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MRI of non-neoplastic cranial complications of malignant disorders

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PURPOSE
To depict the well-known and atypical magnetic resonance imaging (MRI) findings of non-neoplastic central nervous system (CNS) complications of extra-CNS tumors and portray additional information from advanced techniques, such as diffusion and perfusion MRI.

MATERIALS AND METHODS
MRI scans of 92 patients were retrospectively evaluated based on the non-neoplastic effects induced by treatment or the remote effects of the tumor itself. Patients with brain metastases and/or patients who had whole brain radiation therapy were excluded so as not to take the primary radiation effects into consideration.

RESULTS
Sixteen patients (9 females and 7 males; age range, 11–68 years; median age, 45 years) had positive findings other than brain metastases. Six patients had posterior reversible encephalopathies, 3 patients had chemotherapy toxicity to the white matter, and 2 patients had acute strokes involving the posterior fossa and bilateral anterior circulation territory. Three patients had bilateral radionecrosis of the temporal lobe due to radiotherapy given for the vicinal tumor (nasopharyngeal carcinoma). One patient had encephalitis in the bitemporal region and one patient had cerebellar degeneration, each of whom had a paraneoplastic syndrome.

CONCLUSION
One of the major and noteworthy complications of malignancies directly affecting survival is brain metastasis, but non-neoplastic complications are infrequently encountered and are thus underestimated, either due to the absence of a true diagnosis or the lack of information pertaining to the clinical outcome. It is important for the radiologist to recognize these effects so as to help the clinician develop an optimal treatment strategy and avoid irreversible complications.

Key words: • *chemotherapy* • *radiotherapy* • *brain* • *magnetic resonance imaging* • *malignancy*

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The primary neuroimaging features in patients having extra-central nervous system (CNS) tumors other than brain metastases can be classified into three basic categories under the heading of non-neoplastic CNS manifestations: 1) direct toxicity of therapeutic agents; 2) radiation effects of the radiotherapy given primarily not to the brain, but to tumors located adjacent to the brain; and 3) remote effects of the primary tumor (so-called paraneoplastic syndromes). Direct toxicity includes white matter disease, the posterior reversible encephalopathy syndrome (PRES), and vascular effects resulting in either venous/arterial thrombosis or hemorrhage (1–4). Neurotoxic reactions secondary to radiation following whole brain radiotherapy due to primary or metastatic brain tumors are well-known (5) and are anticipated regarding the duration and high dose of the radiation given, but are not the focus here; rather, the unexpected and often missed late sequelae of nasopharyngeal radiotherapy affecting the temporal lobes by vicinity will be described. The paraneoplastic effects of the primary tumor, which are documented in detail with respect to their immunopathologic basis and recognized as paraneoplastic encephalitis, mainly involve the temporal lobes, but may be present in the brainstem and midbrain as well (6); cerebellar degeneration is occasionally seen. It is important to differentiate these non-neoplastic effects from metastases, or sometimes even from each other, since the therapeutic approach differs accordingly. To arrive at a definitive and comprehensive diagnosis, the radiologist should integrate imaging findings, clinical signs, and laboratory results together.

Materials and methods

Ninety-two oncology patients were referred to the magnetic resonance imaging (MRI) unit between January 2004 and May 2005 to exclude brain metastases due to variable neurologic symptoms. The most common symptom was headache, followed by vertigo, dizziness, nausea, cranial nerve palsies, unilateral paresthesias of the upper or lower extremities, orientation deficits, cognitive dysfunction, and acute onset of unconsciousness. The spectrum of malignancies included lung, breast, colon, stomach, prostate, ovarian, and nasophrayngeal carcinomas, malignant melanomas, retinoblastomas, and hematologic malignancies (leukemias and lymphomas). Patients who had a history of brain metastases and had whole brain radiation therapy due to metastatic tumors or for prophylaxis were not included in the evaluation.

MRI was performed on a 1.5 T or 1 T scanner (Signa Horizon Echo Speed and Signa Horizon High Speed, respectively; GE Healthcare, Milwaukee, Wisconsin, USA) using a standard head protocol for metastatic disease, including pre-contrast T1-weighted (T1W) (TR, 502 ms; TE, 13 ms; FOV, 240 mm; and NEX, 1) and fat-saturated T2-weighted (T2W) transverse (TR, 5000 ms; TE, 89 ms; FOV, 240 mm; and NEX, 2), T2W

coronal, pre- and post-contrast fluid attenuated inversion recovery (FLAIR) transverse (TR, 9000 ms; TE, 118 ms; FOV, 240 mm; and NEX, 1), post-contrast T1W in 3 orthogonal planes, and finally, diffusion-weighted images (DIW; b value, 1000 s/mm^2) complemented with apparent diffusion coefficient (ADC) maps. After the retrospective evaluation was completed, 16 patients (9 females and 7 males; age range, 11–68 years; median age, 45 years) had positive findings other than metastases and 76 patients had parenchymal (single or multiple) and/or meningeal metastases consistent with the symptoms. The primary malignancy spectrum of the patients with metastases was non-Hodgkin lymphoma (n = 4), breast carcinoma (n = 2), nasopharyngeal carcinoma (n = 2), acute lymphocytic leukemia (n = 2), small cell lung carcinoma (n = 3), colon carcinoma (n = 1), and ovarian carcinoma (n = 1). To facilitate the analysis of the imaging findings, final diagnoses were grouped under three main categories: 1) direct toxicity of the chemotherapeutic agents; 2) proximal radiation effects; and 3) paraneoplastic neurologic complications (Table 1).

