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Challenges in the diagnosis of leptomeningeal dissemination of glioblastoma in a patient with fever and xanthochromic CSF: a case report

ANDREI NEAGU[1,2], CRISTIAN-MIHAIL NICULAE[1,2,*], IRINA LĂPĂDAT[2], ADRIANA HRISTEA[1,2]

Affiliations: [1]Faculty of Medicine, University of Medicine and Pharmacy "Carol Davila", str. Dionisie Lupu nr. 37, sector 2,Bucharest, Romania;

[2]National Institute for Infectious Diseases "Prof. Dr. Matei Bals", str. Dr. Calistrat Grozovici nr 1, sector 2, Bucharest, Romania;

Running head: Diagnostic challenges in leptomeningeal dissemination of glioblastoma

Abstract

Background

Leptomeningeal spread with carcinomatous meningitis is a severe complication of glioblastoma, with a poor prognosis. Diagnosis is challenging, as the sensitivity of classic diagnostic investigations remains low for detecting cerebrospinal fluid (CSF) tumor spread and exclusion of infectious causes is mandatory, especially if unusual clinical findings are present.

Case presentation

A 71-year-old woman was admitted to our hospital for recurrent episodes of high fever and xanthochromic meningitis, with subacute onset. Her past medical history was significant for a left temporal glioblastoma, treated with surgical resection and adjuvant chemo- and radiotherapy, with associated systemic immunosuppression secondary to chemotherapy. An extensive workup especially with molecular microbiology testing for exclusion of infectious causes was performed. CSF was analyzed for typical bacterial and viral causes, but also pathogens associated with immunosuppression, such as *Listeria monocytogenes* and *Cryptococcus neoformans*. A therapeutic trial of standard antituberculous drugs with repeated lumbar punctures were needed in order to exclude *Mycobacterium tuberculosis* and to confirm the diagnosis of carcinomatous meningitis by cytopathological examination of the CSF.

Conclusions

The case describes an unusual clinical presentation of a patient with glioblastoma associated leptomeningeal dissemination, as high fever and xanthochromic CSF could raise important diagnostic and therapeutic challenges in the clinical practice. The diagnosis of carcinomatous meningitis requires an extensive workup for exclusion of infectious causes which is important for urgent oncologic treatment.

Keywords: glioblastoma, fever, meningitis, xanthochromic CSF;

What is new? What is important? Fever is an unusual presentation for leptomeningeal dissemination of glioblastoma. In association with neurological symptoms and xanthochromic CSF, it can raise important diagnostic challenges, requiring the exclusion of several infectious causes, particularly in immunocompromised patients. We present an illustrative case in which an extensive workup was performed in an infectious diseases department before the diagnosis of carcinomatous meningitis could be established and oncological treatment initiated.

BACKGROUND

Glioblastoma (GBM) is the most aggressive primary malignant brain tumor [1,2]. Leptomeningeal spread (LMS) with carcinomatous meningitis is a severe complication of GBM with a poor prognosis [1-4]. Diagnosis is challenging and it is based on clinical suspicion, neuroimaging and confirmed by cerebrospinal fluid (CSF) examination [4-7]. However, associated systemic immunosuppression and fever in a patient with GBM and new CNS symptoms could raise important diagnostic challenges in the clinical practice. Analysis of CSF is essential to exclude infectious causes, as data regarding fever and xanthochromic CSF in patients with LMS is not reported [5-7].

Case presentation

A 71-year-old woman was admitted to our hospital for recurrent episodes of high fever (39.6 ℃) associated with headache, vomiting and a worsening of her aphasia, over the last two weeks. Her past medical history was significant for a left temporal glioblastoma, diagnosed 14 months before as a grade 4, Ki67 60%, p53 positive, ATRX positive, MGMT negative tumor. The patient underwent subtotal surgical ablation (>90%), followed by adjuvant radiotherapy (RT) (58 Gy, 29 fractions) and chemotherapy with temozolomide (TMZ). Nine months later, a cerebral MRI showed local tumoral progression and TMZ was switched with irinotecan/bevacizumab and a second surgical intervention was planned, with no immediate complications. After discharge, the patient complained of the aformentioned symptoms and she was hospitalised in our department. The chronic treatment included levetiracetam 500 mg twice daily, fluoxetine 10 mg daily and eltrombopag 50 mg daily. On admission, the patients was alert, partially oriented, normal vital signs; the post craniotomy temporal scar was clean, with mild edema of surrounding tissues; no signs of meningeal irritation and no neurological deficits were recorded; the rest of the clinical examination was unremarkable.

The laboratory investigations revealed mild lymphopenia (1100/mm^3 with a CD4+ count of 424/mm^3), a mild anemia (hemoglobin of 11 g/dL) and a platelet count of 117,000/mm^3. The inflammatory markers and chemistry findings were also within the normal ranges. SARS-CoV-2 and influenza tests were negative.

