



Intravascular carcinomatosis of the brain: a report of two cases

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Abstract

Although central nervous system (CNS) metastases are common in advanced cancer, CNS involvement solely by intravascular tumor cells, known as intravascular carcinomatosis, is extremely rare. We report two cases of brain metastasis in which tumor cells were restricted to the vascular lumina without parenchymal involvement, resulting in ischemic lesions. The first patient is a previously healthy young woman who presented with symptoms of community-acquired pneumonia and progressed to respiratory failure. Computed tomography of the brain showed infarcts of differing ages. At autopsy, she was found to have widely metastatic cervical squamous cell carcinoma and cerebral tumor emboli with multifocal infarcts, mainly microinfarcts. The second patient is an elderly man with cognitive impairment and mild Parkinsonism who presented with symptoms of a urinary tract infection. Magnetic resonance imaging of the brain showed atrophy and changes suggestive of chronic microvascular ischemic disease. Postmortem examination demonstrated prostatic adenocarcinoma and cerebral tumor emboli with multifocal infarcts. These cases illustrate that this pattern of intracranial metastasis may rarely be a cause of cerebral ischemic lesions and emphasize the importance of thorough pathologic examination of the brain.

Keywords Cerebral intravascular carcinomatosis · Infarct · Prostatic adenocarcinoma · Cervical squamous cell carcinoma · Autopsy

Introduction

Metastases are the most common central nervous system (CNS) tumors, accounting for approximately half of all intracranial neoplasms and increasing in incidence, usually seen at advanced stages of the malignancy with associated symptoms [1–3]. The reported 9–17% incidence of brain

metastases in patients with cancer is likely an underestimate as intracranial metastases have been found in up to a quarter of cancer patients in autopsy studies [1, 3, 4]. However, many of these studies are older, recent studies being difficult with decreasing autopsy rates [3, 4]. The most common malignancies to metastasize to the brain are carcinoma of the lung (accounting for approximately half of brain metastases) followed by breast carcinoma (13–30%) and melanoma (6–11%), which together account for the majority [3]. Brain

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metastasis may present as the initial manifestation of malignancy in over 10% of cases, most subsequently found to have a lung primary [2, 5]. The most frequent site of metastasis is the brain parenchyma, often at border zones between vascular territories especially between the middle and posterior cerebral arteries, and at the gray-white matter junction due to the decrease in vessel diameter, with 80% occurring in the cerebral hemispheres, 15% in the cerebellum and 5% in the brainstem [1, 2, 6]. Dural metastases have been seen in approximately 9% of patients with cancer, half showing isolated dural involvement, in one autopsy series [1, 4, 7]. They result from hematogenous spread or direct extension from the skull and are most often encountered in breast and prostate carcinoma [1, 7]. There is a similar incidence of leptomeningeal carcinomatosis in which diffuse infiltration of the pia and arachnoid is seen [4, 7]. Miliary metastasis, previously described as carcinomatous encephalitis, is an uncommon pattern of metastasis, usually of lung origin, that can mimic rapidly progressive dementia and demonstrates widespread tumor deposits in the Virchow–Robin spaces that may extend into the subpial space [1, 8, 9]. A very rare form of CNS involvement in which tumor cells are seen exclusively in the vascular lumina without parenchymal extension has been termed intravascular carcinomatosis [10–12].

Here we present two patients who showed multiple cerebral ischemic lesions on imaging with postmortem examination demonstrating CNS metastasis from cervical and prostate carcinoma limited to the intravascular compartment, raising awareness that multifocal ischemic lesions may rarely be a manifestation of metastatic disease and emphasizing the importance of careful brain pathologic examination.

