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ORIGINAL ARTICLE

MRI of central nervous system abnormalities in childhood leukemia

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PURPOSE
To document the imaging abnormalities seen in the central nervous system (CNS) in childhood leukemia or as complications of its treatment.

MATERIALS AND METHODS
Magnetic resonance imaging (MRI) of 15 children with neurologic complications of leukemia or its treatment were reviewed retrospectively. The first group consisted of patients with CNS abnormalities detected prior to or during treatment, or within three months after completion of treatment. Patients with CNS complications detected by MRI three months following completion of treatment were included in the second group.

RESULTS
Among the 15 children, six had two or more different CNS abnormalities. The imaging abnormalities seen in 12 patients prior to or during treatment, or within three months after completion of treatment included orbital, temporal, cerebellopontine angle, and spinal chloroma; bilateral subdural hematoma in the subacute stage; multifocal intraparenchymal hemorrhage; bilateral retinal hemorrhage and detachment; hematoma in the pons and mesencephalon; PRES (posterior reversible leukoencephalopathy syndrome); bilateral leukemic infiltration of the 3rd, left 7th, and 8th cranial nerves; and meningeal leukemia. Three months after completion of treatment, three patients had CNS complications including radiation necrosis and secondary brain tumor, osteomyelitis of the L3 vertebra, and meningeal leukemia.

CONCLUSION
The wide spectrum of CNS abnormalities that occur during and after treatment for leukemia is related to leukemia and to the treatment method. Because many neurologic complications of leukemia are treatable, early diagnosis is essential.

Key words: • *leukemia* • *central nervous system diseases* • *magnetic resonance imaging*

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Leukemia is the commonest form of childhood cancer. In the past, central nervous system complications of leukemia were rare because the disease was almost uniformly rapidly fatal. More recently, advances in imaging techniques and treatment methods have prolonged survival (1); however, the frequency of central nervous system (CNS) complications has increased (2). The CNS complications of leukemia can be divided into those that result directly or indirectly from the underlying leukemic process, and those that can be attributed to antileukemic therapy. The disease itself may involve the leptomeninges, brain parenchyma, or cerebral vasculature (3). CNS complications related to treatment include white matter lesions, small-vessel calcifications, cerebrovascular disorders, secondary tumors and infections, and enlargement of ventricles (4). Children and adolescents who survive leukemia may develop endocrinopathies and/or neurocognitive deficits caused by the "late effects" of their treatment (5).

The purpose of this study was to present the radiological findings of CNS pathologies that have developed due to leukemia, or during or after antileukemic treatment, and to describe the usefulness of magnetic resonance imaging (MRI) in the detection of CNS complications.

Materials and methods

We retrospectively evaluated the cranial and spinal MRI of 15 patients (6 males, 9 females), ranging in age from 0.9 months to 22.3 years (Table). The patients had one of two types of childhood leukemia, including 10 cases of acute lymphoblastic leukemia (ALL), and five cases of acute myelogenous leukemia (AML). These patients were divided into two groups: Group 1 included 12 patients who had CNS abnormalities as detected by imaging prior to or during treatment, or within three months after completion of treatment; Group 2 consisted of three patients with CNS abnormalities detected by imaging that occured as late effects of leukemia and its treatment. CNS complications were divided into cerebral and spinal complications.

The medical records were reviewed with attention to the type of treatment given, the time of onset of symptoms after the last therapy, and the outcome of various CNS complications. Results of surgical biopsies of the brain lesions were also reviewed.

MR images were obtained with 1-T (Expert, Siemens Medical Systems, Erlangen, Germany) and 1.5-T (Symphony, Siemens Medical Systems) scanners. Noncontrast and contrast-enhanced sequences of the brain and spine were obtained in addition to diffusion weighted imaging of the brain.