The lumbar puncture (LP) at admission showed a hypertensive xanthochromic CSF, with 283 cells/mm^3, 85% mononuclears, low CSF glucose of 22 mg/dL (128 serum glucose) and hyperproteinorachia (193 mg/dL).

Extensive CSF/CNS and peripheral etiological workups were done. A Ziehl-Neelsen smear for acid-fast bacilli (AFB) and PCR (GeneXpert MTB/RIF) were negative for *Mycobacterium tuberculosis* (MTB). Gram stain, India ink and the repeated CSF cultures were all negative for bacterial and fungal growth. A multiplex CSF PCR was performed especially for viral pathogens, *Listeria monocytogenes* and *Cryptococcus neoformans*, with negative results (Table 1). PCR for *Aspergillus* spp., JC virus and EBV from CSF were also negative.

The urinalysis and urine culture were negative. The repeated blood cultures were all negative for bacterial and fungal growth. Several viral studies, including antibody tests for HIV, hepatitis B and C, CMV (serology and quantitative blood DNA), EBV and *Coxiella burnetii*, were all negative. Echocardiography was not suggestive of infective endocarditis. Chest, abdomen and pelvic CT scans could not detect any inflammatory focus. Brain CT scan with contrast found a 35/18 mm heterogenous lesion in the left parietal lobe, with important surrounding edema and mass effect on the left lateral ventricle, suggestive of GBM recurrence, and not for a brain abscess, also without signs of mastoiditis or sinusitis. A brain MRI could not be performed for further characterization of the lesion/meninges (unavailable).

We started a therapeutic trial of standard antituberculous treatment considering the following: fever and no other identified cause, subacute onset of

meningitis with no other etiology (negative multiplex PCR), xanthocromic lymphocytic CSF with hypoglycorrachia, immunosuppression, high local endemicity for MTB and the low sensitivity of MTB PCR and AFB from CSF. Corticosteroid therapy was not initiated in order to avoid the influence on CSF parameters. After two weeks of treatment, a follow-up LP was performed and we found no significant changes, with persistent xanthochromia, hypoglicorrahia (CSF/serum glucose ratio of 0.3) and hyperproteinorachia (246 mg/dL). The repetead AFB smear and GeneXpert MTB/RIF were negative. The CT scan found an increase in the edema surrounding the left parietal lesion and the cytopathological examination of the CSF revealed cells consistent with malignancy (Figure 1).

(place of figure 1)

We established the diagnosis of GBM associated carcinomatous meningitis and referred the patient to oncology for further investigations and treatment.

DISCUSSION AND CONCLUSION

Considered initially a rare complication (4%), the incidence of GMB LMS could reach up to 25% on different postmortem neuropathological studies [1,8]. Diagnosis of carcinomatous meningitis in patients with GBM is challenging as the sensitivity of classic diagnostic investigations (MRI and cytological CSF analysis) remains low for detecting CSF tumor spread [1,9-11]. Our case describes the clinical challenges when facing an immunosuppressed patient with GBM, fever and new CNS symptoms. Pleocystosis, protein level above 45 mg/dL and/or glucose levels < 60 mg/dL are CSF findings also consistent with LMS [5]. However, fever and xanthochromic CSF are not common findings in these patients. In a recent systematic review, fever was not among the ten most

prevalent symptoms in glioma patients [12]. Similar, in two large cohorts of 113 and 163 patients with leptomeningeal metastasis, only one patient was mentioned with fever and none of the included patients was mentioned having a xanthochromic CSF [6,7]. Therefore, carcinomatous meningitis becomes a diagnosis of exclusion and a rapid and extensive workup is needed. Given the xanthochromic lymphocytic meningitis with fever and subacute onset, *Mycobacterium tuberculosis*, *Listeria monocytogenes* and *Cryptococcus neoformans* were excluded. Postoperative subarachnoid hemorrhage is another differential diagnosis but the time since surgery, CSF cell count, very low CSF glucose/blood glucose ratio and high proteins in CSF were against this diagnosis. CMV reactivation and *Pneumocystis jiroveci* pneumonia could also be an issue in patients treated with TMZ, but blood DNA for CMV was negative and the chest CT scan was normal. As we excluded CNS and peripheral infectious causes by an extensive workup, the diagnosis of carcinomatous meningitis related to GMB was established by CSF analysis with tumor cells detection. According to other data, the first lumbar puncture is only 50–60% sensitive and a repeated collection increases sensitivity to 80% [5]. As no other cause for fever was identified, we considered the fever as neurogenic in origin.

In conclusion, this case describes an unusual clinical presentation of a patient with glioblastoma associated leptomeningeal dissemination, as high fever and xanthochromic CSF could raise important diagnostic and therapeutic challenges in the clinical practice. The diagnosis of carcinomatous meningitis requires a rapid and extensive workup for exclusion of infectious causes which is important for urgent oncologic treatment.