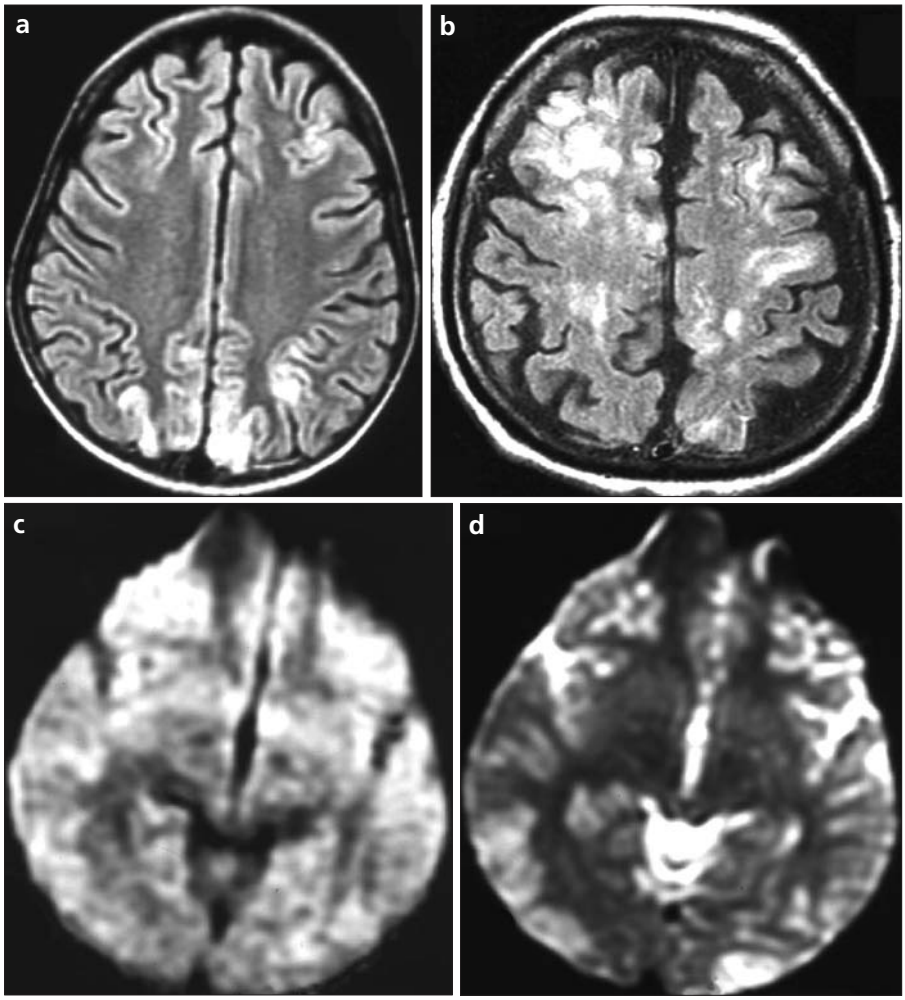

Figure 1. a-d. FLAIR transverse MR images **(a, b)** show cortical involvement in the parietal and frontal **(a)** and frontal and parietal **(b)** lobes of two different patients with posterior reversible encephalopathy syndrome who were diagnosed with acute lymphocytic leukemia and small cell lung cancer and treated with methotrexate and gemcitabine, respectively. Diffusion-weighted MR image **(**DWI; **c)** and apparent diffusion coefficient (ADC) map **(d)**. There is no restricted diffusion noted on the DWI and the corresponding ADC map.

Results

Six patients had findings consistent with a PRES in the direct toxicity group. The common symptom among all the patients was a severe headache. One patient had isolated occipital white matter edema represented by symmetric hyperintensity on the T2W images and FLAIR sequence. Two patients had widespread high signal changes on particular sequences in the posterior portions of the cerebral hemispheres, including the occipital lobes with both white matter and cortical involvement accompanied by cerebellar white matter edema, and three patients had additional frontal and parietal lobe lesions involving the cortex, which are atypical since PRES tends to affect the posterior portions of the brain (Figs. 1a, b). All of the patients with cortical edema had a recent onset of seizures and variable visual disturbances due to the effect on the occipital cortex. Three of six patients had high blood pressure at the time of the onset of symptoms. None of the lesions exhibited contrast enhancement after gadolinium injection. Diffusion was not restricted in any of the patients on DWI. Lesions were iso/hyperintense on DWI and slightly hyperintense on ADC maps due to a T2 shine-through effect (Figs. 1c, d). Two patients died following MRI, but all of the other patients recovered with near-normal MR scans during follow-up. Two patients with acute lymphocytic leukemia received intrathecal methotrexate for prophylaxis with no additional radiotherapy.

