

CASE REPORT

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Paraneoplastic vasculitis of central nervous system presenting as recurrent cryptogenic stroke

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Abstract We report the case of paraneoplastic vasculitis of the central nervous system associated with breast cancer. A 54-year old woman had a complete workup because of recidivant seizures. Magnetic resonance imaging (MRI) showed cerebral and medullary cryptogenic lesions, and a diagnosis of encephalomyelitis of unknown origin was made. She was treated with corticosteroids, but because of cognitive impairment and recurrence of epileptic seizures, she was finally transferred to our Neurology Department. The previous diagnosis was then changed, because a poorly differentiated invasive lobular breast cancer was discovered. Thoracic and abdominal computed tomography (CT) scans diagnosed pulmonary, pericardial, adrenal, and renal metastases. Because MRI findings did not fit with the diagnosis of brain metastases, a CT-guided cerebral biopsy was performed, and she was eventually diagnosed with paraneoplastic vasculitis of the central nervous system.

Key words Paraneoplastic · Vasculitis · Stroke · Cancer · Central nervous system

Introduction

Paraneoplastic syndromes are caused by mechanisms other than metastasis or any other complications ascribed to the tumor itself. They may sometimes reveal the malignancy and have important diagnostic implications.¹ Cerebral paraneoplastic vasculitis is an exceptional syndrome, which involves small or medium-sized vessels. Lesions are often small and disseminated, and clinical presentation is more

often a picture of diffuse acute or subacute encephalopathy rather than an acute focal deficit.² Cerebral paraneoplastic vasculitis is more frequently associated with hematological disorders,³ but may occur even with solid tumors, such as small-cell lung cancer, and renal and gastroenteric neoplasias.⁴

The pathogenetic mechanisms of these vasculitides are still unknown, but they are probably mediated by unknown immunological mechanisms associated with the tumor, such as the formation of immune complexes, direct antibody-mediated vascular effects on endothelial cells, or the direct effects of tumoral cells on the vascular wall.¹ The current concept concerning central nervous system (CNS) vasculitis is that the expression of neuronal proteins by a tumor provokes an immune response that possibly causes the neurological disorder. The best proof of immune reaction is the frequent detection of antineural antibodies in the serum and in the cerebrospinal fluid of these patients, even if the role of such antibodies remains unknown.⁵ Several studies suggest that tumor treatment is the main step in controlling, or at least stabilizing, the neurological involvement. Prognosis is generally bad even if specific treatment with steroids may give excellent response. Immunosuppressive therapies could be used for systemic vasculitic disorders, although the multiple adverse effects should be considered, and these effects make their administration a last resort.¹

Case report

A 54-year-old woman was admitted to the Neurology Department for recidivant seizures. The patient had been well until 5 months earlier when she began to have diffuse muscular and articular pain, associated with mild asthenia and intermittent fever. Routine blood tests and chest X-rays showed no abnormalities, and the symptoms were relieved with anti-inflammatory drugs. Two months before the current admission, she presented with a sudden, diffuse headache followed by dysarthria and generalised tonico-clonic seizures. At recovery, non-fluent aphasia was noted that