Diseminarea leptomeningeală cu meningită carcinomatoasă este o complicație severă a glioblastomului, cu prognostic rezervat. Diagnosticul pozitiv este dificil, deoarece sensibilitatea investigațiilor clasice pentru detecția diseminarii tumorale la nivelul lichidului cefalorahidian (LCR) este redusă, iar excluderea cauzelor infecțioase este obligatorie, mai ales în cazul unui tablou clinic neobișnuit.

Prezentare de caz: O pacientă în vârstă de 71 de ani a fost internată în clinica noastră pentru episoade recurente de febră înaltă și tablou de meningită cu LCR xantocrom, cu debut subacut. Din istoricul medical al pacientei reținem un glioblastom temporal stâng tratat prin rezecție chirurgicală urmată de chimio- și radioterapie adjuvantă, cu imunodepresie sistemică secundară chimioterapiei. Un bilanț extensiv, în special cu teste de microbiologie moleculară a fost efectuat pentru excluderea cauzelor infecțioase. LCR-ul a fost analizat pentru cauze bacteriene și virale tipice, dar și pentru patogeni asociați imunodepresiei, cum ar fi Listeria monocytogenes și Cryptococcus neoformans. O probă terapeutică de medicație antituberculoasă și puncții lombare repetate au fost necesare pentru excluderea infecției cu Mycobacterium tuberculosis și pentru confirmarea diagnosticului de meningită carcinomatoasă prin examen citopatologic al LCR.
*Concluzii **:** Acest caz descrie o prezentare clinică atipică a unei paciente cu diseminare leptomeningeală asociată glioblastomului, deoarece febra înaltă și aspectul xantocrom al LCR ridică provocări diagnostice și terapeutice importante în practica clinică. Diagnosticul de meningită carcinomatoasă necesită un bilanț extensiv pentru excluderea cauzelor infecțioase, esențială pentru un tratament oncologic urgent.*

Correspondence to: Cristian-Mihail Niculae**, M.D,** National Institute for Infectious Diseases "Prof. Dr. Matei Bals", str. Dr. Calistrat Grozovici nr 1, sector 2, Bucharest 021105, Romania

E-mail: cristian.niculae@drd.umfcd.ro

Ethical Approval and consent to participate: This case report was published according to the ethical guidelines of the Helsinki Declaration and was approved by the Local Ethics committee, NIID *Prof. Dr. Matei Bals*. Written informed consent regarding the participation in this study was obtained from the patient;

Consent to publication: Written informed consent regarding the submission and publication of this manuscript was obtained from the patient;

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Bacteria	**Viruses**	**Fungi**
Escherichia coli K1 – negative	Cytomegalovirus – negative	Cryptococcus neoformans – negative
Haemophilus influenzae – negative	Enterovirus – negative	Cryptococcus gattii – negative
Listeria monocytogenes – negative	Herpes simplex virus 1 – negative	
Neisseria meningitidis – negative	Herpes simplex virus 2 – negative	
Streptococcus agalactiae – negative	Human herpes virus 6 – negative	
Streptococcus pneumoniae – negative	Human parechovirus – negative	
	Varicella zoster virus – negative	

Table 1. Multiplex PCR results from CSF (BioFire FilmArray Meningitis/Encephalitis Panel, Biomerieux)

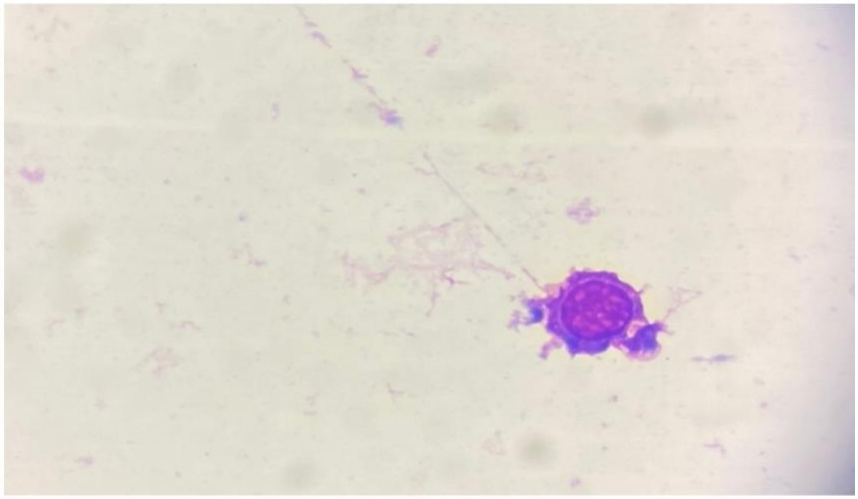

Figure 1: Cytopathological examination of the CSF revealed frequent large, polygonal cells with voluminous, inhomogeneous nuclei with infrequent inclusions, consistent with malignancy, cytopathological category C4.