



Case Report

# Stroke secondary to leptomeningeal carcinomatosis with radiologic signs of arterial invasion

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## ABSTRACT

**Background:** Compared to the general population, cancer patients are more likely to suffer from cerebral ischemia, either caused by the tumor itself or by the treatments applied.

**Case Description:** We hereby present the clinical case of a patient treated for lung adenocarcinoma, who, years later, developed a case of the right frontal-temporal-insular ischemia secondary to leptomeningeal spread of the primary neoplasm, with an invasion of the walls of the right-middle cerebral artery and its branches.

**Conclusion:** This should be considered an extremely rare form of recurrence of a primary solid tumor with clinical and radiological features that can mimic those of vascular inflammatory entities.

**Keywords:** Arterial wall metastasis, Brain metastasis, Leptomeningeal carcinomatosis, Stroke

## INTRODUCTION

Approximately 15% of cancer patients suffer from cerebrovascular events, either ischemic or hemorrhagic in nature, while 4.4% of stroke patients also show signs of active neoplastic disease.<sup>[1]</sup> Although these events may be present at the beginning of the oncological process, they usually develop over the course of the disease's lifespan or, alternatively, as an acute or delayed complication of the treatments applied.<sup>[1]</sup> Ischemic strokes in cancer patients are usually caused by a state of hypercoagulability; otherwise, the neoplasm can also directly affect the vessels – a phenomenon that rarely occurs during the spread of a solid neoplasm.<sup>[1,5,17]</sup> In this document, we report the case of a patient previously treated for lung adenocarcinoma, who, years later, developed cerebral ischemia secondary to leptomeningeal carcinomatosis (LMC). We provide radiologic evidence supporting a triggering mechanism of arterial wall invasion by the neoplasm and also include a brief analysis of the features in similar cases published in scientific literature to date.

## CLINICAL PRESENTATION

### Presentation and examination

A 76-year-old woman had been treated 6 years ago for a Stage IA lung adenocarcinoma (T1aN0M0; TTF1+ and thyroglobulin-immunostaining; nonrearranged ALK gene locus;

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nonmutated K-RAS, BRAF, and EGFR) by the left upper pulmonary lobectomy and mediastinal lymphadenectomy. She remained free of disease according to the records of their last cancer follow-up appointment. The patient was transferred to the emergency department with a clinical picture of a headache, self-limited and recurrent episodes of dizziness, unsteady gait and diaphoresis, and occasional loss of consciousness over the past few months. She presented unsteady gait with lateralization to the left, without additional signs of focal involvement in the neurological examination. Since the patient also had a history of arterial hypertension, dyslipidemia, and ischemic heart disease, she had recently been evaluated as an outpatient by her cardiologist, who ruled out any structural or functional pathology that would justify her current clinical picture.

### Complementary studies

The analysis of peripheral blood returned nominal measurements. Imaging studies revealed signs of ischemia in different stages affecting the right insula together with the frontal and temporal opercula, frontal lobe white matter edema, and LMC with an invasion of the right middle cerebral arterial wall and its branches [Figures 1a-l]. Signs of pial neoplastic deposits were also observed surrounding the corpus callosum, associated with focal ischemia, and the anterior optic pathways [Figures 1l-n]. The FDG PET scan did not reveal any relevant alterations except for an irregular, hypometabolic area at the right frontal lobe. The biochemical and cytological studies of the cerebrospinal fluid (CSF) obtained by lumbar puncture revealed no pathological findings. Postsurgical imaging studies are shown in Figures 1o-p.

### Histological diagnosis

Finally, an open brain biopsy was performed [Figure 2a] that included a leptomeningeal-cortical-subcortical block of tissue from the frontal lobe. Microscopic findings were consistent with a definite diagnosis of LMC with multifocal cortical lymphovascular invasion [Figures 2b-d]. The immunohistochemical profile, positive for TTF1 and napsin A, diffusely positive for CK7, and negative for CK20, indicating the pulmonary origin of the neoplasm.

