

Neuroimaging in Pediatric Leukemia and Lymphoma: Differential Diagnosis¹

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LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- List the main neurologic pathologic conditions seen in pediatric patients with leukemia or lymphoma.
- Identify the neuroimaging findings of the toxic effects secondary to the different forms of therapy used in pediatric patients with oncohematologic disease.
- Recognize the imaging features of metabolic alterations, coagulopathic disorders, and opportunistic infections in children with these neoplastic processes.

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Recent advances in therapy for pediatric hematologic neoplasms have greatly improved the prognosis but have resulted in an increased incidence of associated complications and toxic effects. The main neuroimaging features in pediatric patients with leukemia or lymphoma treated with chemotherapy or radiation therapy were retrospectively reviewed. To simplify the approach and facilitate differential diagnosis, the neuroimaging features have been classified into three main categories: central nervous system manifestations of primary disease, side effects of therapeutic procedures (radiation therapy, chemotherapy, bone marrow transplantation), and complications due to immunosuppression, particularly infections. Manifestations of primary disease include cerebrovascular complications (hemorrhage, cerebral infarction) and central nervous system involvement (infiltration of the meninges, parenchyma, bone marrow, orbit, and spine). Effects of radiation therapy include white matter disease, mineralizing microangiopathy, parenchymal brain volume loss, radiation-induced cryptic vascular malformations, and second neoplasms. Effects of chemotherapy and bone marrow transplantation include hemorrhage, dural venous thrombosis, white matter disease, reversible posterior leukoencephalopathy syndrome, and anterior lumbosacral radiculopathy. Both the underlying malignancy and antineoplastic therapy can cause immunosuppression. Fungi are the most frequent causal microorganisms in immunosuppressed patients with infection. Familiarity with the imaging findings is essential for proper diagnosis of neurologic symptoms in pediatric patients with oncohematologic disease.

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Abbreviations: ALL = acute lymphoblastic leukemia, CNS = central nervous system

Index terms: Leukemia, complications, **.34² • Leukemia, in infants and children, **.34 • Lymphoma, in infants and children, **.34 • Nervous system, infection, 10.20, 30.20 • Nervous system, neoplasms, 10.34, 30.34 • Nervous system, therapeutic radiology, 10.40, 30.40

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²**. Multiple body systems

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Introduction

Lymphoreticular malignancies account for about 40% of all malignant disorders in children. Leukemia represents nearly 30% of all malignancies, with 75% of cases corresponding to acute lymphoblastic leukemia (ALL). Lymphoma constitutes 11% of pediatric malignancies (6% non-Hodgkin lymphoma and 5% Hodgkin disease) (1). In the past, central nervous system (CNS) complications were rarely seen due to the rapid course of the disease. Recent therapeutic advances such as aggressive polychemotherapy, intrathecal cytostatic prophylaxis, and cranial irradiation have improved the prognosis of acute leukemia and high-grade lymphoma, with survival in up to 60% of patients, but complications and adverse effects have also increased (2).

Bone marrow transplantation, with the possibility of eradicating remaining malignant cells and suppressing the recipient's immune system, has also revolutionized the treatment of these patients. The typical conditioning regimen used for this purpose includes cytotoxic drugs (usually cyclophosphamide) followed by total body irradiation given in several fractions. Significant acute side effects such as graft-versus-host disease, infections, veno-occlusive disease of the liver, and the more unusual neurologic complications due to the associated total body irradiation and cytotoxic agents are well established (3).

We retrospectively evaluated the results of cranial and spinal neuroimaging studies in all pediatric patients with leukemia or lymphoma referred to our department for investigation of neurologic symptoms and signs. Abnormal imaging findings were subsequently correlated with medical records or a histopathologic diagnosis, when available. The diverse pathologic entities that can affect the CNS in these patients have been grouped to simplify the approach (Table), and representative cases are presented. The pathologic entities are classified into three main categories: CNS manifestations of primary hematologic disease, side effects of therapeutic measures, and infectious complications. Early recognition and diagnosis of CNS complications in these patients is important to establish proper treatment and increase the chance for overall survival.