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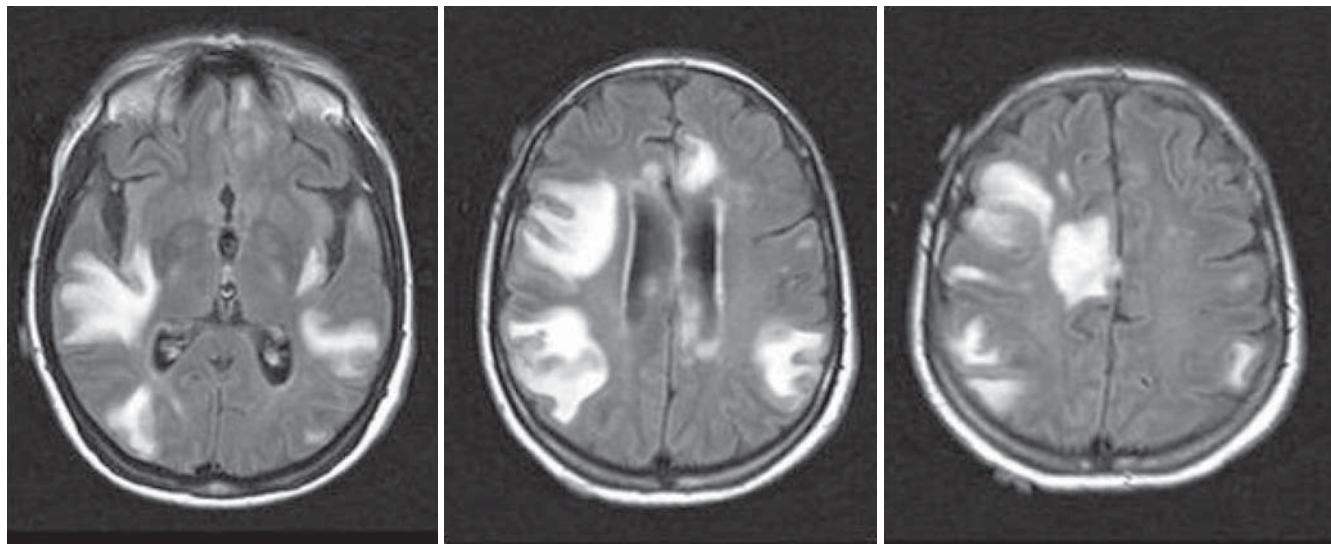
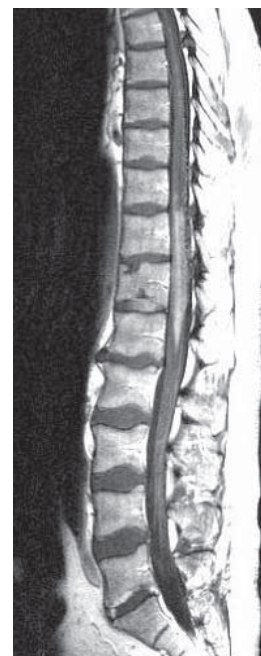


Fig. 1. Cerebral magnetic resonance imaging (MRI) scan obtained with fluid-attenuated inversion recovery (FLAIR) showing areas of hyperintensity in both cerebral hemispheres

persisted for a few days. A complete workup, including cerebral computed tomography (CT) scan, EEG, and routine biology found no abnormalities and the patient was discharged with oral valproic acid (500 mg three times daily). Two weeks later, she presented with a recurrent tonic-clonic seizure, which required intensive care unit (ICU) admission. Valproate was exchanged for intravenous phenytoin. Magnetic resonance imaging (MRI) showed left frontal and right fronto-parietal lesions, suggestive of ischemic strokes (Fig. 1). A second workup, including transesophageal echocardiography and screening for coagulation abnormalities, was normal. Antiplatelet therapy with clopidogrel was started. A week later, urine and fecal incontinence, perineum hypoesthesia, and progressive gait disorder appeared. Spinal cord MRI yielded a hyperintense lesion with gadolinium enhancement in the conus terminalis (Fig. 2). Cerebrospinal fluid (CSF) examination was normal, except for proteinorrhachia at 87 mg/dl (normal range, 15–45 mg/dl). A diagnosis of encephalomyelitis of unknown origin was suspected and corticosteroid treatment was started. The patient was transferred to a rehabilitation center and showed progressive improvement of her condition. Unfortunately, a few days after she had been transferred, cognitive impairment and gait worsening recurred. After a new epileptic seizure, the patient was referred to our hospital. Her vital signs were normal. Slight tumefaction was noticed in the left superior area of the right breast, with axillary adenopathies. Cardiac and pulmonary examinations were normal. The abdomen was unremarkable. No splenomegaly, cutaneous abnormalities, or digital clubbing were found. On neurological examination, she was alert but her cognitive function was impaired, showing severe global aphasia with parietal dysarthria. The optic fundus was normal. Cranial nerve functions revealed bilateral complete facial paresis and left IX, X, and XII palsies. Motor power tests yielded proximal and distal paresis in both limbs (3/5). Bilateral hyperreflexia (4/4) and indifferent plantar response were