### Evolution

According to the findings in diagnostic tests carried out, a Stage IVA neoplastic disease was established. The patient received two cycles of treatment with capmatinib in monotherapy (400 mg/12 h), indicated after the identification through next-generation sequencing studies of neoplastic variants (MET splice site 2888-15\_2891del19) sensitive to

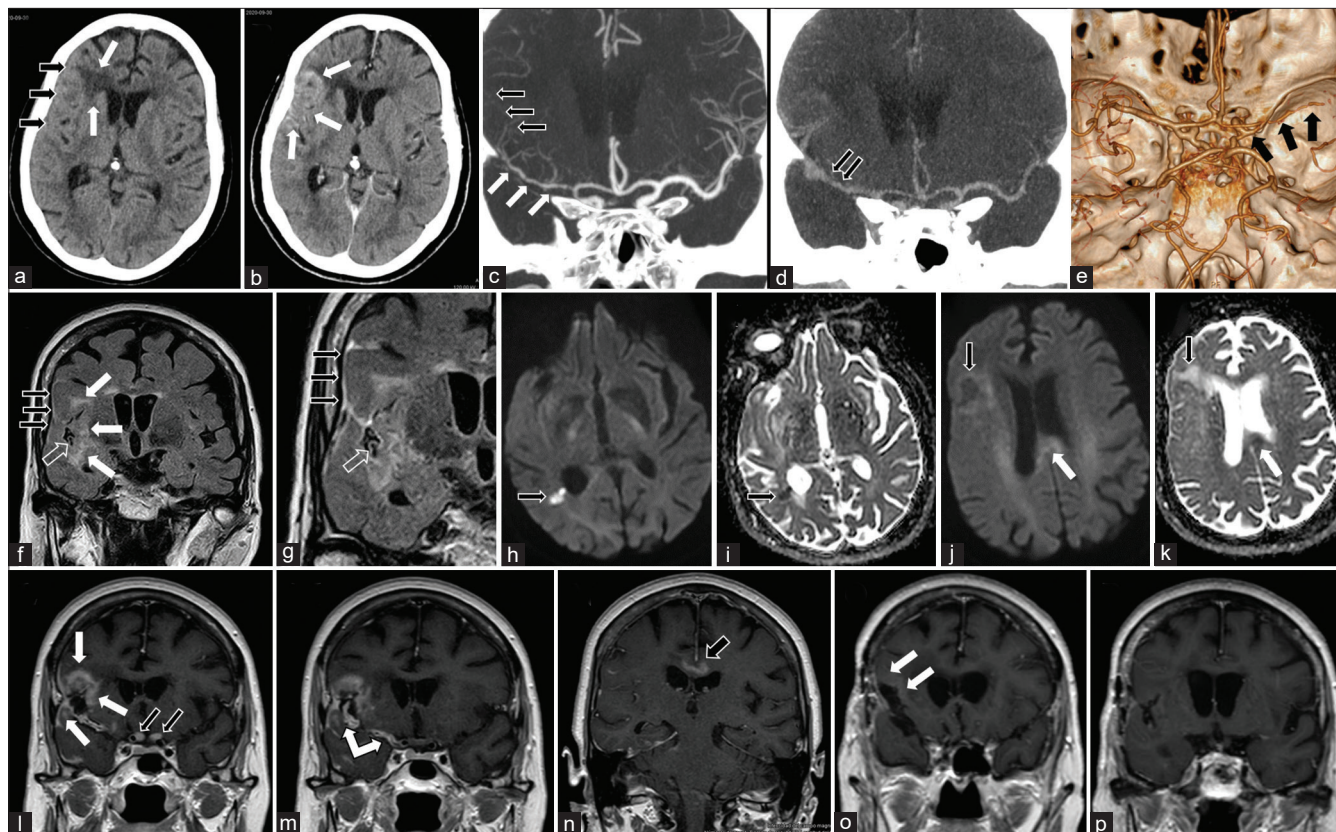
the aforementioned drug in the biopsy sample. The initial response was favorable, manifesting neuroradiological improvement in the MRI control study obtained 4 months after the surgical procedure [Figures 1o-p].