Clinical summary and pathological findings

Case 1

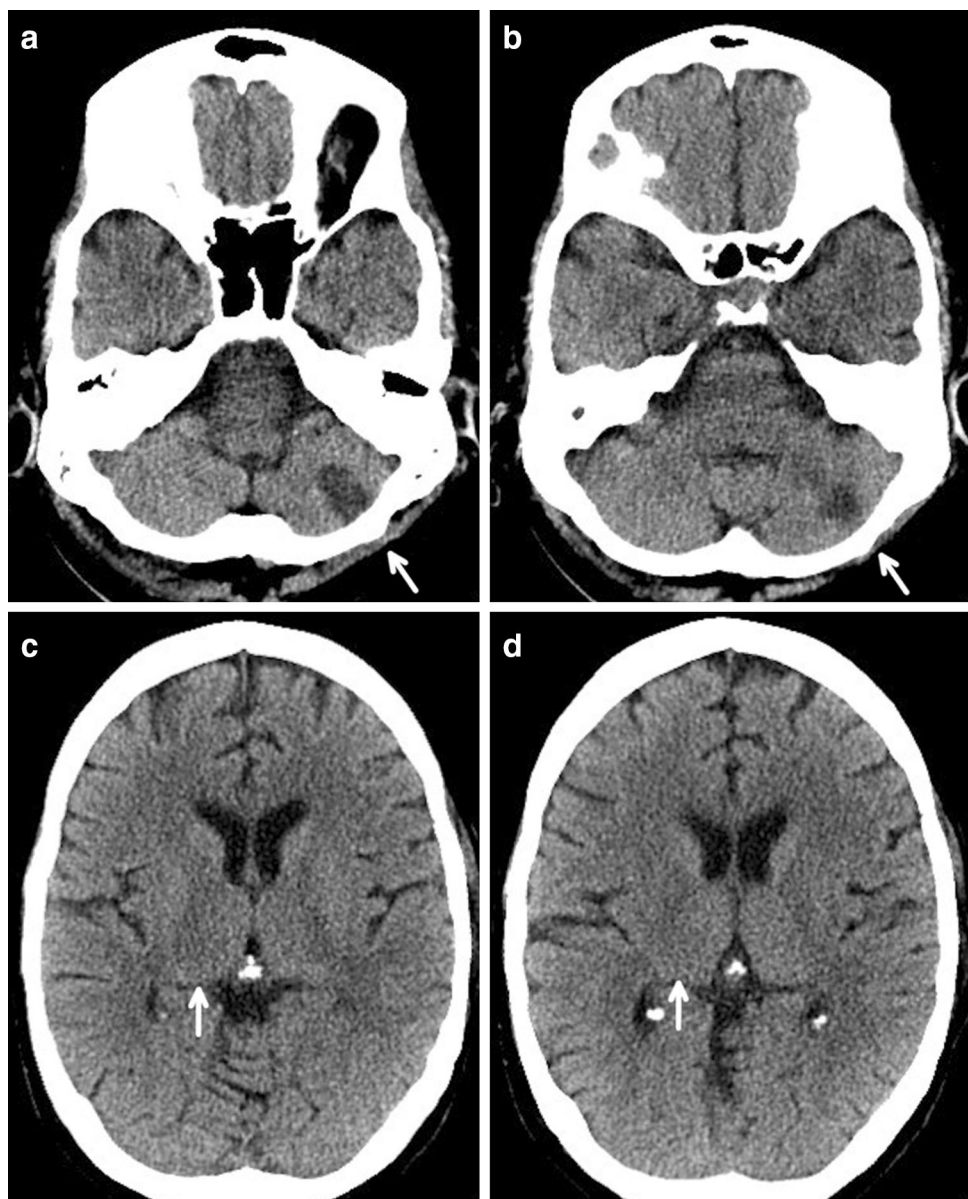
A 37-year-old woman was transferred for a 2-week history of progressive cough and dyspnea that did not resolve after completing a course of antibiotics for presumed community-acquired pneumonia. She had no significant past medical history except for uterine fibroids and two episodes of Methicillin-resistant *Staphylococcus aureus* skin abscess due to injury at work. Chest computed tomography (CT) showed multifocal airspace and ground-glass opacities in the periphery of bilateral lungs and reactive lymphadenopathy consistent with atypical pneumonia. She completed a course of intravenous antibiotics and was discharged on home oxygen. However, the patient was admitted to the intensive care unit at an outside hospital a few weeks later for progressive respiratory failure. An extensive infectious disease workup showed transient positivity for enterovirus/rhinovirus on

bronchoalveolar lavage PCR and subsequent positivity for *Candida albicans* in sputum, blood, and urine, and she was placed on broad-spectrum antibiotics and antifungals. Repeat chest CT showed extensive ground-glass opacities and development of cystic bronchiectasis. She had also been placed on steroids and undergone plasmapheresis for a possible autoimmune etiology, although evaluation for autoimmune disease, including serologic testing for anti-GBM, ANCA, ANA, and anti-dsDNA, was negative. As urinalysis showed hematuria and proteinuria, a renal biopsy was performed but was unremarkable with no evidence of vasculitis. CT of the head showed cortical atrophic changes, an old left cerebellar infarct (Fig. 1a, b), and more recent small right thalamic perforator infarct (Fig. 1c, d). The patient eventually required intubation and extracorporeal membrane oxygenation. She was placed on the waitlist for lung transplantation and started on cyclophosphamide, but developed multiorgan failure and died after being transitioned to comfort care, one month after admission.