Results

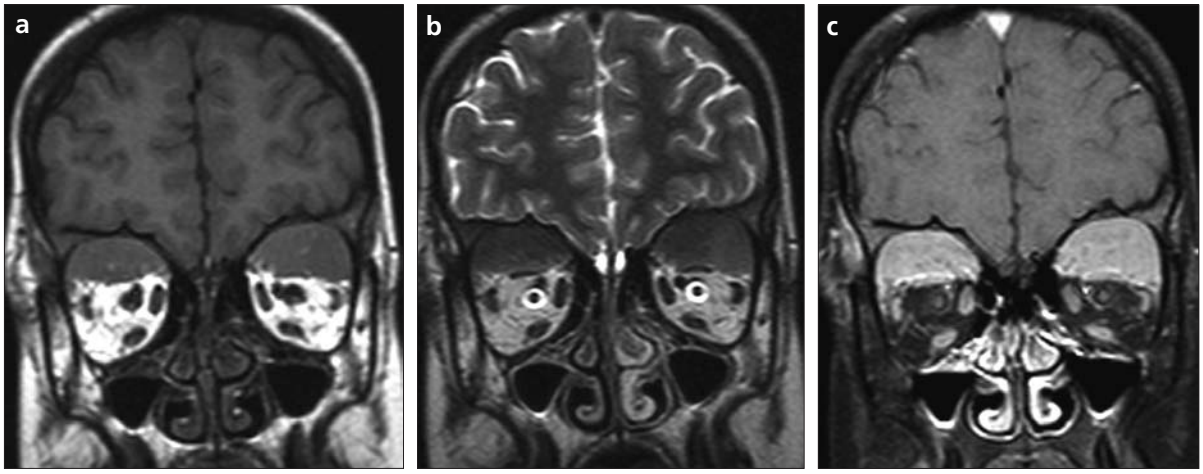
Five patients (three with ALL and two with AML) presented with CNS symptoms at the initial diagnosis. There were 12 patients in the first

Table. Clinical information, symptoms, type of treatment and diagnosis for the 15 patients with leukemia who had central nervous system abnormalities

No.	Age (years)/ gender	Leukemia type	Treatment	Age at first diagnosis (years)/interval (months)[a]	Symptoms	CNS diagnosis defined by imaging
1	0.9/F	AML	First diagnosis	0.9 years/first diagnosis	Cough, high fever, eye swelling	Presumed orbital leukemia Bilateral frontoparietal subdural hematomas in subacute stage
2	4.3/M	ALL	Intrathecal chemotherapy	4.3 years/20 months	Headache	Bilateral subdural effusions Meningeal leukemia
3	22.3/F	ALL	BFM	12 years/3 months	Lumbar pain	Presumed tumor infiltration in L3
4	20.3/F	AML	BFM	12 years/2.5 months	Intentional tremor, dysarthria, peripheral facial paralysis, weakness in bilateral lower extremities	PRES
5	6/M	ALL	Intrathecal MTX-ara-c, steroid. Intravenous vincristine	5.9 years/0.3 months	Tremor in right hand, confusion, drowsiness	PRES
6	7.8/F	AML	BFM	5.5 years/2 months	Confusion, lethargy	Presumed cerebellopontine angle chloroma, triventricular hydrocephaly, ventriculoperitoneal shunt catheter
7	15/F	AML	Cisplatin, adriablastine	14.9 years/1 month	Confusion, tendency to sleep	Bilateral retinal hemorrhage
8	13/F	ALL	Chemotherapy and cranial radiotherapy	10 years/36 months	Headache	Radiation necrosis High grade glial tumor
9	1.4/F	ALL	First diagnosis	1.4 years/first diagnosis	Tendency to sleep, inability to follow objects	Multiple focal intraparenchymal hemorrhages Bilateral retinal detachment and subretinal hemorrhages
10	15.5/M	AML	First diagnosis	15.5 years/first diagnosis	Proptosis, abdominal pain	Presumed chloromas Bilateral orbital masses Right temporal bone mass Presacral mass extending to the spinal canal
11	8.5/M	ALL	BFM	5.8 years/24 months	Headache	Meningeal leukemia
12	16/F	ALL	BFM	5 years/2 months	Ptosis, weakness in the right leg, limitations in eye movements	Bilateral 3rd, left 7th and 8th cranial nerve leukemic infiltration Meningeal leukemia
13	13/M	ALL	BFM	12.5 years/3 months	Headache	Meningeal leukemia
14	7.5/M	ALL	First diagnosis	7.5 years/first diagnosis	Tendency to sleep	Hematoma in the pons and mesencephalone
15	5.8/F	ALL	First diagnosis	5.8 years/first diagnosis	Vomiting, headache	Presumed meningeal and dural leukemia infiltrating bone