## DISCUSSION

LMC is a rare and severe complication which can manifest over the course of an oncological disease's lifespan.<sup>[4]</sup> It affects approximately 5% of cancer patients, a percentage that rises to 20% if asymptomatic cases, or those without a confirmed diagnosis, are included.<sup>[11,20]</sup> LMC occurs more frequently after the dissemination of solid neoplasms, including those originating in the breast (up to 30%) and the lung (up to 26%) or primary high-grade neoplasms of the central nervous system.<sup>[16,19]</sup>

LMC usually develops as a consequence of hematogenous dissemination of the primary tumor, but neoplastic cells can also spread to contiguous structures after infiltration of perivascular spaces, and/or perineural spaces, the ependyma, and/or the choroid plexuses.<sup>[11,16,19,20]</sup> Both disturbances of the vascular endothelial microenvironment<sup>[2,9,22]</sup> and clonal subselection of metastatic cells may play a role in its pathogenesis, together with the potential protective contribution of the blood-brain barrier against systemic chemotherapy drugs.<sup>[3]</sup>

From the physiopathological point of view, as LMC is characterized by neoplastic infiltration of the pia-arachnoid membranes and the perivascular and perineural spaces, the typical clinical presentation usually includes cranial nerve involvement; nevertheless, dissemination through the CSF may lead to a diffuse or multifocal disease characterized by symptoms of meningeal irritation and/or intracranial hypertension due to hydrocephalus.<sup>[3,11]</sup> The development of cerebral ischemia secondary to narrowing of arterial vessels, in the context of LMC, is an extremely rare phenomenon. To the best of our knowledge, only five cases – excluding our patient's – have been reported to date [Figure 3 and Table 1].<sup>[6,7,10,14,21]</sup> To explain the pathogenesis of such an extraordinary event, several hypotheses have been formulated, including flow obstruction of small arteries by extrinsic (high subarachnoid neoplastic cell density) and/or luminal (neoplastic cell emboli) factors.<sup>[4,7,8,10,12,13]</sup> In our patient, once LMC was verified by biopsy, we interpreted the findings in the imaging tests as highly suggestive of vascular wall involvement of the right MCA and its branches by neoplastic cells [Figure 1] as the main mechanism triggering cerebral ischemia, despite the lack of direct pathological support, since biopsy of large caliber arteries was abandoned to avoid further severe complications in the patient. Vasospasm has also been suggested as a potential cause of the angiographic changes associated with LMC,<sup>[7]</sup>