CNS Manifestations in 49 Patients with Oncohematologic Disease

CNS Manifestation	No. of Patients
Manifestations of primary disease (<i>n</i> = 11)	
Hemorrhage	1
CNS involvement	
Meningeal infiltration	2
Parenchymal infiltration	1
Bone marrow infiltration	2
Orbital infiltration	3
Spinal infiltration	2
Effects of therapeutic methods (<i>n</i> = 38)	
Effects of radiation therapy	
White matter disease	3
Mineralizing microangiopathy	3
Parenchymal volume loss	12
Radiation-induced cryptic malformations	2
Second neoplasms	2
Effects of chemotherapy and bone marrow transplantation	
Hemorrhage	3
Dural venous thrombosis	3
White matter disease	2
Reversible posterior encephalopathy	4
Effects of immunosuppressive states	
Infectious processes	4

CNS Manifestations of Primary Hematologic Disease

Cerebrovascular Complications

Parenchymal cerebral thrombosis or hemorrhage can occur in patients with leukemia or lymphoma as a result of leukocytosis, thrombocytopenia, sepsis, or coagulopathy (2).

Hemorrhage is most common in acute leukemia and often leads to death. Alterations in coagulation factors, thrombocytopenia, and the possible associated disseminated intravascular coagulation all contribute to the bleeding diathesis. Owing to the common disseminated intravascular coagulation during therapy, the acute promyelocytic form of leukemia has particular risk for massive brain hemorrhage, and this type of hemorrhage is the cause of death in more than 60% of cases (2,4). In patients with fulminant leukocytosis (blast crisis), particularly those with a leukocyte count over 300,000/mm³, leukostasis or blast cell thrombi within small arterioles can also pro-

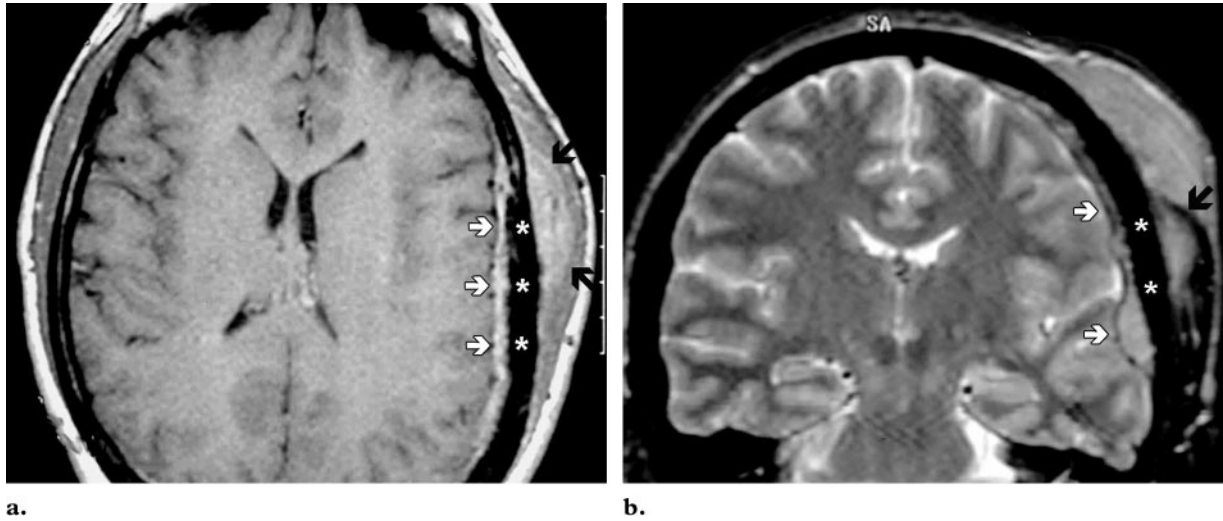


Figure 2. Non-Hodgkin lymphoma with transcalvarial infiltration in an 18-year-old man with a left-sided calvarial mass and no other symptoms. Axial contrast-enhanced T1-weighted (**a**) and coronal T2-weighted (**b**) MR images show abnormal signal intensity of bone marrow (*) with an extraosseous subperiosteal (black arrows) and epidural (white arrows) enhancing soft-tissue mass. Surgical biopsy demonstrated a non-Hodgkin lymphoma.