Three patients had leukomalacia secondary to chemotherapeutic agents with a variable time onset (i.e., subacute or chronic changes) on MRI; one patient had subacute changes with gait

Table 1. Non-neoplastic brain effects related to an extra-CNS tumor

Direct toxicity of the chemotherapeutic agents	Proximal radiation effects	Paraneoplastic effects
PRES	Bilateral temporal radionecrosis *(nasopharyngeal cancer radiation therapy)*	Encephalitis
White matter disease		Cerebellar degeneration
Vascular events *(Arterial/venous thrombosis and hemorrhage)*		

CNS, central nervous system; PRES, posterior reversible encephalopathy syndrome.

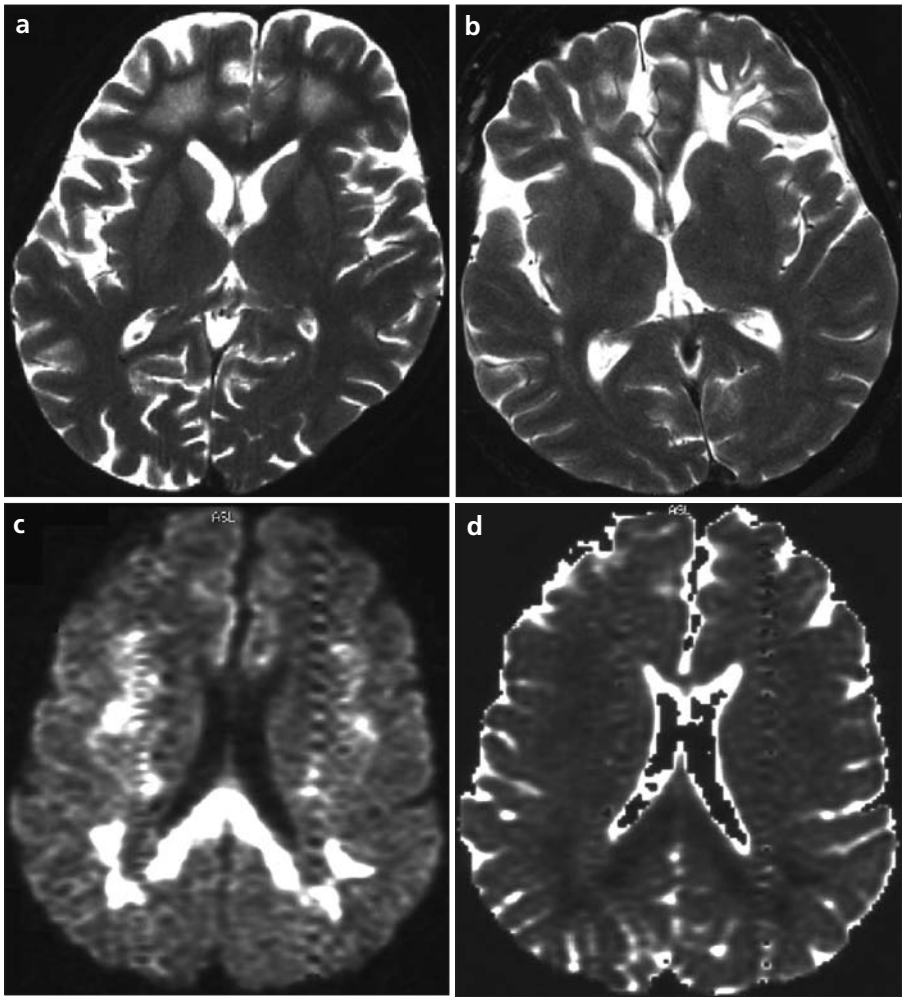

Figure 2. a-d. Transverse T2-weighted MR image **(a)** shows the early leukomalacic changes detected in the periventricular white matter in the frontal lobe of a patient with non-Hodgkin lymphoma treated with intrathecal methotrexate. Note the homogenous high signal sparing the subcortical U-fibers. In the late phase, prominent white matter loss accompanied by cystic encephalomacia is seen on the transverse T2-weighted MR image **(b)** of a different patient treated with paclitaxel-topotecan due to ovarian cancer. Restricted diffusion on diffusion-weighted MR image **(c)** and ADC map **(d)**, involving not only the periventricular white matter, but also the corpus callosum in a patient diagnosed with colon cancer and treated with 5-fluorouracil is demonstrated.

impairment and dementia-like symptoms, 1 patient with chronic changes had a gait disturbance and urinary incontinence, and one patient with chronic changes had progressive, severe confusion. The MR appearance was typical with periventricular, confluent, hyperintense signals on the T2W images and FLAIR sequence and restricted diffusion on the DWI in the early stages (Fig. 2). The subcortical U-fibers were characteristically spared. One patient had total corpus callosal involvement accompanied by periventricular white matter lesions. The patients who had serial imaging developed encephalomalacia within 3 months and the restriction of diffusion was discontinued and replaced with a T2 high signal due to cystic/encephalomalacic changes in the white matter. Generally, the chronic lesions did not show enhancement.