M, male; F, female; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster protocol; CNS, central nervous system; PRES, posterior reversible leukoencephalopathy syndrome.
[a] Time between the first diagnosis and appearance of CNS abnormalities.

group and three patients in the second group. Of the five patients who presented with CNS manifestations at the time of diagnosis, one had orbital chloromas and bilateral subdural hematomas in the subacute stage, one had bilateral orbital chloromas, and right temporal and spinal chloromas (Fig. 1), one had multifocal intraparenchymal hemorrhages, and bilateral retinal hemorrhage and detachment (Fig. 2), one had hematomas in the pons and mesencephalon, and one had dural leukemia infiltrating bone (Fig. 3). Among the 10 patients who had received antileukemic treatment, seven (three with AML, four with ALL) had early CNS complications identified on MRI. These complications included posterior reversible leukoencephalopathy syndrome (PRES) (n = 2) (Fig. 4); left cerebellopontine angle chloroma (n = 1); bilateral retinal hemorrhage (n = 1); and leukemic infiltration of the 3rd cranial nerve bilaterally, left 7th and 8th cranial nerves, and the fibers of the cauda equina (n = 1); and meningeal leukemia (n = 2). The second group, with late-occurring CNS complications, comprised three patients



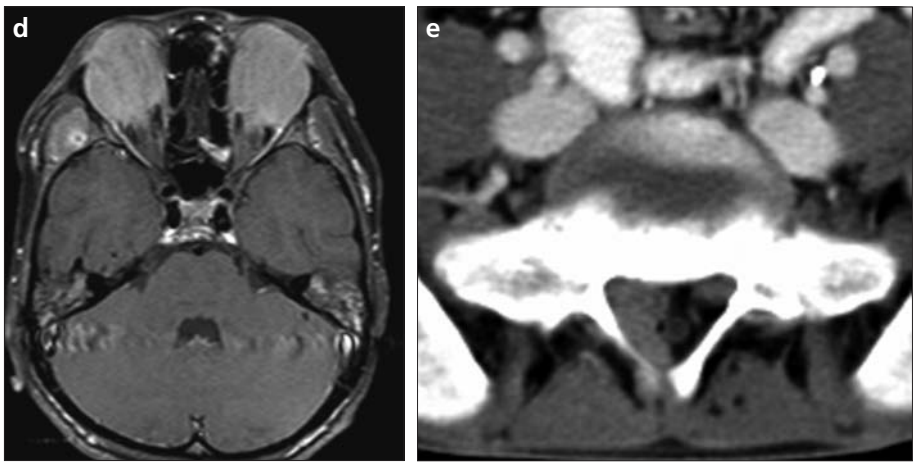


Figure 1. a–e. A 15 ½ -year-old boy with acute myelogenous leukemia and multiple chloromas. Coronal T1- **(a)** and T2-weighted **(b)** cranial MR images show bilateral masses in the superior orbital region which are isointense with gray matter on T1-weighted MRI, and isointense with white matter on T2-weighted MRI, and enhanced homogenously on post-contrast coronal **(c)** and axial **(d)** T1-weighted images. There was also another lesion located in the right temporal bone and temporalis muscles, seen on axial contrast enhanced T1-weighted image **(d)**. In postcontrast abdominal CT examination **(e)** there was an enhancing mass in the right epidural region of spinal canal.

