, the patient had new sudden episodes of severe holocranial headache refractory to simple analgesia, which were associated with nausea and vomiting. A new brain MRI scan showed progression of the infiltrate

with meningeal enhancement (Figure 1). MRI and CSF findings were compatible with a diagnosis of leptomeningeal carcinomatosis.

The patient gradually developed mental confusion, time and space disorientation, and psychomotor agitation. On the fourth day after the leptomeningeal carcinomatosis diagnosis, he developed a generalized tonic-clonic seizure associated with desaturation, decreased consciousness (score of six on the Glasgow Coma Scale), and respiratory effort requiring intubation.

The desaturation remained refractory to ventilatory parameter adjustments, culminating in cardiorespiratory arrest with pulseless electrical activity. Advanced cardiovascular life support maneuvers were then performed for 15 min. In the last cycle, considering the patient's asystole and fixed middle pupils, the efforts were discontinued.



**Figure 1.** Contrast-enhanced axial T2/FLAIR images of the brain at basal ganglia level. The image on the right shows hypersignal adjacent to cortical sulci in bilateral insular region, with slight progression from the control exam (April 14, 2021). The control exam is represented by the image on the left.

**Table 1.** Laboratory data of cerebrospinal fluid pre-antifungal treatment.

Cerebrospinal Fluid Variable	Laboratory data
<b>Sample characteristics</b>	
Volume (ml)	2
Reticule	Absent
Aspect	Clear
Color	Colorless
Color after 1500 rpm centrifugation	Colorless
<b>Cytology</b>	
Red blood cells (/mm <sup>3</sup> )	25
Leukocytes (/mm <sup>3</sup> )	1
<b>Biochemical</b>	
Glucose (mg/dl)	29.2
Total protein (mg/dl)	234.7
<b>Viral meningitis detection panel</b>	
Herpes Simplex Virus 1	Negative
Herpes Simplex Virus 2	Negative
Varicella Zoster Virus	Negative
Paramyxovirus	Negative

Human Parechovirus	Negative
Enterovirus	Negative
<b>Microbiological Cultures</b>	
N. meningitidis	Negative
S. pneumoniae	Negative
Yeasts in direct mycological examination	Negative
<b>Tuberculosis (Polymerase Chain Reaction)</b>	Negative
<b>Cryptococcal Antigen (Latex fixation test)</b>	Positive
<b>Cytopathological</b>	
Oncotic cytology	Negative for malignancy

**Legend.:** Cerebrospinal fluid reference values for altered characteristics: **Red blood cells:** 0 /mm<sup>3</sup>; **Leukocytes:** 0-5 /mm<sup>3</sup>; **Glucose:** 40-80 mg/dL; **Total protein:** 15-60 mg/dL; **Latex fixation test:** Negative [2].

## Discussion and Conclusion

Cryptococcosis is an invasive fungal infection that may manifest as meningoencephalitis and is an important cause of mortality in immunosuppressed patients, particularly in developing countries [5,6].

The etiological agents are distributed worldwide; *C. neoformans* is generally associated with pigeon droppings and opportunistic infections. However, *C. gattii* causes infections in immunocompetent hosts and is found in decaying organic matter [5-7].

As in the present case, the signs and symptoms include intracranial hypertension associated with severe headache, nausea, and vomiting. Meningeal irritation, fever, and photophobia are rarely described in the initial presentation [5-8].

Neurocryptococcosis is diagnosed by the identification of

cryptococcal antigens in the CSF latex fixation test. While imaging findings are not frequently altered or specific for this disease, they can show cortical hypotrophy, expansive lesions (cryptococcoma), hydrocephalus, diffuse edema, or gelatinous pseudocysts, contributing to a diagnosis. The factors related to a worse prognosis include increased intracranial pressure, antigen titers >1:1,000 in the latex fixation test, and decreased leukocyte number in the CSF [2,5-8].

Like the immunocompromised patient with metastasis due to prostate cancer, Duarte (2017) described the involvement of cryptococcosis in the central nervous system in 19 patients with or without immunological compromise evaluated by MRI. The most common imaging finding was leptomeningeal enhancement [9].

The patient in our case presented only one leukocyte in the CSF analysis, but a positive latex agglutination test

and MRI radiologic impression of meningeal infection (which could not rule out associated secondary involvement). The hypothesis of a false-positive latex fixation finding was widely discussed by our team and directly influenced the choice of initiating antifungal treatment.

Boulware (2014) and Wang (2015) validated the diagnostic value of latex fixation tests in patients with cryptococcal meningitis. The estimated sensitivity, specificity, positive predictive value, and negative predictive value were 91.1%, 96%, 92.6%, and 95.3%, respectively. The interpretation of the test requires an evaluation of the other components of the CSF, as well as the clinical condition of the patient [10,11].