Complete autopsy revealed heavy lungs with diffuse parenchymal hemorrhage, consolidation and necrotizing cavitory lesions throughout. The uterus showed a 7 cm hemorrhagic and necrotic myometrial mass in the anterior wall that was adherent to the bladder. On microscopic examination, the uterus (Fig. 2a), bladder wall, ovaries, lungs (Fig. 2b), and hilar/mediastinal and peripancreatic lymph nodes were involved by poorly differentiated squamous cell carcinoma with extensive necrosis. The liver showed intravascular and sinusoidal tumor cells with focal hemorrhage and necrosis. Immunohistochemistry was performed with the following antibodies: CK AE1/AE3 (Dako, mouse monoclonal, AE1/AE3, predilute), p63 (Dako, mouse monoclonal, DAK-p63, 1:100), p40 (Biocare, mouse monoclonal, BC28, 1:100), p16 (Roche, mouse monoclonal, E6H4, 1:5), CK7 (Dako, mouse monoclonal, OV-TL 12/30, 1:100), and CK20 (Dako, mouse monoclonal, Ks20.8, predilute). On immunohistochemistry, the tumor cells were positive for pankeratin AE1/AE3, p63, p40 (Fig. 2c), and p16 (Fig. 2d), patchy positive for CK7, and negative for CK20. The tumor was positive for HPV 16 on genotyping. The lungs demonstrated multiple metastatic deposits and extensive angiolymphatic invasion in a background of diffuse alveolar damage. There were also multifocal parenchymal infarcts with clusters of budding yeast and pseudohyphae morphologically consistent with *Candida* species on Gomori methenamine silver (GMS) stain (Fig. 2b, inset).

Gross examination of the brain showed no areas of encephalomalacia in the cerebral hemispheres or deep gray matter, and no lesions in the brainstem. There was an approximately 1 cm linear region of encephalomalacia in the left cerebellar hemisphere. No significant atherosclerosis was identified. On histologic sections, multifocal subacute to chronic infarcts (mainly microinfarcts) were seen in the

Fig. 1 Axial CT demonstrating an area of encephalomalacia in the posteroinferior aspect of the left side of the cerebellum (arrows) consistent with a previous remote left posterior inferior cerebellar artery infarct (a, b). Axial CT showing some decreased attenuation within the right thalamus (arrows) in keeping with a more recent right thalamic perforator infarct (c, d)



cortex, subcortical white matter (Fig. 2e) and cerebellum, with scattered cortical and subcortical microvessels containing luminal plugs of epithelioid cells showing enlarged, atypical nuclei (Fig. 2e, f) and immunopositivity for CK AE1/AE3 (Fig. 2f, inset), compatible with tumor emboli from squamous cell carcinoma.

Case 2

A 75-year-old man with a 7-year history of frontal predominant cognitive impairment and 4-year history of mild Parkinsonism with frequent falls, dysphagia and dysarthria, who was being followed for possible progressive supranuclear palsy, was admitted to an outside hospital for increasing weakness and fever, concerning for a urinary tract infection

(UTI). The patient had been placed on antibiotics for a possible UTI several weeks prior. He had a history of urinary frequency and nocturia attributed to benign prostatic hyperplasia but with recent elevated prostate-specific antigen (PSA) levels concerning for prostate cancer. However, he had declined further intervention. His past medical history also included recurrent venous thromboembolism with pulmonary embolism on warfarin, hypertension, hyperlipidemia, and coronary artery disease with stent placement. At the outside hospital, CT of the brain demonstrated no acute intracranial process. Portable chest X-ray was unremarkable. Laboratory testing showed creatinine of 0.80 mg/dL, hemoglobin of 9.5 g/dL, white blood cells of $5.8 \times 10^3/\text{mm}^3$, and platelets of $120 \times 10^3/\text{mm}^3$. Urinalysis showed proteins and ketones but was negative for leukocyte esterase and nitrites.