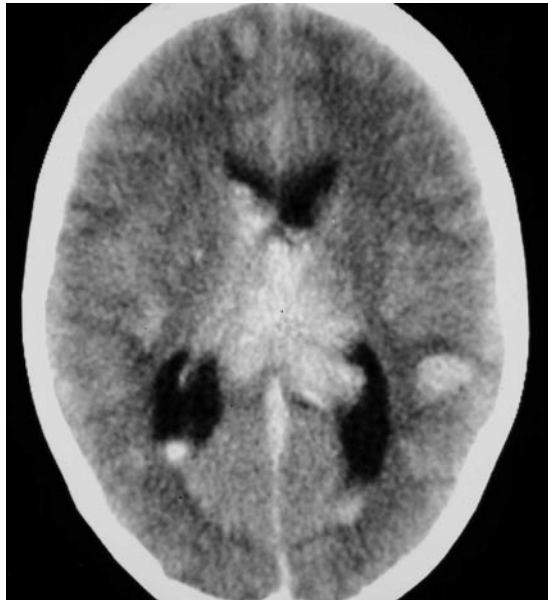


Figure 1. Leukemic debut with fulminant leukocytosis in an 8-year-old boy who presented with a sudden headache, progressive lethargy, and coma. Enlargement of the spleen was detected at physical examination; hyperleukocytosis (white blood cell count of $800,000/\text{mm}^3$) and thrombocytopenia (platelet count of $58,000/\text{mm}^3$) were significant laboratory parameters. ALL of the L1T type with cerebrospinal fluid involvement was diagnosed. Axial computed tomographic (CT) scan shows multiple hemorrhagic lesions involving the corpus callosum and cerebral white matter with intraventricular extension. The lesions did not enhance after administration of contrast medium. Chemotherapy was started, but the patient died in 48 hours.

duce vascular damage and massive hemorrhage (Fig 1). The risk of major spontaneous intracranial hemorrhage in thrombocytopenia is minimal until the platelet count drops below $10,000/\text{mm}^3$, although this risk can be increased if coagulopathy is present or with the use of medications such as prednisone or L-asparaginase (5).

Cerebral infarction is far less common in oncohematologic patients than hemorrhage and is mainly related to sinovenous thrombosis. The pathogenic mechanisms contributing to venous occlusion are leukostasis, hypercoagulability, and use of certain chemotherapeutic agents, particularly L-asparaginase, which may be compounded with the concurrent use of prednisone (2,4–6).

Another cause of ischemic accidents is radiation-induced vascular damage, with thrombosis reported up to 22 years after therapy (5).

CNS Involvement

Involvement at sites other than the hemopoietic organs and skeleton is uncommon at presentation of pediatric leukemia or lymphoma. Nevertheless, the so-called sanctuary sites (CNS, testes, and kidneys) are affected in 50% of children who experience a relapse after therapy (1,2), even during bone marrow remission. Incidence of CNS relapses has been dramatically reduced with methotrexate prophylaxis (7), but they still occur.

Leukemic or lymphomatous cells can involve the calvarial bone marrow, dura, leptomeninges, or all three (8). Involvement may be diffuse or focal with abnormal meningeal enhancement at contrast material-enhanced CT and particularly at magnetic resonance (MR) imaging (Fig 2).