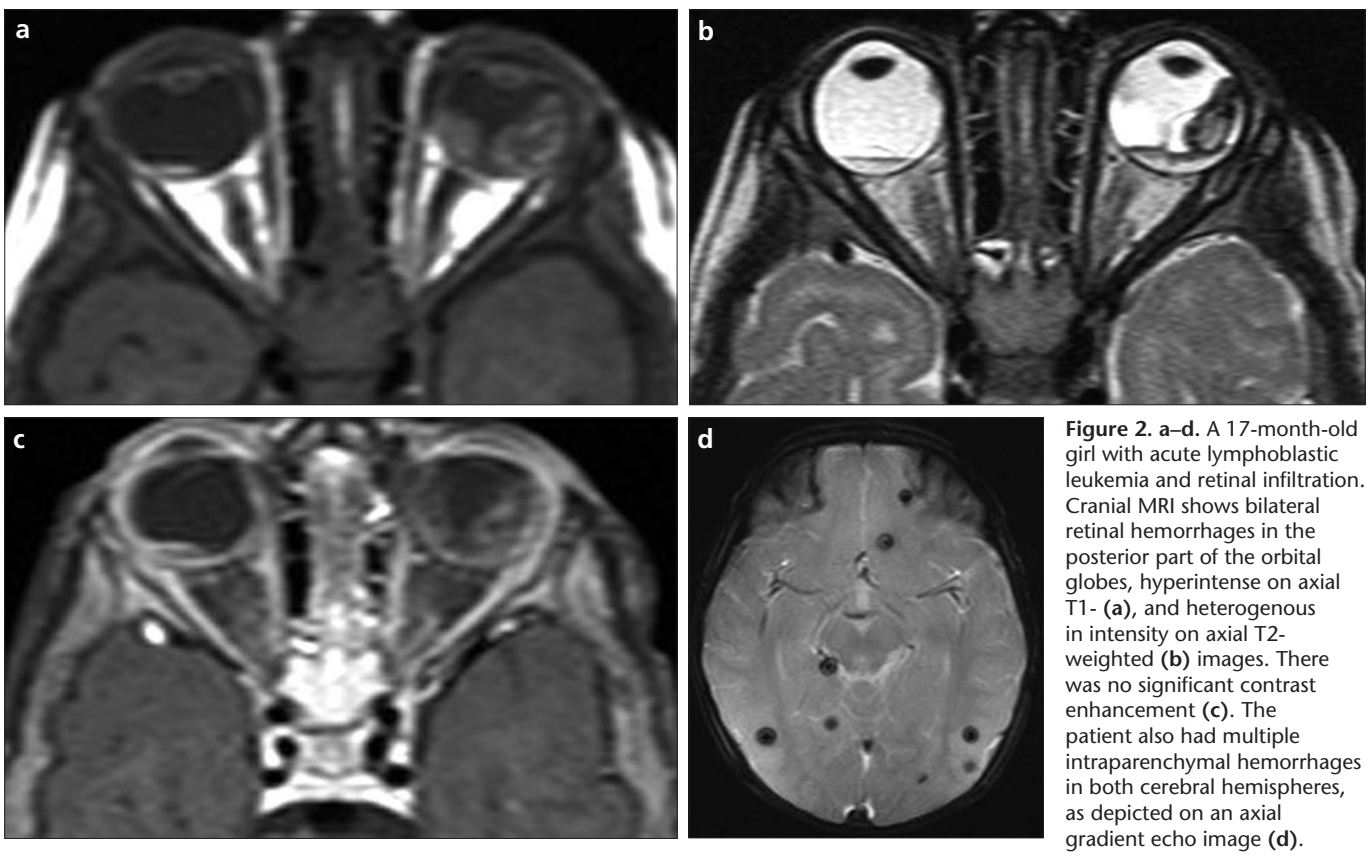


Figure 2. a–d. A 17-month-old girl with acute lymphoblastic leukemia and retinal infiltration. Cranial MRI shows bilateral retinal hemorrhages in the posterior part of the orbital globes, hyperintense on axial T1- **(a)**, and heterogenous in intensity on axial T2-weighted **(b)** images. There was no significant contrast enhancement **(c)**. The patient also had multiple intraparenchymal hemorrhages in both cerebral hemispheres, as depicted on an axial gradient echo image **(d)**.