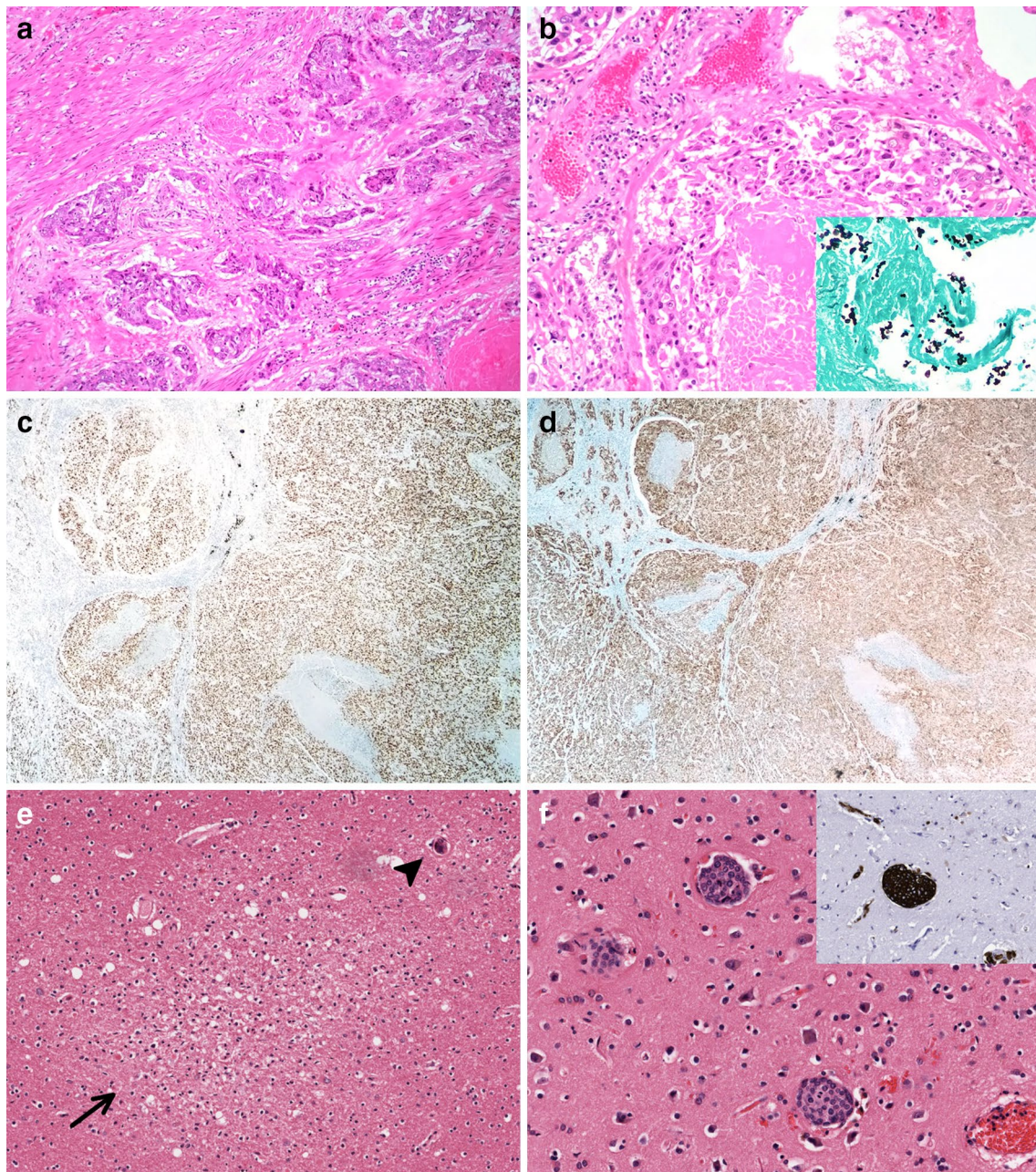


Fig. 2 Squamous cell carcinoma invading myometrium (**a**, $\times 100$). Left lung with metastatic squamous cell carcinoma with necrosis (**b**, $\times 200$) as well as fungal organisms morphologically consistent with *Candida* species on GMS stain (**b** inset, $\times 400$). Metastatic deposits in the hilar lymph nodes demonstrating immunopositivity for p40 (**c**, $\times 40$) and p16 (**d**, $\times 40$). Subacute microinfarct (arrow) with histiocytic infiltrate, neuroaxonal spheroids and gliosis with an adjacent