Fig. 2. Sagittal FLAIR-MRI scan of lumbar spine with gadolinium injection, showing an area of abnormal increased signal within the conus terminalis



also noticed. Sensory, coordination, and walking examinations were not evaluable. Blood tests were normal. Cerebral and spinal cord MRI findings were unchanged. Lumbar puncture analysis and additional blood analyses are shown in Table 1. Mammogram confirmed a dense breast lesion, and fine-needle aspiration was performed under ultrasound control. Histological analysis showed poorly differentiated invasive lobular carcinoma without overexpression of hormone receptors or HEU/neu. Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 15–3 were within the normal limits. Thoracic and abdominal CT scans diagnosed pulmonary, pericardial, adrenal, and renal metastases. Cardiac echocardiography showed no valvular ab-

Table 1. Cerebrospinal fluid and blood analysis

| | |
|--|--------------------|
| Laboratory findings on lumbar puncture | |
| Appearance of fluid | Clear |
| Pressure (cm of water) | 12 |
| Red cells (per mm ³) | 1 |
| White cells (per mm ³) | 1 (lymphocyte) |
| Total protein (mg/dl) | 85 |
| Albumin (mg/dl) | 55 |
| IgG (mg/dl) | 8 |
| Agarose-gel electrophoresis | No banding |
| Glucose ^a | 60 |
| Microscopic findings | No micro-organisms |
| Culture | Negative |
| Test for <i>Borrelia burgdorferi</i> | Negative |
| Test for <i>Mycobacterium tuberculosis</i> | Negative |
| PCR test for <i>Herpes simplex virus</i> | Negative |
| PCR test for <i>Mycobacterium tuberculosis</i> | Negative |
| Antibodies anti-Hu and anti-Ri | Negative |
| Additional blood analyses (all normal) | |
| Antibodies | |
| – <i>Treponema pallidum</i> | |
| – Human immunodeficiency virus | |
| – Hepatitis B and C viruses | |
| – <i>Toxoplasma gondii</i> | |
| – <i>Borrelia burgdorferi</i> | |
| – <i>Herpes simplex virus</i> | |
| Immunoelectrophoresis | |
| IgA | |
| IgM | |
| IgG | |
| Cryoprotein | |
| Erythrocyte sedimentation rate | |
| Rheumatoid factor | |
| Complement (C3, C4, C1q, C50) | |
| Angiotensin converting enzyme (ACE) | |
| Autoantibodies | |
| – Antinuclear (ANA) | |
| – Anti-double stranded | |
| – Antineutrophil cytoplasmic antibodies (ANCA) | |
| – Antiphospholipid antibodies | |
| – Anti-Hu and anti-Ri | |

PCR, polymerase-chain reaction

^a Plasma glucose: 88 mg/dl

normality and no sign of bacterial or nonbacterial thrombotic endocarditis. Because MRI findings did not fit with the diagnosis of brain metastases, a CT-guided cerebral biopsy was performed. Several specimens were obtained and submitted for both routine pathological and microbiological analysis. The cerebral parenchyma was characterized by diffuse ischemia with tissue rarefaction and pyknotic neuronal nuclei. Microscopic findings showed small arteries surrounded by inflammatory infiltrates, which contained several perivascular and intravascular lymphocytes, with polyclonal phenotype. Granuloma and amyloid deposits were not found (Fig. 3). Histological stains for bacteria, fungi, virus, and acid-fast bacilli were negative. Concomitant renal biopsy was performed to evaluate the presence of the systemic vasculitic findings, and it showed no abnormality. This suggested that the disease was extended only in the CNS. A diagnosis of isolated paraneoplastic vasculitis of the CNS with subsequent ischemic strokes was then made. Despite receiving high-dose intravenous corticosteroid treatment, the patient died 2 weeks after this diagnosis was made.