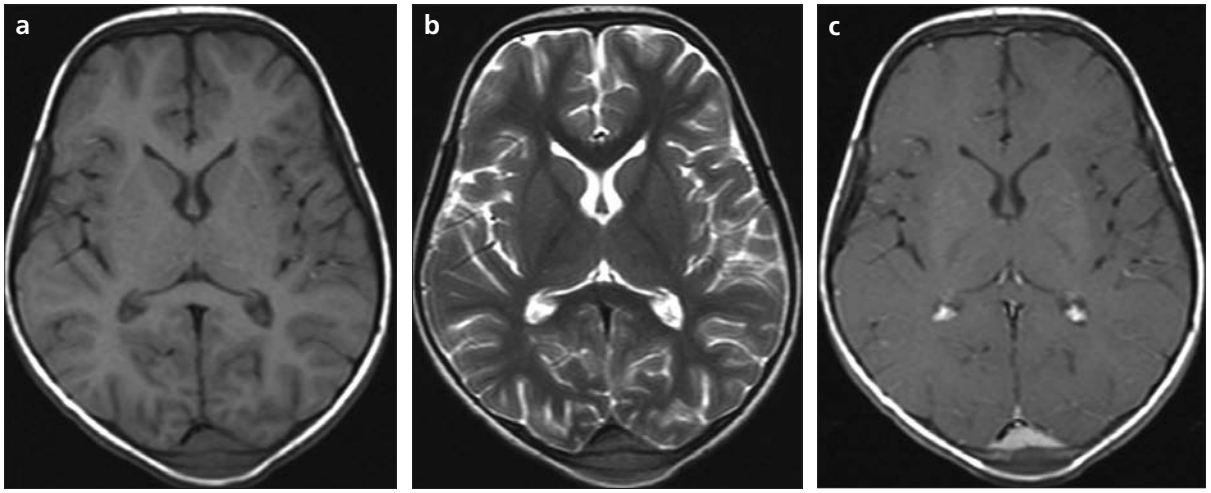


Figure 3. a–c. A 5-year-10-month-old girl with acute lymphoblastic leukemia and calvarial involvement. Cranial MRI shows a lesion in the dura, occipital bone, and scalp which was hypointense on T1- **(a)** and T2-weighted **(b)** images. There was enhancement in the dural and bony components of the lesion on contrast-enhanced axial T1-weighted images **(c)**.

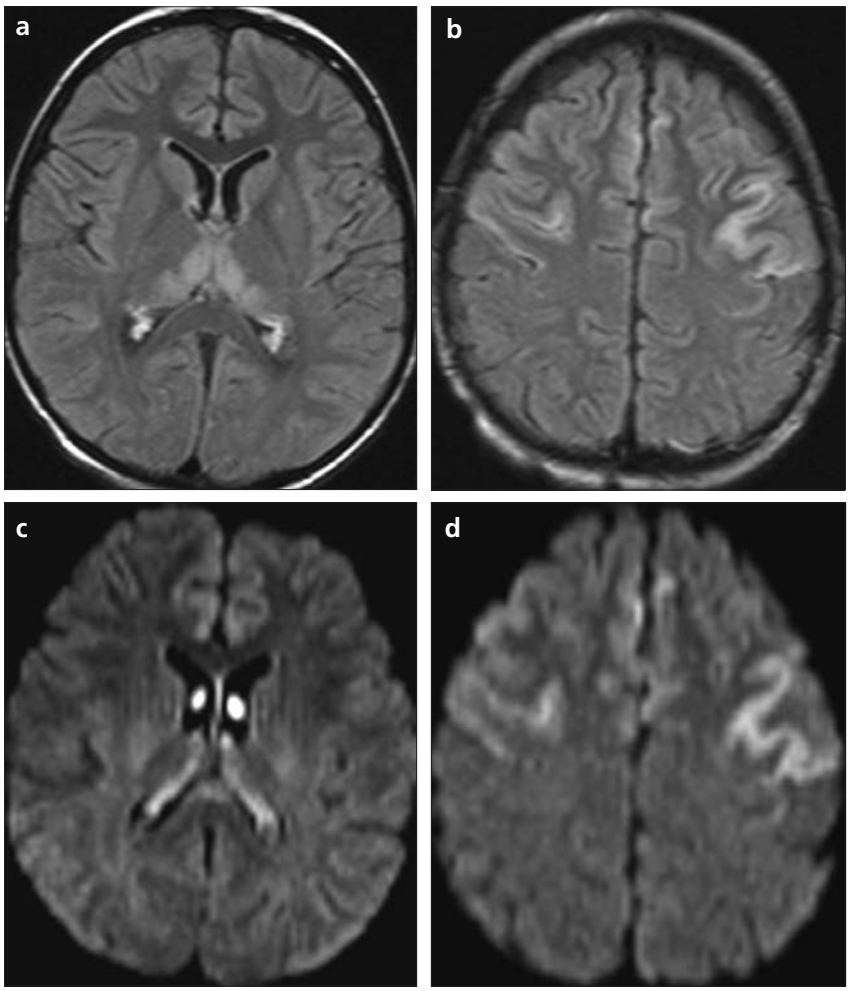


Figure 4. a–d. A 20-year-4-month-old female with acute myelogenous leukemia and posterior reversible leukoencephalopathy syndrome. Cranial MRI shows symmetrical high signal intensities in the bilateral posterior parts of the thalamus, bilateral frontal cortex, and subcortical white matter on axial fluid attenuated inversion recovery (FLAIR) images **(a, b)**. Diffusion weighted MRI **(c, d)** shows high signal intensity in the areas of FLAIR abnormality. Apparent diffusion coefficient maps showed increased values in the same areas (not shown).