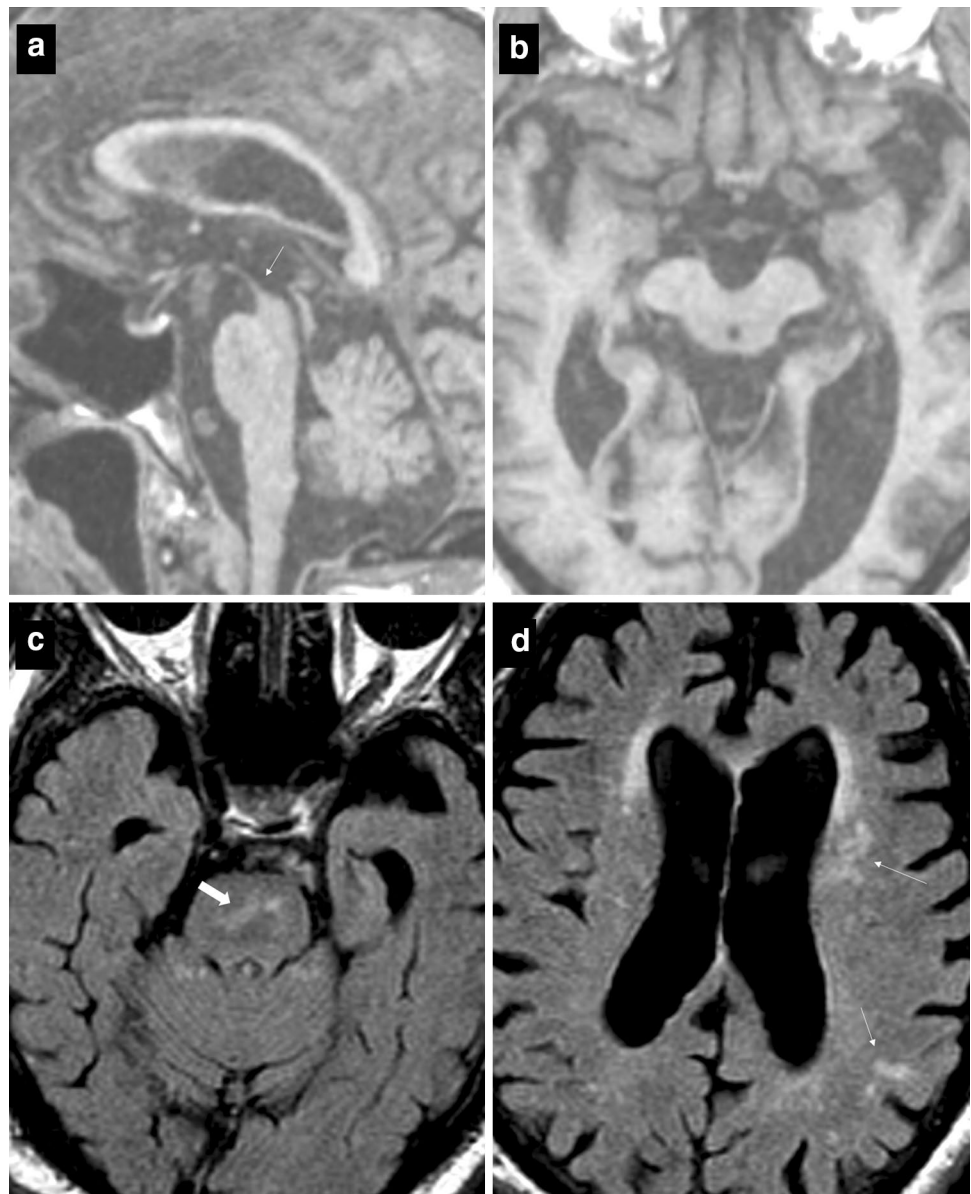
small vessel containing a cluster of tumor cells (arrowhead) in the subcortical white matter (**e**, 100x) and multiple emboli of squamous cell carcinoma in the cortex (**f**, $\times 200$), positive for CK AE1/AE3 on immunohistochemistry (**f** inset, $\times 200$), in the right middle cerebral artery/anterior cerebral artery watershed region. Note immunoreactivity of cells within adjacent capillaries

He was discharged to a skilled nursing facility for hospice care where he exhibited a rapid decline in mental status and minimal food intake and died one week after admission to the facility and one month after his hospital admission.