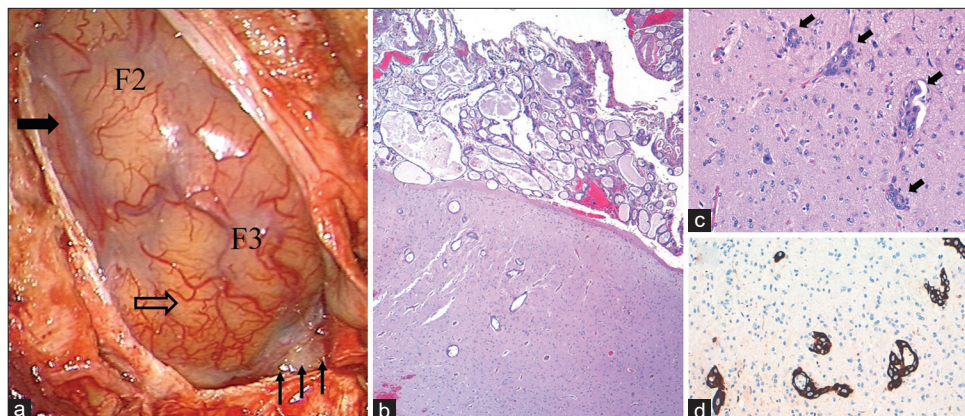
**Figure 1:** Diagnostic imaging gallery. (a and b) Emergent brain CT. (a) This baseline study shows cortical thickening with sulcus collapse in the right frontotemporal region (black arrows), and an area of low density involving the adjacent frontal white matter (white arrows). (b) Focal gyriform enhancement can be observed (white arrows) after the administration of intravenous contrast. (c-e) Coronal (c and d) and 3D (e) reconstructions of a cerebral CTA study obtained immediately (c and e) and 4 min after contrast administration (d). The former reveals a striking multisegmental luminal stenosis, with narrowing of the right middle cerebral arterial tree (white arrows in c and black arrows in e) and distal vascular occlusion (black arrows in c); the late-phase study (d) shows prominent contrast deposits (black arrows) in said arterial structures. (f-n) Preoperative brain MRI study. (f) Coronal slices corresponding to the FLAIR sequence that demonstrates an abnormally increased signal coating the opercular brain surface (black arrows) and the arterial vessels running through an unoccupied Sylvian cistern (transparent arrow); also notice the signal alteration involving the right insular, frontal, and temporal parenchyma (white arrows); (g) Coronal slice corresponding to FLAIR sequence obtained after administration of paramagnetic contrast. It demonstrates abnormally increased sign at the opercular brain surface (black arrows), and the arterial vessels through the Sylvian cistern (transparent arrow). (h-k) Diffusion-weighted MRI slices (h and j) displaying increased signal in the frontal lobe (black arrow in j), temporal, periventricular area (black arrow in h), and corpus callosum (white arrow in j); the two latter show signal restriction in the corresponding ADC maps (i and k), restriction periventricular area (black arrow in i) k) note the corresponding alterations in the frontal lobe (black arrow) and periventricular area (white arrow). (l-n) T1 sequence after the administration of gadolinium coronal sections is shown in a sequential, anteroposterior order – reveals irregular opercular and insular gyral enhancement (white arrows in l), diffuse and irregular thickening of the walls of the right middle cerebral artery from its origin (double-headed white arrow in m), a homogeneous uptake of both optic nerves (black arrows in l), and irregular enhancement in the corpus callosum (black arrow in n). (o-p) Control MRI study obtained after oncologic treatment; these coronal slices from the T1W sequence after administration of paramagnetic contrast, demonstrate no enhancement of previously affected structures with faint, apparently residual, and right frontal leptomeningeal uptake (white arrows in o).

so we cannot rule out that this dynamic process contributed to a certain extent to the cerebral ischemia developed by our patient.

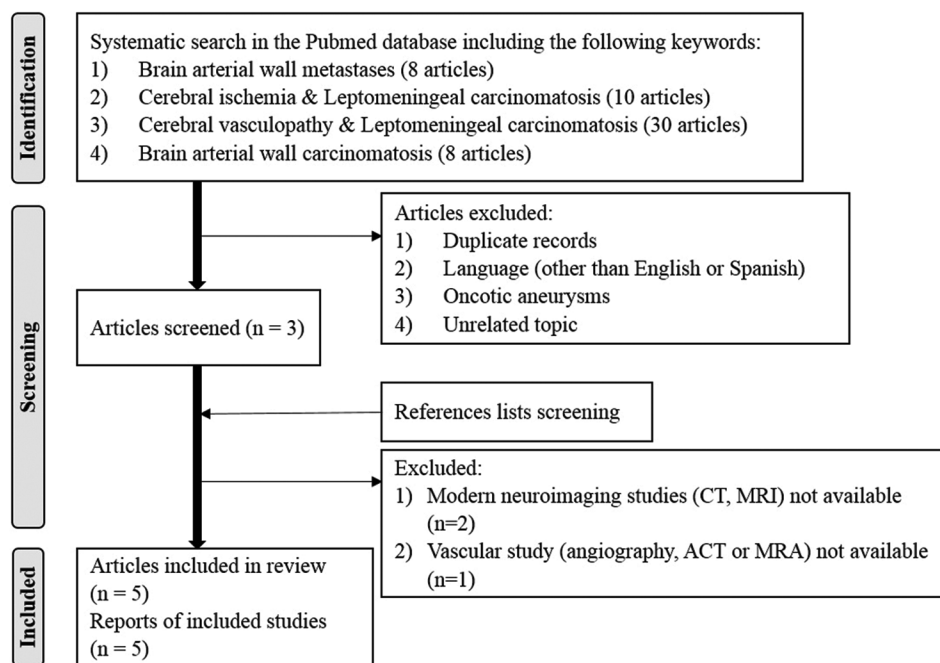
Despite the presence of characteristic findings in neuroimaging studies,<sup>[15]</sup> a definite diagnosis of LMC usually requires the demonstration of neoplastic cells in the CSF obtained by lumbar or ventricular puncture, with cytology being positive in up to 90% of cases.<sup>[20]</sup> However, the sensitivity of this test falls to 20% in cases similar to ours