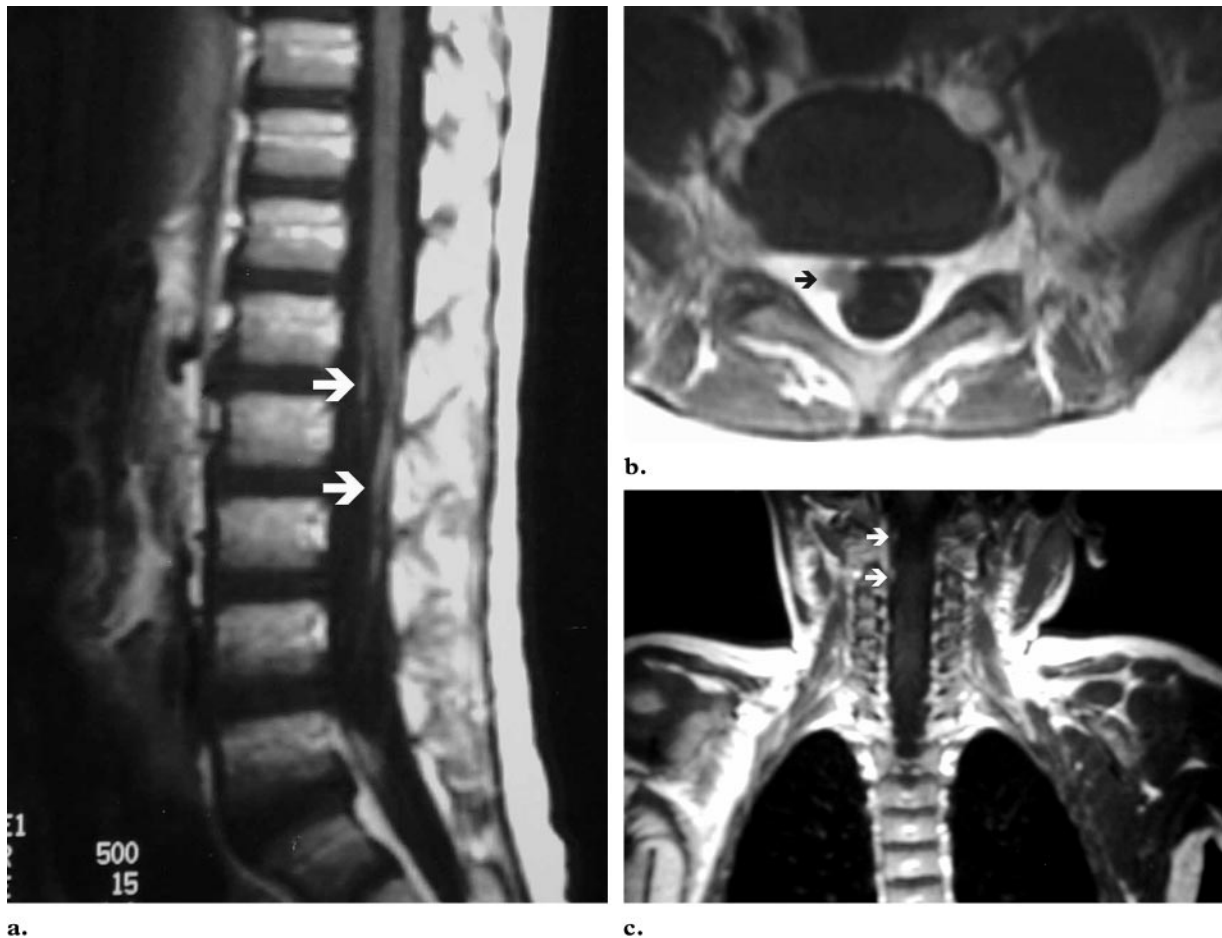


Figure 3. Leptomeningeal seeding by non-Hodgkin lymphoma in a 4-year-old boy with right arm and leg paresis who had been treated for primary abdominal Burkitt lymphoma. Sagittal (**a**) and axial (**b**) contrast-enhanced T1-weighted MR images of the lumbosacral region and coronal contrast-enhanced T1-weighted MR image of the cervical spinal cord (**c**) show multiple enhancing subarachnoid nodules (white arrows) with coating of the nerve roots on the right side (black arrow), findings consistent with leptomeningeal seeding. A lymphomatous leptomeningeal relapse was confirmed at cytologic examination of cerebrospinal fluid. Follow-up MR images obtained after treatment were normal.

Cytologic examination of cerebrospinal fluid or histologic confirmation is necessary for diagnosis because several conditions, such as infectious or chemical meningitis, can mimic neoplastic seeding (Fig 3).

Granulocytic sarcomas, formerly known as *chloromas*, are masses of primitive precursors of the granulocytic cells, which include myeloblasts, promyelocytes, and myelocytes. They mainly occur in patients with myelogenous leukemia, although they can be seen in other myeloproliferative disorders such as myelofibrosis with myeloid metaplasia. Children are more often affected than adults (9). These masses may be a presenting sign of myelogenous leukemia or develop during the course of the disease. Parenchymal leukemic

masses are very uncommon and often are hyperattenuating at CT, are contiguous with a meningeal surface, and enhance after contrast material administration (10). Leukemic masses can also affect the head and neck, particularly the orbital soft tissues, as focal intra- or extraconal masses (Fig 4).

Other ophthalmic manifestations in patients with leukemia or lymphoma are extraocular muscle, optic nerve, and intraocular involvement (Fig 5). The presence of enhancing optic nerve enlargement in children with a history of leukemia should suggest the diagnosis of leukemic infiltration even in the absence of previous CNS involvement. This area might represent another “sanctuary” for leukemic cells due to suboptimal penetration of chemotherapy in the retrobulbar optic nerve (11).