Two patients had acute strokes within hours following treatment. One patient was a 53-year-old female with breast cancer who was treated with paclitaxel and who developed small ischemic foci in the right cerebellar hemisphere, thalamus, and left middle cerebellar peduncle consistent with small caliber vessel involvement, subsequent to administration of intrathecal methotrexate for a suspected dural metastasis. The other patient was a 10-year-old boy who was treated with cyclophosphamide and who developed a serious acute stroke involving the anterior circulation with bilateral occlusion of the middle and anterior cerebral arteries (Fig. 3).

Three patients diagnosed and previously treated for nasopharyngeal carcinomas (all had the time of diagnosis at least 2 years before) were referred for a brain scan due to enhancing lesions suspicious for malignancy, which were partially included in the scan performed in the nasopharyngeal area to visualize the primary tumor site. All three of the patients had radiotherapy for their carcinomas, were in total remission, and free from any neurologic symptoms. The brain scans showed heterogeneous (cystic/necrotic parts centrally and gliotic/edematous areas peripherally), hyperintense areas on T2W, which were iso/hypointense on T1W. The lesions were located in the temporal lobe and showed intense and heterogeneous enhancement (Fig. 4a). The lesions were symmetric in 2 patients and asymmetric in 1 patient. A perfusion MR study was performed to exclude metastases, and the results revealed hypoperfused lesions (Fig. 4b) consistent with radiation necrosis secondary to the radiation therapy with extended safety margins, including the temporal lobes.

One patient showed signs of limbic encephalitis, which is typically limited to the hippocampus, but affected the insular cortex, revealing bilateral symmetric hyperintensity on the T2W images and FLAIR sequence with restricted diffusion. Cerebrospinal fluid cytology was negative for metastatic disease. The clinical signs were prominent cognitive decline accompanied by seizures.

One patient with breast carcinoma complaining of severe dizziness and ataxia was examined with the routine MRI protocol described above and no signs of metastasis were detected. The scan was normal, other than slight cerebellar atrophy. During the next two months, the MRI revealed the development of fast, progressive cerebellar atrophy consistent with paraneoplastic cerebellar degeneration consistent with the clinical signs (Fig. 5). All the patients diagnosed with one of the paraneoplastic effects had negative cerebrospinal fluid cytologies for malignant disease, but there was no evidence of antineuronal antibodies.

The patients' demographic data, MRI characteristics of the lesions, and the probable etiologies are summarized in Table 2.

Discussion

Non-neoplastic neurologic complications related to malignancy may be life-threatening, reversible, or even stable, and the continuum which exists between the loss of the patient and recovery without any sequelae deserves attention in terms of establishing a correct and comprehensive diagnosis. MRI plays an important part of this process and gives the opportunity for a fast and non-invasive diagnosis.

The most common complication, according to our retrospective data, was PRES, which was considered a disease of patients with renal disorders in the past as it was strongly linked to hypertension and metabolic dysfunction secondary to kidney failure (1). In the recent literature, however, direct toxicity of chemotherapeutic agents or tumor lysis affecting the kidneys increase the risk of patients for PRES during the course of malignancy (1, 7–10). The term was first used by Hinchey et al. (11), suggesting reversibility upon control of hypertension and the tendency to involve the posterior parts of the brain, particularly the cerebellum and the occipital lobes. Yet, some sources consider this terminology as a misnomer since the lesions are not always reversible and are not necessarily