Discussion

About 15% of patients with cancer have cerebrovascular lesions, resulting from different effects of the tumor on the CNS.⁶ In cancer patients, stroke can generally be due to a hypercoagulability state, nonbacterial thrombotic endocarditis (NBTE), or atherosclerosis. Other causes, such as non-metastatic cerebral venous thrombosis, tumor or infectious emboli, radiation-induced or granulomatous arteritis, and intravascular malignant lymphomatosis, are rarer.^{2,6} In cancer patients, the differential diagnosis of multiple ischemic involvement in both cerebral hemispheres and spinal cord with chronic and progressive evolution includes several pathologies. In the patient reported here, imaging and histological findings did not suggest cerebral metastases, which are a common cerebral complication in cancer patients and can mimic the clinical presentation of stroke. We could easily exclude carcinomatous meningitis, which usually presents with diffuse central and peripheral involvement of the nervous system, such as cranial nerve palsy, and is characterized by typical meningeal enhancement on MRI scans when gadolinium is injected, and by the presence of neoplastic cells on CSF histological examination. Infectious diseases, such as viral meningitis or encephalitis, tuberculous and fungal meningitis, or brain infarcts caused by *Mucor* and *Aspergillus* species have peculiar CSF and histological findings, which were not found in this patient. Infectious or NBTE was excluded by transesophageal cardiac echography and blood specimens; no hematological abnormalities such as disseminated intravascular coagulation or thrombotic microangiopathy were found.

Lymphocytic vascular damage associated with brain infarcts strongly suggested the possibility of vasculitic autoimmune disease. The absence of extracerebral involvement and the lack of high plasma titers of autoantibodies weighed against the diagnosis of systemic pathologies associated with vasculitis, such as sarcoidosis, Churg Strauss syndrome, polyarteritis nodosa, systemic lupus erythematosus, or Wegener's granulomatosis.⁷ In our patient, the vascular disease appeared to be limited strictly to the CNS, evoking the diagnosis of intravascular lymphoma or isolated vasculitis of the CNS. Intravascular lymphoma, characterized by the proliferation of lymphocytes with B-cell or T-cell markers within the lumen of capillaries, venules, or arterioles in the brain, was excluded because of the absence of specific microscopic findings on brain biopsy. Isolated vasculitis of the CNS was first described in 1959, by Cravioto and Feigin, who described eight patients who died of what they termed "noninfectious granulomatous angiitis".³ The disease, actually known as primary angiitis of the CNS (PACNS), although mostly seen in the brain, has also been associated with spinal cord lesions. Multiple ischemic events are secondary to a necrotizing process associated with the infiltration into vessel walls of lymphocytes, macrophages, plasma cells, and epithelioid cells.⁸ In the absence of diffuse necrotic damage of the vessel wall, the pathological findings in the present patient were compatible with the diagnosis of non-granulomatous vasculitis of the CNS. A definitive diagnosis