(all three with ALL) with the following lesions: radiation necrosis and secondary brain tumor (n = 1) (Fig. 5), osteomyelitis of the L3 vertebra (n = 1), and meningeal leukemia (n = 1).

Six patients had two or more different CNS abnormalities. Of these retrospectively ascertained CNS abnormalities, seven were intracerebral, 12 were extracerebral and three were spinal complications.

The most common complication was meningeal leukemia, associated with the infiltration of adjacent bone and scalp (n = 5), followed by orbital chloroma (n = 2), PRES (n = 2), bilateral retinal hemorrhages (n = 2), and intraparencyhmal hemorrhage (n = 2).

Five patients with AML and imaging abnormalities included those with imaging performed prior to treatment (n = 2), and those with imaging within three months of completion of treatment (n = 3).

Ten patients with ALL who showed imaging abnormalities included three patients with CNS abnormalities that occured as presenting symptoms, and four patients with CNS abnormailties that occurred within three months of completion of treatment, and three patients with CNS abnormalities that occured as late effects of leukemia and its treatment.

As we classified the 22 complications, 17 were related to the disease itself, and only four were secondary to treatment. It was unclear whether one of the complications, osteomyelitis of the L3 vertebra, was related to leukemia or treatment.

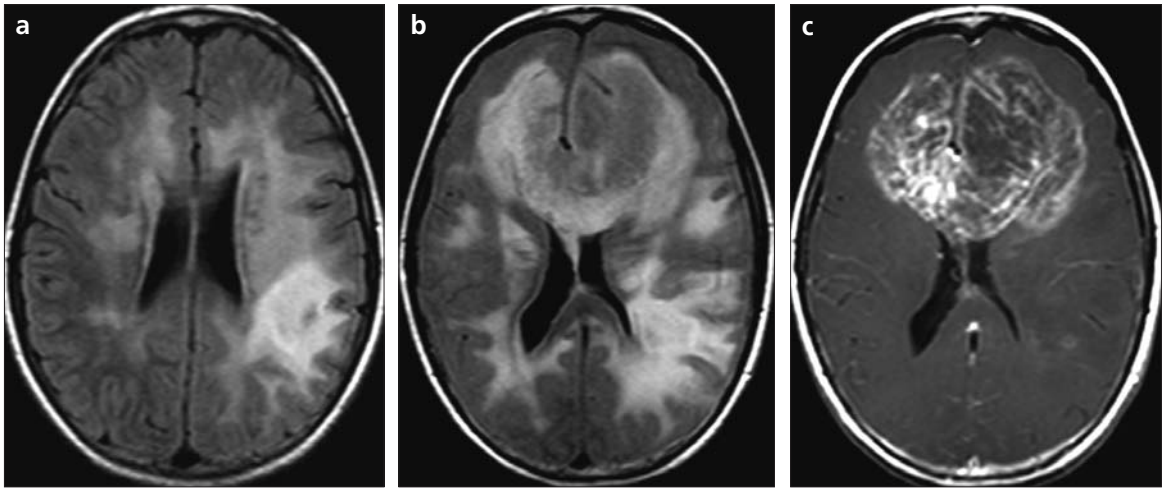


Figure 5. a–c. A 13-year-old girl with acute lymphoblastic leukemia and high grade glial tumor. Cranial MRI shows bilateral frontal, parietal, and occipital hyperintense lesions, containing cystic/necrotic areas in the right parietal lobe on axial fluid attenuated inversion recovery (FLAIR) image **(a)**, diagnosed as radiation necrosis due to the history of cranial irradiation. There was no contrast enhancement of the lesions (not shown). Six months after the first examination, the patient had a contrast-enhancing, irregularly shaped, partially cystic mass in both frontal lobes, infiltrating the body of the corpus callosum, consistent with high grade glial tumor secondary to radiotherapy, seen on axial FLAIR **(b)** and contrast enhanced T1-weighted **(c)** images.