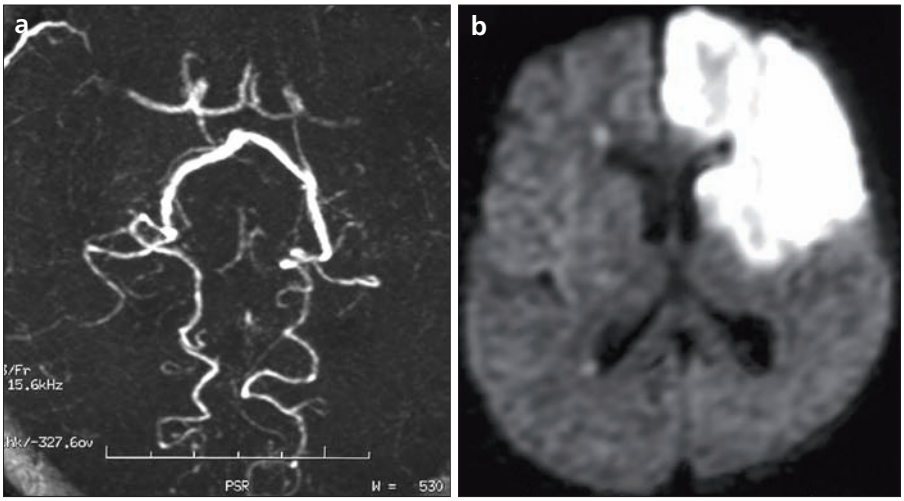

Figure 3. a, b. MR angiography **(a)** obtained with 3D-TOF sequence shows the bilateral occlusion of both middle and anterior cerebral arteries, with a severe stroke affecting the anterior circulation territory, demonstrated on diffusion-weighted MR image **(b**; right cerebral involvement is not shown here**)**, in a patient detected right after cyclophosphamide infusion.

Table 2. Patient details, MRI findings, and causative factors

Patient	Malignancy	MRI diagnosis	Lesion location	Cause
11F	ALL	PRES	Cerebellum, occipitoparietal cortex, and subcortical WM	Methotrexate (it)
56M	Small-cell lung cancer	PRES	Cerebellum, occipitoparietofrontal cortex, and subcortical WM	Gemcitabine
14M	NHL	PRES	Cerebellum, occipitoparietal cortex, and subcortical WM	CHOP
11F	NHL	PRES	Occipital cortex and subcortical WM	CHOP
21F	ALL	PRES	Occipital subcortical WM	Methotrexate (it)
54F	Small-cell lung cancer	PRES	Cerebellum, occipitoparietofrontal cortex, and subcortical WM	Cisplatin
53F	Breast	Acute ischemia	Cerebellum, cerebellar peduncle, and thalamus	Paclitaxel/methotrexate (it)
10M	NHL	Acute ischemia	Bilateral anterior circulation territory	Cyclophosphamide
68M	Colon cancer	WMD	Bilateral periventricular WM and corpus callosum	5-fluorouracil
35M	NHL	WMD	Bilateral periventricular WM	Methotrexate (it)
48F	Ovarian cancer	WMD	Bilateral periventricular WM	Paclitaxel/topotecan
50F	Small-cell lung cancer	PNE	Bilateral hippocampus and amygdale	Antineuronal antibodies?
53F	Breast cancer	PNCD	Cerebellum	Antineuronal antibodies?
62M	NF cancer	RN	Bilateral temporal lobe	Radiation therapy
42M	NF cancer	RN	Bilateral temporal lobe	Radiation therapy
40F	NF cancer	RN	Bilateral temporal lobe	Radiation therapy

F, female; M, male; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin lymphoma; NF, nasopharynx; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; WMD, white matter disease; PNE, paraneoplastic encephalitis; PNCD, paraneoplastic cerebellar degeneration; RN, radiation necrosis; WM, white matter; it, intrathecal; CHOP, cyclophosphamide/doxorubicine/oncovine/prednisone therapy.

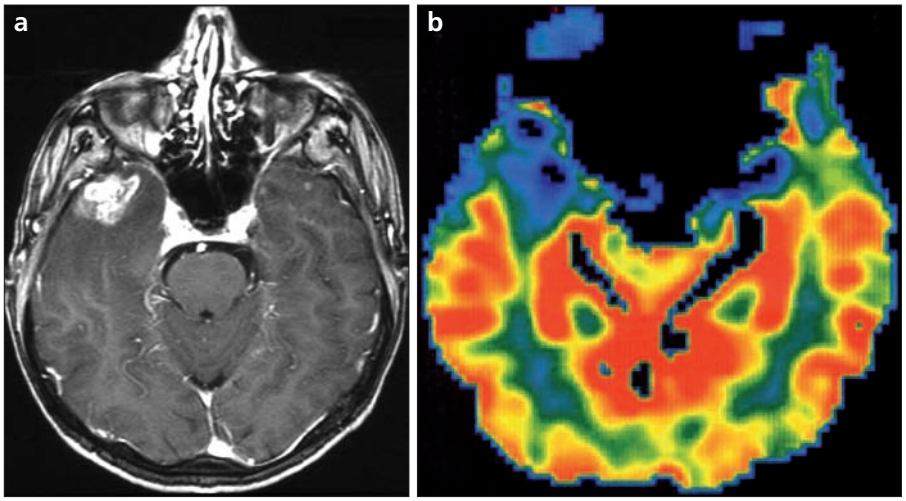

Figure 4. a, b. Post-contrast transverse T1-weighted MR image **(a)** shows bilateral (left is not shown here) radionecrosis in the temporal lobe of a patient treated for nasopharyngeal carcinoma 2 years ago. Perfusion MR study **(b**; obtained with echo-planar-imaging gradient-echo sequence**)** reveals the hypoperfused nature of the radionecrosis, differentiating it from a space-occupying malignant lesion.