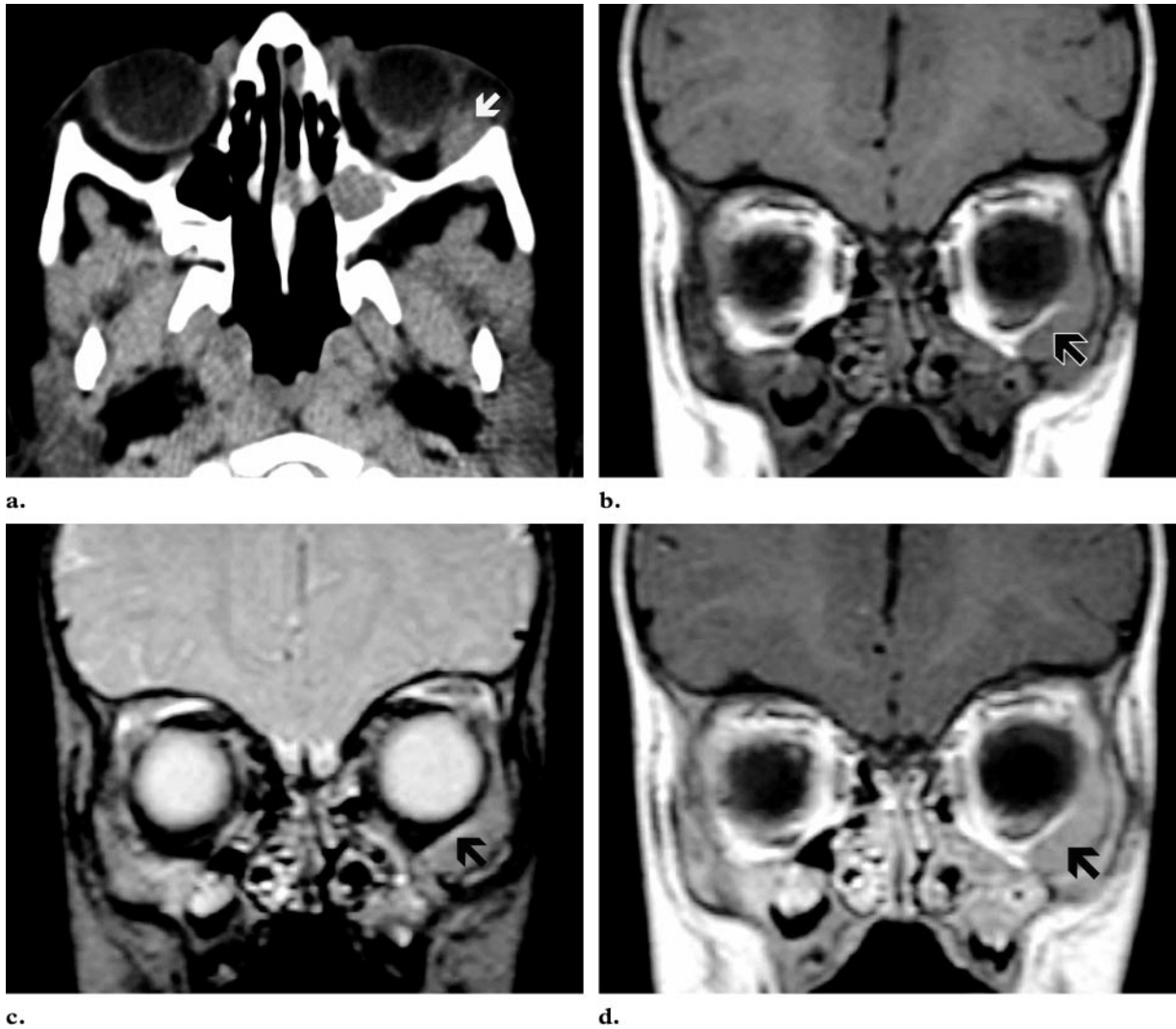


Figure 4. Acute myeloblastic leukemia with an orbital granulocytic sarcoma in a 1-year-old girl with a left orbital mass. Axial CT scan (a) and coronal T1-weighted (b), T2-weighted (c), and gadolinium-enhanced T1-weighted (d) MR images show a mass in the left inferior preseptal region (arrow). The mass is isoattenuating relative to muscle on the CT scan (a) with no bone involvement. It is slightly hypointense on the T2-weighted image (c) and has homogeneous enhancement on the gadolinium-enhanced image (d). Surgical biopsy demonstrated a granulocytic sarcoma.