Discussion

Leukemias are a heterogenous group of hematologic malignancies that result from neoplastic proliferation of hematopoietic cells at an undifferentiated or partially differentiated stage of maturation. The proliferation of leukemic cells can have a profound effect on hematopoietic stem cells, and on the normal cells of the immune system. As a result, leukemia can cause anemia, alterations in hemostasis, and increased susceptibility to infection. By direct or hematogenous spread, leukemic cells can infiltrate virtually any anatomic location. Recent therapeutic advances including aggressive polychemotherapy, intrathecal prophylaxis, and cranial irradiation have improved the prognosis of acute leukemia, but complications and adverse effects also have increased. Both early and late CNS complications can be related to the neurotoxicity of chemotherapeutic regimens, radiation therapy, bone marrow transplantation, and immunosupression caused by the disease itself or by its treatment (2).

The most common pathology in our series was leukemic meningitis, which occured in 33% of the patients (n = 5). Leptomeningeal or subarachnoid disease typically presents with signs and symptoms of increased intracranial pressure, including headache, nausea and vomiting, irritability, lethargy, and papilledema. Cytologic confirmation is necessary for diagnosis, but repeated analysis of cerebrospinal fluid (CSF) may be necessary because of the high frequency of false-negative cytologic findings (6). Imaging can play an important role, especially if it can demonstrate leptomeningeal disease in the face of negative cytologic studies. Leukemic involvement of the subarachnoid space can be identified on radiologic images as abnormal enhancement of the meninges and nerve roots.

In our study, CSF cytology was negative in all but one of the patients. In one other patient, CSF analysis was not available. All patients with leptomeningeal disease had been diagnosed with ALL. In four patients, the cranial meninges were affected. In one patient, the cauda equina fibers were affected with leukemic cell infiltration as were bilateral 3rd, and left 7th and 8th cranial nerves. Meningeal leukemia was associated with bilateral subdural effusions in one patient and with bone and scalp infiltration in the other (Fig. 3).

Granulocytic sarcoma (chloroma) is a rare extramedullary collection of immature cells with myelogenous differentiation (7). It occurs in 3–5% of pediatric patients with AML. It is most commonly detected in bone, periosteum, soft tissue, lymph nodes, and skin, although it can occur anywhere throughout the body. The discovery of this tumor may represent the first sign of AML at initial diagnosis or relapse, but also has been described in association with other myeloproliferative diseases, including chronic myelogenous leukemia, polyctemia vera, hypereosinophilia, and myeloid metaplasia (8).

In our study, chloromas were detected in the orbits, temporal bone, cerebellopontine angle, and spinal canal (Fig. 1). Orbital chloroma was detected in two patients with AML at the initial presentation, was associated with a spinal chloroma in one patient (Fig. 1), and was detected in the course of treatment for leukemia in another.

On MR imaging the orbital, temporal, spinal, and left cerebellopontine chloromas were isointense with gray matter on T1-weighted images, and isointense with white matter on T2-weighted images, enhancing homogenously after gadopentetate dimeglumine was administered (9).

One patient with chloroma of the left cerebellopontine angle had previously reported hemorrhages of this lesion (10). In all patients except one, chloroma was the initial manifestation of the disease. Radiologically, it is not possible to distinguish granulocytic sarcoma from lymphoma, meningioma, or pseudotumor on the basis of imaging findings (11).

Because chloromas are radiosensitive, treatment for intracranial chloroma is radiotherapy, chemotherapy (systemic and intrathecal), surgery, or any combination of these (12). Surgery is generally reserved for patients presenting with neurologic symptoms or acute spinal cord compression (13).

Leukemic patients may develop disseminated intravascular coagulation with resulting hypofibrinogenemia, and a pattern of multiple small hemorrhages in subcortical white matter. In addition, hemorrhage also can occur during chemotherapy or bone marrow transplantation. Subdural or subarachnoid hemorrhage is less common than intraaxial hemorrhage (2, 5, 14). Bilateral subacute hematomas and multiple small intraparenchymal hemorrhages were detected as the initial manifestation of the disease in two of our patients (Fig. 2). Ocular manifestations of acute leukemia are present in 39–53% cases. The retina is the most frequently involved structure, and retinal hemorrhage is the most frequent finding. As demonstrated in our two patients, retinal hemorrhages are usually bilateral and located in the posterior pole (15, 16) (Fig. 2).