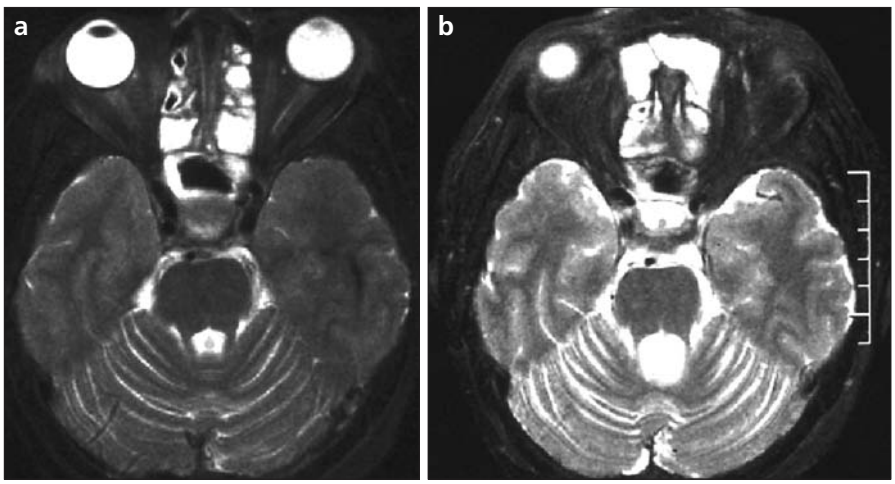

Figure 5. a, b. Transverse T2-weighted MR images taken one month apart **(a** and **b**, respectively) show the prominent cerebellar atrophy characterized by white matter loss and enlargement of the 4th ventricle. The final diagnosis was paraneoplastic cerebellar degeneration due to breast carcinoma.

confined to the posterior regions, but may also affect the frontal or parietal lobes (12) (Table 3). Reversible posterior leukoencephalopathy syndrome and hypertensive encephalopathy are commonly used as synonyms, but imaging studies have shown that gray matter (cortical) involvement accompanies the white matter changes in up to 94% of the patients, so the term posterior reversible encephalopathy is preferred (12). Chemotherapeutic agents could damage the blood-brain barrier by direct toxic effects on the vascular endothelium, vasoconstriction caused by elaboration of endothelin, or by inducing microthromboses (11). This direct toxicity may explain why PRES is more frequently noted in intrathecal chemotherapy applications and in patients without underlying hypertension during the onset of the disease. Yet another physiopathologic explanation for PRES is tumor lysis, which is attributable to acute tubular necrosis (8). On MRI, edema is typically demonstrated with a symmetric distribution, although asymmetry is not rare. Diffusion is not restricted in the affected areas and this is the most important clue in differentiating PRES from acute ischemia, especially in asymmetric and cortical dominant lesions, which may be confusing. Contrast enhancement is not expected, but it is reported that MR examination performed right after the onset of the seizures may reveal some degree of contrast enhancement as the breakdown in the blood-brain barrier continues, which is supposed

Table 3. Lesion location, symmetricity, and MRI signal characteristics, including contrast enhancement pattern and diffusion restriction

Lesion	Location	MRI signal	CE	DWI
PRES	Occipital=cerebellum≥parietal≥frontal≥brain stem; white matter ± cortex Usually symmetrical	T1W iso/hypo T2W hyper FLAIR hyper	None (may be + if BBB break still exists)	Not restricted (may be + if BBB break occurs)
WMD	Periventricular white matter (Subcortical U-fibers spared) Symmetric	T1W iso/hypo T2W hyper FLAIR hyper	None	Restricted (early phase)
PNE	Temporal Usually symmetric	T1W iso/hypo T2W hyper FLAIR hyper	+ subtle	Restricted ±
RN	Always limited to the affected portion of the brain Usually symmetric	T1W iso/hypo T2W hyper FLAIR hyper	+ intense heterogenous	Restricted ±
Acute ischemia	Depends on the artery involved Not symmetric	T1W iso/hypo T2W hyper FLAIR hyper	None (± if early subacute phase)	Restricted

MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; WMD, white matter disease; PNE, paraneoplastic encephalitis; RN, radiation necrosis; T1W, T1-weighted image; T2W, T2-weighted image; FLAIR, fluid attenuated inversion recovery; CE, contrast enhancement; BBB, blood-brain-barrier; DWI, diffusion-weighted image.

to be transient and persist a very short period of time (12, 13). Accompanying ischemia and/or hemorrhage also occur occasionally and with the above-described contrast enhancement, predicts a poorer outcome (12). Ischemia complicates the situation if PRES is left untreated as massive edema induces impairment in the microcirculation due to an elevated tissue perfusion pressure (1, 12). Thus, early recognition followed by timely treatment is crucial, even with simple cautions, such as discontinuation of the offending chemotherapeutic agent, controlling the hypertension, and administering anticonvulsive/antiedema therapy (11). Many drugs are known to be responsible for PRES individually, but combined agents, particularly as used in the treatment of hematologic malignancies, are also reported to be a causative factor (Table 4) (3, 8, 12, 14, 15).