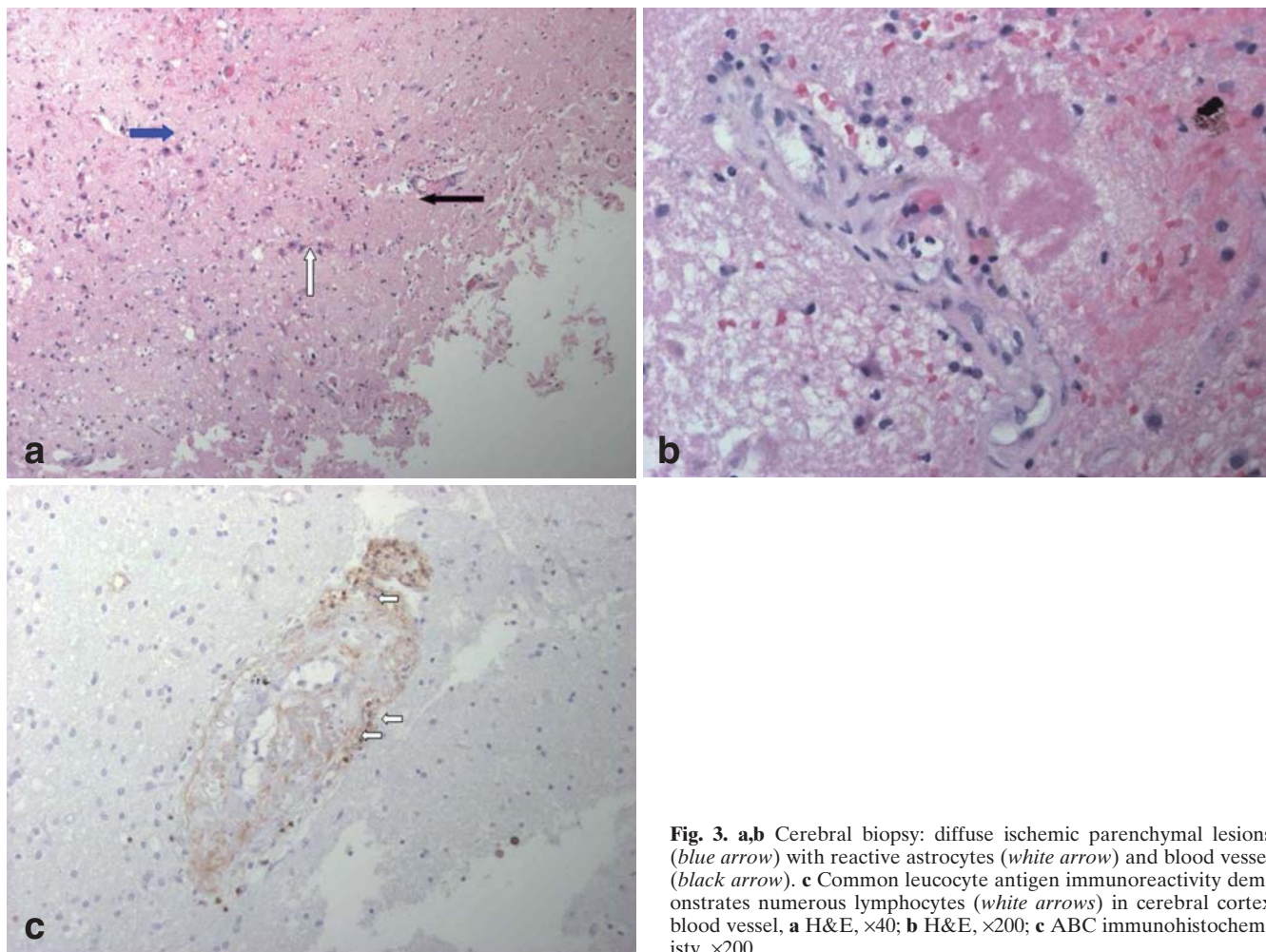


Fig. 3. **a,b** Cerebral biopsy: diffuse ischemic parenchymal lesions (blue arrow) with reactive astrocytes (white arrow) and blood vessel (black arrow). **c** Common leucocyte antigen immunoreactivity demonstrates numerous lymphocytes (white arrows) in cerebral cortex blood vessel, **a** H&E, $\times 40$; **b** H&E, $\times 200$; **c** ABC immunohistochemistry, $\times 200$

of vasculitis was given by cerebral biopsy,⁹ with findings of inflammatory infiltrate in the vessel wall without any sign of neoplastic or infectious origin. Medical research investigating the association between vasculitic disease and malignancies does not provide evidence that cancer is an etiologic factor in the development of these disorders,¹⁰ but the close temporal relationship of breast cancer and vasculitis in our patient suggested that the vasculitis could be considered as a paraneoplastic disorder.¹¹

Conclusions

In the medical literature we did not find other cases previously describing stroke in association with isolated CNS vasculitis as paraneoplastic disorder, although several articles have reported this association for systemic vasculitic disorders, like giant-cells arteritis, polyarterite nodosa or Wegener's granulomatosis.¹² The rarity of the association between cancer and vasculitis has led to scepticism about this syndrome being a paraneoplastic syndrome and, moreover, data from the literature enable us to identify clinical clues that might distinguish patients with cancer-associated

vasculopathies from those unaffected by malignancies. Nevertheless, patients with a cryptogenic cerebral infarct, which rapidly recurs despite optimal treatment, should be accurately investigated to eliminate, in differential diagnosis, the presence of an underlying malignant process, especially if clinical or biological evidence of disseminated intravascular coagulation is evident.

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