Magnetic resonance imaging (MRI) performed 2 months prior to his last hospital admission demonstrated cerebral

volume loss, especially in the frontal lobes, mild midbrain atrophy (Fig. 3a, b) on magnetization-prepared rapid gradient-echo (MP-RAGE) sequence, and patchy areas of fluid-attenuated inversion recovery (FLAIR) hyperintensity in the pons (Fig. 3c) and periventricular and subcortical white matter (Fig. 3d), suggestive of chronic microvascular ischemic

Fig. 3 Sagittal (a) and axial (b) MP-RAGE images demonstrating midbrain atrophy. On the sagittal image, this classic appearance of midbrain atrophy is known as the “hummingbird sign” (arrow). Axial FLAIR images (c, d) showing patchy areas of hyperintensity in the pons (thick arrow) and periventricular and subcortical cerebral white matter (thin arrows)



disease. Lumbar spine X-ray performed over 1 year prior to death showed moderate degenerative disc disease.

An autopsy limited to the brain and abdomen showed a nodular prostate with invasive adenocarcinoma with a Gleason score of at least 4 + 5 = 9 (Fig. 4a), with extensive autolysis. The gastrointestinal tract, liver, pancreas, spleen, adrenal glands, kidneys, and bladder showed no metastatic tumor. Examination of the brain showed a smooth dura with no masses or hemorrhage. There was mild cortical atrophy in the frontal lobes and mild hydrocephalus ex vacuo. No infarcts or masses were seen grossly. The substantia nigra and locus coeruleus were well-pigmented. The basal vasculature demonstrated moderate to severe atherosclerosis. Immunohistochemistry was performed with the following antibodies: A β 42 (EMD Millipore,

rabbit polyclonal, AB5078P, 1:150), A β 40 (EMD Millipore, rabbit polyclonal, AB5074P, 1:400), phospho-tau (Thermo Fisher, mouse monoclonal, AT8, 1:200), and PSA (Dako, rabbit polyclonal, A0562, 1:10,000). On microscopic examination, there were abundant tau-immunoreactive neurofibrillary tangles in the frontal cortex, hippocampus, basal ganglia, midbrain, pons, and dentate nucleus of the cerebellum, as well as tufted astrocytes and oligodendroglial coiled bodies, consistent with progressive supranuclear palsy. There was no evidence of significant amyloid plaques, as demonstrated by A β immunohistochemistry, to suggest changes of Alzheimer disease. Additionally, there were multifocal acute/subacute (Fig. 4b) and chronic microinfarcts in the cerebral cortex and subcortical white matter, basal ganglia, and brainstem