One of the treatment-related complications was drug-induced PRES in two patients in our series. One of the patients received BFM protocol (IV methotrexate, vincristine, doxorubicine, and asparaginase) and the other patient had intrathecal MTX (methotrexate)-ara-c (cytarabine), steroid, and IV vincristine. Both patients had symptoms within three months of treatment. The high-intensity lesions on T2-weighted images located in the cortex and subcortical white matter of cerebral hemispheres were detected on cranial MRI. In one of the patients the thalamus was also affected bilaterally. The lesions were hyperintense on diffusion-weighted images and ADC maps, indicating vasogenic edema (Fig. 4).

Drug-induced PRES has been associated with cyclosporine, tacrolimus, antiretroviral therapy, erythropoietin, interferon alpha, corticosteroids, and chemotherapeutic agents such as cisplatin, methotrexate, cytarabine, vincristine, and asparaginase (17, 18). Methotrexate is often implicated as the major cause of acute neurotoxicity. Risk factors for methotrexate-induced neurotoxicity include high-dose treatment, intrathecal treatment, young age, and association with cranial radiation (18). Methotrexate neurotoxicity and its effects can be classified as immediate, acute or subacute, and delayed neurologic symptoms. Immediate methotrexate neurotoxicity can present as aseptic meningitis, transverse myelopathy, or stroke-like syndrome. The acute or subacute form is characterized by demyelination and leukoencephalopathy (19). The delayed form is characterized by necrotizing leukoencephalopathy or mineralizing microangiopathy (19). Mineralizing microangiopathy is detected as dystrophic calcifications in the basal ganglia and subcortical white matter.

Rollins et al. reported five adolescents with acute neurotoxicity related to intrathecal methotrexate typically occurring 22-23 weeks into chemotherapy for pre-B cell ALL (20). They explained that the metabolic derangement in folate and homocysteine induced by the cumulative effects of repeated administration of methotrexate might be the cause of neurotoxicity. In their study, diffusion-weighted imaging showed restricted diffusion limited to white matter in five of six patients, and involving the cortex in one. In addition, they showed that diffusion abnormalities were not consistently correlated with neurologic events (20).

In our patients, the drugs responsible for neurotoxicity were assumed to be methotrexate, vincristine, and asparaginase. Clinical symptoms improved, and follow up MRI showed complete absence of high signal intensity white matter abnormalities seen previously on T2-weighted MR images and diffusion weighted MRI.

In our series, one patient with ALL had radiation-induced pathology, i.e., radiation necrosis, and secondary tumor (Fig. 5). The most common secondary neoplasms that occur following cranial radiation therapy are sarcoma and meningioma. The occurrence of glioblastoma multiforme following radiation and chemotherapy in ALL is rare (21). Although cranial irradiation has clearly been implicated in the development of secondary brain tumors, cases of a second malignant tumor have been reported in the CNS in survivors of childhood leukemia with no history of prophylactic irradiation. Proposed mechanisms include loss of immune surveillance, and genetic factors (22). Side effects of radiation therapy other than necrotizing diffuse leukoencephalopathy and secondary tumors are mineralizing microangiopathy, parenchymal brain volume loss, and cryptic vascular malformations (14).

Infectious complications are among the most significant causes of morbidity and mortality in pediatric cancer patients. Both the underlying malignancy and the antineoplastic therapy can cause immunosuppression. Candida and Aspergillus species are the organisms most frequently identified (22). In one of our patients with ALL, there were contrast-enhancing lesions bilaterally in the pedicles of the L3 vertebra. The patient was diagnosed as having leukemic infiltration, but biopsy disclosed chronic osteomyelitis. As we looked into infectious complications outside the CNS, we found that three patients died from sepsis.

In conclusion, the wide spectrum of CNS abnormalities that occur during and after treatment for leukemia is related to the disease itself and to the treatment. Because many neurologic complications are treatable, early diagnosis is essential. Improved neuroimaging techniques help to characterize CNS abnormalities caused by direct leukemic involvement of CNS structures, as well as treatment-related neurotoxicity, secondary brain tumors, infections, and cerebrovascular disorders.

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