White matter toxicity due to drugs is known as treatment-induced leukoencephalopathy and occurs frequently, especially in patients with lymphomas who are treated with methotrexate (16–18). Other chemotherapeutic agents reported to cause leukoencephalopathy are listed in Table 4 (1, 17–20). Symptoms of neurotoxicity usually develop a median of 1 month after completion of treatment, although it has been reported that symptoms and neuroradiologic findings do not always correlate (16, 18). Thus, PRES and vascular events are acute situations compared to white matter toxicity, which seems to result from the cumulative effect of specific drugs. MRI findings can be classified in 3 groups (grades I-III) according to the National Cancer Institute, version 3.0 (1), which describes the high T2 signal intensity in the periventricular white matter based on severity (T2 hyperintensities: focal periventricular [grade I], focal periventricular extending to the centrum semiovale [grade II], and confluent total white matter [grade III]). Varying degrees of white matter loss characterized by enlarged subarachnoid spaces and ventricular enlargement always occurs. Signal intensity spares the U-fibers which is very specific to the condition. Sparing of the corpus callosum, as with the subcortical U-fibers, is the expected pattern, although one of our patients showed diffuse callosal involvement, which is very rare (1). Imaging findings change with time when an acute onset demonstrates diffusion restriction, which may be attributable to demyelination and axonal loss histopathologically (18), but as chronic changes stabilize, gliosis and encephalomalaica develop and result in the loss of high signals on diffusion-weighted series and higher T2 signal occurrence, which was observed in a patient with non-Hodkin lymphoma by serial MRI (Table 3). The symptoms may be predominantly due to impaired cognitive function, as well as gait disturbance and urinary incontinence (16, 18).

Vascular effects, such as venous thrombosis, arterial occlusion, and hemorrhage, have been associated with the use of various antineoplastic agents, specifically cisplatin (2, 21, 22). A review of the literature regarding the untoward vascular events associated with chemotherapeutic agents revealed that neurovascular toxicity does not dominate compared to the other parts of the body and venous thromboses account for a substantial portion of the cases (2, 23–26). Acute stroke is the main focus here, as the 2 patients described in this study were diagnosed with acute ischemic changes immediately after the intravenous administration of chemotherapy. Small caliber vessels were affected in the first patient, as indicated by small foci of infarcts in the posterior circulation territory, without any evidence of arterial occlusion on MR angiography. She was given an intravenous paclitaxel infusion for breast carcinoma and intrathecal methotrexate due diffuse dural thickening and enhancement, which might be compatible with dural metastasis; she was diagnosed with multiple foci of small infarcts immediately after the initial intrathecal drug application. Methotrexate was thought to be responsible for the adverse effect rather than paclitaxel, since methotrexate, particularly when administered intrathecally, has been reported to cause vascular events (4, 21). Further, the patient developed ischemic changes while she was having paclitaxel treatment, although there has been no association between stroke and paclitaxel reported (Table 4) (1, 4, 21–27). The other patient had both middle cerebral arteries occluded, evident on MR angiography, with large infarcts affecting both cerebral hemispheres; the patient died shortly after the MR examination. Cyclophosphamide, which is known to cause vascular events in cancer patients, was administered just before the occurrence of the stroke (27). The mechanism underlying cyclophosphamide-induced vasculopathy is thought to be direct toxicity on the vascular endothelium, which is similar to the physiopathology underlying PRES (4). It has also been reported that vasospasm develops in the smooth muscle of the outer layers of the arterial wall that are directly exposed to the agent rather than from a bloodborne route, especially following intrathecal drug applications (4). The differential diagnosis should include paraneoplastic microangiopathy, which is pervasive, rather than limited to the CNS and is a chronic process (28). Acute stroke may also be an independent condition without any relation to the chemotherapy or tumor itself in patients with athreosclerosis or vasculitis, but the onset of stroke within

Table 4. Agents that can induce PRES, WMD, and vascular events

PRES	WMD	Vascular events
Cyclosporine	Methotrexate	Cisplatin
Cytarabine	5-fluorouracil	Bleomycin
Cisplatin	Topotecan	Etoposide
Methotrexate	Cisplatin	Vinblastine
Gemcitabine	Cytarabine	Methotrexate
Paclitaxel	Carmustine	Cytarabine
Cyclophosphamide	Thiotepa	Tamoxifen
Combined therapy (CHOP, CVP)		L-asparaginase
Tacrolimus		Cyclophosphamide
Interferon alpha		Paclitaxel
Steroids (high dose)		