[Table 1]. In our patient, the absence of even biochemical alterations in the samples of CSF obtained was striking and inescapably led to the performance of a brain biopsy. From a technical point of view, we recommend performing an open biopsy through craniotomy, and to obtain a sample that must include leptomeninges together with cortical and subcortical brain parenchyma, since needle biopsy could reveal only signs of brain ischemia without evidence of neoplastic infiltration, as occurred in the case reported by Klein *et al.* [Table 1]. It





**Figure 2:** Macro- and microscopic pathological findings. (a) Surgical photograph obtained after performing a right frontal craniotomy, with partial exposure of the second (F2) and third (F3) convolutions. The opercular area presents an apparently normal superficial vascular pattern (transparent arrow), while the dorsal area of the exposed surgical field presents a hypovascular appearance (solid arrow); note the opacity of the Sylvian cistern and some neighboring sulci that display a grayish-yellowish coloration (small arrows in the lower right margin). (b) Low magnification view of the biopsy specimen showing epithelial cell proliferation with glandular differentiation, together with diffuse leptomeningeal infiltration and multiple cortical neoplastic foci (HE,  $\times 4$ ). (c) At higher magnification, it is observed that the latter (arrows) are arranged inside spaces delimited by endothelium (HE,  $\times 20$ ). (d) Intense staining for cytokeratin 7, denoting the epithelial nature of the tumor cells (CK7,  $\times 20$ ).



**Figure 3:** PRISMA flow diagram summarizing the methodology employed in the literature review.

should be highlighted that, in the setting of a diffuse and vasculitis-like pattern of vascular involvement, pathological demonstration of LMC becomes even more important as the establishment of an ineffective treatment regime could potentially result in a fatal clinical course [Table 1].

Although the prognosis for LMC is dire,<sup>[3,20]</sup> the identification of molecular markers in response to specific chemotherapy drugs holds promise for improving survival expectancy<sup>[3]</sup> as we were able to observe in our patient who experienced a favorable initial response to treatment with capmatinib, a

**Table 1:** Cases of brain ischemia secondary to arterial involvement by leptomeningeal carcinomatosis published in the scientific literature.