In their systematic review of meningitis cases without CSF pleocytosis, Troendle et al (2019) reported that, despite the rarity of this condition leading clinicians to prematurely exclude this diagnosis, meningitis without pleocytosis has been reported in both adult and pediatric patients. Although bacterial organisms are the most implicated, viral or fungal infections may also occur. Of the 124 cases identified in the literature, only nine were fungal infections (seven of which were caused by *Cryptococcus*). Patients who were severely immunocompromised and with

malignancies or meningitis secondary to inoculation of organisms from another primary source were more likely to present fungal meningitis in the absence of pleocytosis [12].

The absence of pleocytosis in CSF is hypothesized to occur in meningitis cases due to increased disease severity and rapid progression, leaving insufficient time for an adequate inflammatory response before obtaining CSF samples [13,14]. Thus, due to the high accuracy of the latex agglutination test, the imaging examination findings, the patient's clinical condition, and the scientific basis indicating empiric antibiotic/antifungal administration for suspected meningitis regardless of the initial leukocyte count on CSF analysis, the medical team administered neurocryptococcosis treatment.

The Brazilian Ministry of Health recommends cryptococcal meningitis treatment comprising intravenous amphotericin B (0.7 mg/kg/day) and fluconazole (400 mg/day) until CSF sterilization, followed by fluconazole (400 mg/day) maintenance until 8 weeks from treatment initiation. As reported in the present case, during maintenance, a transition to oral fluconazole is possible to facilitate administration and patient adherence [1,5-7].

Despite guideline recommendations, diagnosis, and treatment of cerebral cryptococcomas is



very heterogeneous due to the lack of high-quality data. Chastain (2022) described an important systematic review on Cerebral Cryptococcomas and the possible recommendations for managing patients with cerebral cryptococcomas. Though the most efficacious treatment remains undefined, a multipronged approach should include antifungal therapy for a minimum of 6 months with considerations for concomitant corticosteroids in the setting of perilesional edema, as well as surgical intervention [15].

Passerini et al. (2020) described cryptococcosis in a patient with metastatic prostate adenocarcinoma who exclusively presented with nonspecific skin lesions (papules, pustules, nodules, abscess, edema, panniculitis, and ulcers). The patient in the present case had neurological symptoms characteristic of neurocryptococcosis. This case highlights the wide spectrum of clinical manifestations of cryptococcosis, which is an important differential diagnosis in cancer patients with acute neurological conditions [16-20].

Leptomeningeal carcinomatosis is a late-stage complication of malignant neoplasms that metastasize to the leptomeninges (pia mater, arachnoid, CSF, and the subarachnoid space). This complication is the third most common

metastatic manifestation affecting the CNS; its incidence is growing due to the increased survival of patients with cancer. The treatment is limited to palliative care [2,20-22].

Metastatic breast, lung, and melanoma cancers are the main cancers affecting the leptomeninges in the form of carcinomatosis. Adenocarcinoma is the most common histology associated with this complication. An estimated 5–10% of patients with metastatic tumors develop carcinomatosis at some point during disease evolution [2,18-22].

Meningeal cancer cells have a hematogenous origin from the arterial dissemination or Batson's venous plexus. As they spread through the subarachnoid space, the leptomeninges are reached by CSF flow. Hydrocephalus may occur in the brain, spinal cord dorsal surface, and cauda equina owing to tumor adhesions that obstruct CSF flow [23-25].

Leptomeningeal carcinomatosis has several clinical manifestations that are commonly associated with cerebral hemispheres, cranial nerves, and root and spinal cord involvement. The initial clinical symptoms include mental confusion, decreased consciousness, cerebellar signs, low back pain, and limb paresis. Although the classic presentation is related to clinical manifestations on a multifocal axis, it can less frequently exhibit isolated

symptoms. The patient in the present case presented only with headache symptoms, which was sufficient to consider carcinomatosis as a differential diagnosis [21,25].

A high index of suspicion must be considered when diagnosing leptomeningeal carcinomatosis. Other differential diagnoses that could explain the patient's clinical condition included tuberculosis, sarcoidosis, viral infections, other forms of fungal infections, and toxic and metabolic encephalopathies [21,25].

The differential diagnosis of intracranial hypertension due to leptomeningeal carcinomatosis was based on the initial clinical evaluation of the patient's headache complaint. Although the opening pressure of the CSF was slightly increased, the negative oncotic cytology, lack of clinical improvement immediately after puncture, and the radiological impression of meningeal infection on MRI (even though it could not exclude associated secondary neoplastic involvement) suggested that the neoplastic etiology was not exclusively responsible for the patient's clinical condition. Thus, even if the combination of findings in clinical and complementary examinations pointed to neurocryptococcosis as the main diagnostic hypothesis, malignancy

could also be present with symptoms overlapping the patient's complaint.

The present case report highlights the possibility of overlapping symptoms of neurocryptococcosis and leptomeningeal carcinomatosis in a patient complaining of acute headache with red flags. The diagnostic doubt regarding false-positive latex fixation test results and the decision to initiate anti-fungal specific treatment underscored the complexity of this case.

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