PRES, posterior reversible encephalopathy syndrome; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone therapy; CVP, cyclophosphamide, vincristine, prednisone therapy; WMD, white matter disease.

hours following chemotherapy is suspicious if the patient has no clinical signs of microvascular disease. Late sequelae of nasopharyngeal carcinoma treated with radiotherapy as radionecrosis of the temporal lobes may infrequently be seen, and although a neuroradiologist can easily recognize the process, a diagnostic challenge exists in differentiation from a space-occupying lesion. Radiation therapy of head and neck cancers can result in unwanted effects of neighboring tissues when the temporal lobes are affected by nasopharyngeal carcinoma located within the safety margins. Many tumors, such as pituitary macroadenomas and clival chordomas, which are in close proximity to the brain, require radiotherapy, yet because of their benign behaviour, the dose of radiation is lower than the dose given to nasopahryngeal carcinoma (≤50 or ≤60Gy vs. >70 Gy). Moreover, the safety margins are narrower. Thus, no other head and neck tumor seems to result in radiation necrosis in the vicinal brain tissue. The affected areas are the temporobasal lobes, which usually show a symmetric pattern close to the parasellar region, having the typical gliotic-necrotic signal intensity with heterogenous contrast enhancement and irregular borders. Brain metastasis secondary to nasopharyngeal carcinoma is uncommon, and the temporal lobe lesions almost always occur in patients in total remission and pertain to the primary tumor without any evidence of neurologic abnormalities. With the given patient profile, MRI findings should address radionecrosis, and confirming the diagnosis should be made by an additional perfusion MR study, which has the ability to differentiate a malignant lesion, either a primary glial tumor or metastasis (5).

Paraneoplastic syndromes (remote effects of cancer), which are detectable with MRI include encephalitis and cerebellar degeneration. The dominant causative primary cancers are small cell lung cancer followed by gastrointestinal and genitourinary cancers (ovary/renal/uterus), Hodgkin lymphoma, breast cancer, and testicular cancer (6). Paraneoplastic limbic encephalitis is an uncommon disorder and the clinical diagnosis may be challenging since the clinical markers are often lacking and symptoms usually precede the diagnosis of cancer or mimic other complications. Antineuronal antibodies, which are diagnostic, are present in but 50%–60% of affected patients group; the two affected patients in the current study were seronegative for antineuronal antibodies (6, 29). The typical MR appearance is characterized by bilateral hippocampal involvement, patchy contrast enhancement, and restricted diffusion, as expected in any kind of encephalitis despite the etiology. Atypical forms may show extension to the insula, gyrus cinguli, or subfrontal cortex, or involvement of the thalamus may occur in testicular carcinoma. Lack of hemorrhage is the main clue in differentiating from paraneoplastic limbic encephalitis from herpes encephalitis as the lesions are limited to the hippocampus and amygdala (6).

Paraneoplastic cerebellar degeneration (PNCD) is a rare, but well-known entity, depending on the typical cerebellar signs occurring during the course of the disease or as a manifestation of an occult underlying carcinoma, particularly of ovarian or breast origin. PNCD is also believed to be immune-mediated and high titers of autoantibodies directed against both neurons (particularly Purkinje cells) and the tumor have been detected in the patient's serum and cerebrospinal fluid in some forms of this syndrome (30). PNCD is associated with anti-Yo antibodies in middle-aged women with ovarian or breast cancer, and with anti-Hu antibodies in middle-aged men or women with risk factors for lung cancer (31). Not all patients presenting with PNCD and its clinical features have recognizable antineuronal antibodies; however, this does not exclude the likelihood of malignancy. The onset of PNCD symptoms can be very rapid or gradual; symptoms begin with the acute onset of cerebellar dysfunction, which evolves over days-to-weeks (30, 31). It may be difficult to specify the condition with MRI, as the only sign would be atrophic features affecting the posterior fossa. Even if the cerebellar signs make the diagnosis likely, MRI diagnosis may only be made by serial imaging demonstrating the rapid time course changes in the posterior fossa. There are no such reports regarding the development of progressive cerebellar atrophia within weeks as detected by MRI in the literature, which allowed us to make the definite diagnosis for the patient described in the current study. In more than 60% of the patients, primary disease remains occult at the time of the diagnosis of the paraneoplastic event, although our patient developed cerebellar degeneration right after she was diagnosed with breast carcinoma (30, 31).

Non-neoplastic cranial complications of malignant disease are infrequently addressed in the extant literature. The data provided herein is valuable because all of the complications are covered in their entirety, regardless of the varying pathogenesis, and focus on the imaging findings supported with the latest MRI advances covering typical and atypical forms together. MRI is thus the *sine qua non* for the understanding and awareness facilitating the correct diagnosis and developing optimal treatment strategies for cancer patients with non-neoplastic cranial complications.

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