Figure 5. ALL with orbital relapse in a 5-year-old girl with left proptosis who was previously treated for ALL with no CNS involvement. Axial contrast-enhanced CT scan of the orbit shows an enlarged enhancing left optic nerve (arrow). Examination of cerebrospinal fluid demonstrated a leukemic relapse. Results of follow-up examinations performed after local radiation therapy and systemic chemotherapy were normal.



Figure 6. Spinal involvement by Hodgkin lymphoma in a 17-year-old boy with low back pain and sciatica. Sagittal T1-weighted (**a**) and T2-weighted (**b**) MR images show abnormal signal intensity of bone marrow (arrows). An anterior mediastinal mass was found at chest radiography and CT. The patient responded well to therapy, and follow-up spinal MR images were normal.

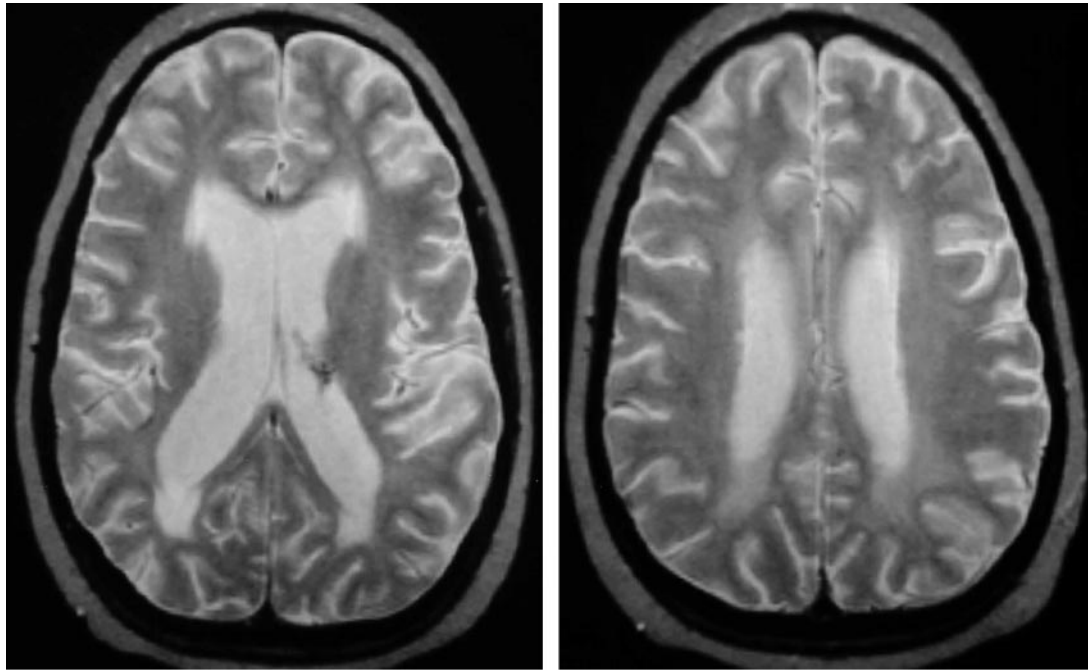
Spinal involvement is also frequent in leukemia and lymphoma, either as initial manifestation or in relapse, with bone marrow or meningeal infiltration (Fig 6). MR imaging of the bone marrow in affected children demonstrates low-signal-intensity leukemic infiltrates on T1-weighted images, particularly apparent in areas where red marrow is converting to yellow marrow (1).