Case	References	Age/sex	Presentation	Primary neoplasm	Imaging	CSF BQ/cytology	Biopsy	Treatment/outcome (F-U)
1	Klein <i>et al.</i> , 1989 <sup>[10]</sup>	47/F	C/Meningism, bradypsychia, dysphasia, L hemiparesis and hemihypesthesia	Adenocarcinoma (unknown primary)	Brain MRI: LMC, R parieto-occipital and corpus callosum infarction Angiography: L ACA narrowing	Mononuclear pleocytosis, ↓Gl, ↑Pr/ negative	Needle biopsy: ischemia, no malignancy Autopsy: LMC, arterial wall encasement and wall infiltration; multifocal infarctions in different stages	Steroids (suspected vasculitis)/dead (9 m)
2	Gutmann <i>et al.</i> , 1990 <sup>[6]</sup>	30/F	C/Headache, blurred vision, R hemiparesis, hemihypesthesia, and hemianopsia	Breast ductal carcinoma	Brain TC, MRI: LMC, L hemispheric patchy ischemia Angiography: L ICA, MCA and ACA narrowing	Normal white cell count, ↓Gl, ↑Pr/negative	Open biopsy (L parietal): LMC	Steroids (suspected vasculitis)/dead (3 m)
3	Herman <i>et al.</i> , 1995 <sup>[7]</sup>	54/F	A/Meningism, seizures, R III cn, L hemiparesis	Glioblastoma	Brain MRI: LMC, R MCA ischemia Angiography: R M1 and BA and BL PCA-SCA-AICA narrowing	Mononuclear pleocytosis, ↓Gl, ↑Pr/negative	Open biopsy (R temporal): LMC (GB) Autopsy: LMC, arterial branches encasement and wall infiltration	Steroids (suspected vasculitis), VPS/ dead (1 m)
4	Kastenbauer <i>et al.</i> , 2000 <sup>[8]</sup>	33/F	SA/Meningism, L VI, R VIII cn, paraparesis, urinary incontinence	Breast ductal carcinoma	Brain MRI: LMC, BL MCA, and ACA ischemia MRA: BL ACA and MCA narrowing	Mononuclear pleocytosis, ↓Gl, ↑Pr/positive	No	Intrathecal MTX, steroids, nimodipine/dead (days)
5	Sierra-Hidalgo <i>et al.</i> , 2009 <sup>[18]</sup>	42/M	A/Aphasia, R hemiparesis, unsteadiness	Lung microcytic carcinoma	Brain MRI: LMC, deep bilateral supratentorial ischemic foci; MRA: BL MCA and ACA narrowing	Pleocytosis, ↓Gl, ↑Pr/negative	No	ND/dead (ND)

(Contd...)

**Table 1:** (Continued).

Case	References	Age/ sex	Presentation	Primary neoplasm	Imaging	CSF BQ/ cytology	Biopsy	Treatment/ outcome (F-U)
6	Present case	76/F	C/Headache, unsteadiness, pseudosyncope	Lung adenocarcinoma	Brain MRI: LMC, R frontal, temporal, callosal ischemia CTA: R MCA narrowing and enhancement	Normal/ negative	Open biopsy (R frontal): LMC	Chemotherapy/ improved (4 m)

A: Acute (clinical symptoms for less than 1 day), ACA: Anterior cerebral artery, AGE: Age in years, BL: Bilateral, BQ: Biochemical analysis, C: Chronic (clinical symptoms lasting more than a month), cn: Cranial nerve dysfunction, CTA: Computed tomography angiography, d: Days, F: Female, F-U: Follow-up, GB: Glioblastoma, Gl: Glucose, ICA: Internal carotid artery, L: Left, M: Male, m: Months, MCA: Middle cerebral artery, MRA: Magnetic resonance angiography, MTX: Methotrexate, ND: Not described, PCA: Posterior cerebral artery, PICA: Posterior-inferior cerebellar artery, Pr: Proteins, R: Right, SA: Subacute (clinical symptoms for less than a week), SCA: Superior cerebellar artery, VPS: Ventriculoperitoneal shunt

potent selective inhibitor of the MET receptor that crosses the blood–brain barrier.<sup>[23]</sup>

## CONCLUSION

Infiltration of the wall of cerebral arteries by tumor cells is an extremely rare phenomenon that can lead to atypical clinical presentations. These may include ischemic events which, in the absence of other evidences of the underlying oncological disease or highly suggestive radiological signs, can either delay the diagnosis or lead to misdiagnosis, with a direct impact on the final clinical prognosis of the patient.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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## Conflicts of interest

There are no conflicts of interest.

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