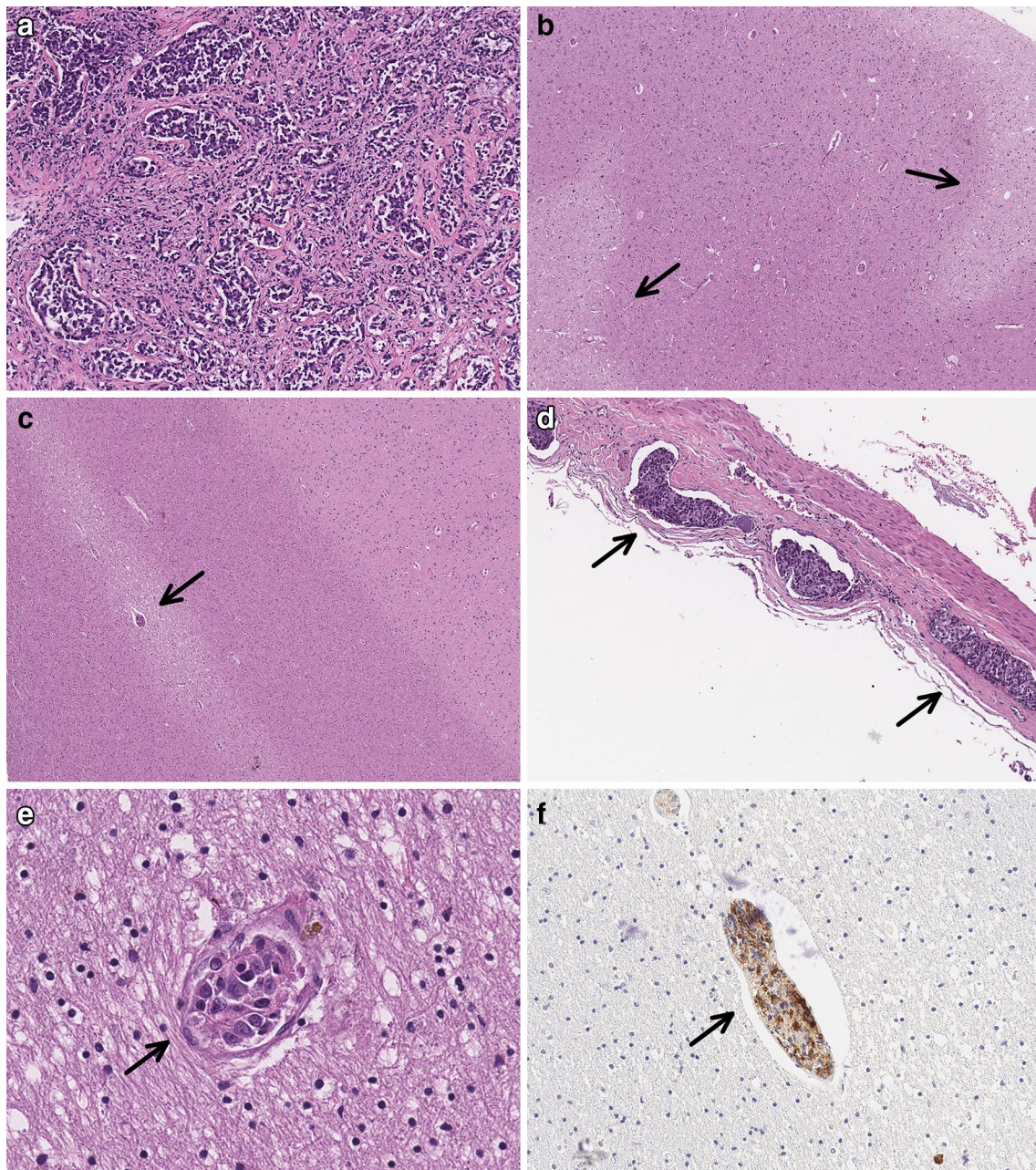


Fig. 4 Prostate with extensive involvement by high-grade prostatic adenocarcinoma (**a**, $\times 100$). Multifocal acute/subacute microinfarcts in the parietal cortex (arrows) (**b**, $\times 40$). Metastatic prostatic adenocarcinoma in a small vessel (arrow), with surrounding rarefaction in the subcortical white matter of the right frontal lobe (**c**, $\times 40$), and

within the vasa vasorum (arrows) of the right middle cerebral artery (**d**, $\times 100$). Intravascular tumor cells (arrows) with enlarged nuclei and prominent nucleoli (**e**, $\times 400$) positive for PSA on immunohistochemistry (**f**, $\times 200$)

with clusters of atypical epithelioid cells within multiple small vessels in the cortex, subcortical white matter, some with surrounding rarefaction (Fig. 4c), leptomeninges overlying the cerebellum, and vasa vasorum of the right middle cerebral artery (Fig. 4d). The cells demonstrated

enlarged nuclei with irregular nuclear contours, granular chromatin, prominent nucleoli, moderate amounts of eosinophilic cytoplasm (Fig. 4e), and were positive for PSA on immunohistochemistry (Fig. 4f), consistent with metastatic prostatic adenocarcinoma.

Discussion

The incidence of brain metastases is rising, likely due to the aging population, more effective treatments that prolong survival in patients with cancer, and improved detection techniques [2, 3], and is a significant cause of morbidity and mortality [13]. Two-thirds of metastatic lesions result in symptoms including headache, focal neurologic deficits, altered mental status, and seizures [2, 14]. Approximately 5–10% of patients may present with sudden stroke-like symptoms from hemorrhage into the tumor, especially in melanoma and renal cell carcinoma [13]. The majority of metastases reach the CNS through the hematogenous route; less frequently spread occurs in a retrograde manner along the nerves, especially in squamous cell carcinoma and salivary gland neoplasms of the head and neck [1, 2]. However, it is extremely rare to see CNS tumor involvement limited to intravascular spaces with only three cases reported in the literature [10–12]. The most recent report was in a 52-year-old female with a history of inflammatory breast carcinoma treated with right mastectomy and chemoradiation who presented with altered mental status; autopsy demonstrated multifocal areas of ischemic injury with tumor cells of breast origin occluding many capillaries throughout the brain [10]. This pattern has also been reported in a previously healthy 38-year-old female with acute onset of recurrent thrombotic disease including cerebral infarcts who was found on postmortem examination to have thrombosis of the right middle cerebral artery with luminal poorly differentiated adenocarcinoma of undetermined primary [11]. The third case is of an 84-year-old female who presented with acute bilateral ballism and at autopsy was found to have gastric adenocarcinoma with widespread intravascular dissemination involving lung, liver, pancreas, adrenal glands, and the cerebrum, cerebellum, and meninges with multiple infarcts in the cerebral hemispheres, cerebellum and brainstem [12]. Interestingly, all cases have been in patients with no known history of malignancy except for the patient with a history of inflammatory breast carcinoma, and all were in females except for our second patient in whom there was a suspicion for, but no diagnosis of malignancy.

On MRI, intra-axial metastatic lesions usually present as contrast-enhancing masses near the gray and white matter junction with the majority demonstrating T1 hypointensity, T2 hyperintensity and FLAIR hyperintensity, although hemorrhagic metastases show T1 hyperintensity [15]. Leptomeningeal metastases can be seen as pial enhancement along the sulci or basal cisterns, hydrocephalus or cranial nerve deposits while dural metastases may be difficult to differentiate from meningiomas as both show T1 hypointensity, homogeneous contrast enhancement and

dural tail sign [15]. Miliary metastases are often observed as numerous punctate lesions with contrast enhancement and T2 hyperintensity, usually without ischemic changes, mimicking infection such as tuberculosis, but may also be undetectable [1, 8, 9]. Isolated tumor emboli have manifested as multifocal infarcts in the patients with a history of breast carcinoma and adenocarcinoma of unknown primary [10, 11]. In the patient with gastric adenocarcinoma, CT brain was normal although limited by movement artifact [12]. Both of our patients also showed multifocal ischemic changes although they were subtle in our second case. Graus et al. also describe cerebral infarcts from tumor emboli, including metastases from breast and osteosarcoma occluding the middle cerebral artery, and tumor emboli and infarcts in two patients with squamous cell carcinoma, one with esophageal primary and the other with pharyngeal origin, but it is unclear if there were other sites of involvement [16].

This pattern of CNS involvement in which tumor cells are restricted to the intravascular compartment is reminiscent of intravascular large cell lymphoma (IVLCL), a rare type of lymphoma typically of B-cell lineage, in which malignant lymphoid cells proliferate almost exclusively within capillaries and small arteries and veins [17, 18]. This entity was previously referred to as neoplastic/malignant angioendotheliosis or angioendotheliomatosis proliferans systemisata, thought to be due to widespread malignant transformation of endothelial cells until the tumor cells were demonstrated to be of lymphoid origin [17–19]. The lack of adhesion molecules such as CD29 (integrin β 1) and CD54 (ICAM-1) has been suggested to underlie its predisposition for intravascular growth [20]. Adhesion molecules including VLA-4 (α 4 β 1) and ICAM-1 also play a key role in carcinoma metastasis, with tumor cells metastatic to the brain demonstrating elevated VLA-4 expression [21]. IVLCL has a predilection for the brain and skin for unclear reasons and also causes cerebral ischemic lesions in approximately half of cases [17]. It is difficult to diagnose, previously often only at autopsy, and important to keep in the differential of multiple cerebral infarcts [17].

Brain metastases from cervical carcinoma are rare but have been increasing, likely due to extended survival with improved therapies [7, 22]. The majority have presented as intraparenchymal masses, but they have rarely manifested as dural or leptomeningeal metastases, and appear to spread via the hematogenous route from the lungs, the most common site of metastasis, as was likely in our first case [7, 23]. Prostate carcinoma also rarely metastasizes to the CNS, with a predilection for the dura, possibly through retrograde spread through the valveless Batson venous plexus [1]. The degree of contribution of the tumor emboli and microinfarcts to the rapid mental decline in the second patient is unclear as he declined further workup or intervention. Although there was

no evidence of metastatic tumor elsewhere, the evaluation was limited as permission for postmortem examination was restricted to the brain and abdomen.

Our cases increase awareness of tumor emboli as a pattern of CNS metastasis. It often presents as multifocal ischemic lesions and is especially important to consider in unusual clinical presentations when extensive workup fails to reveal an etiology. Our first patient and the reported patient with unknown primary were both previously healthy young females in their late 30s with multifocal ischemic lesions in the brain [11]. The differential diagnosis may be broad in this setting, including inflammatory and infectious etiologies, but undetected malignancy, among other prothrombotic processes, should be considered, particularly as affected patients commonly do not have a history of a primary neoplasm. Ischemic lesions in cancer patients may be due to intravascular carcinomatosis in addition to malignancy-associated coagulopathy [11].

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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