Side Effects of Therapeutic Measures

Radiation Therapy

White Matter Disease.—Neurotoxic reactions to radiation therapy can be divided into acute (1–6 weeks after treatment), early delayed injury (3 weeks to several months after irradiation), and late delayed injury (months to years after treatment). In acute injury, there is increased capillary

permeability and vasodilatation leading to vasogenic edema. Early delayed injury includes vasogenic edema and demyelination. The late delayed effects include white matter necrosis, demyelination, astrogliosis, and vasculopathy (12,13). Acute lesions are in general mild and reversible, with areas of periventricular white matter edema seen at CT or MR imaging, whereas the delayed toxic effects are more severe and usually irreversible, resulting from white matter vasculopathy and infarction. Patients with this latter injury can manifest focal deficits or stupor, but no direct association between mild or moderate changes at imaging and clinical symptoms has been found (Fig 7). Focal or multiple white matter lesions with edema and demyelination will appear on MR images, usually sparing the subcortical U-fibers and the corpus callosum, often with mass effect and enhancement, and always within the previously irradiated area (14). One of the most severe processes, necrotizing diffuse leukoencephalopathy, which is seen with combined chemotherapy



a.

b.

Figure 7. Delayed therapeutic injury in a 9-year-old boy with seizures who had been treated for ALL with chemotherapy and radiation therapy. Axial T2-weighted MR images (**a** obtained at a lower level than **b**) show abnormal signal intensity of periventricular white matter with some parenchymal volume loss.

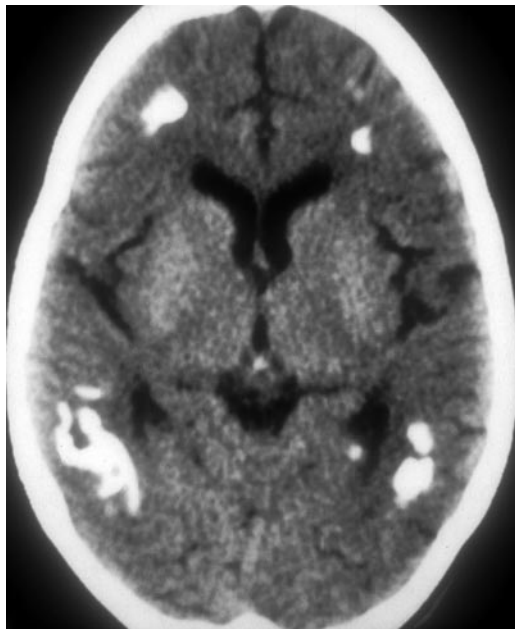
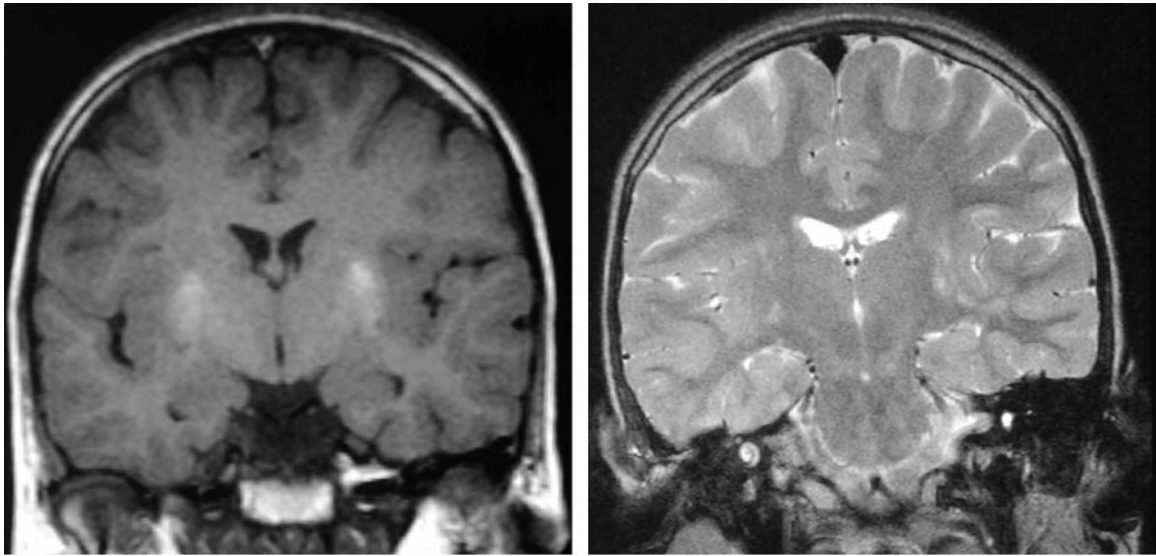


Figure 8. Mineralizing microangiopathy in a 17-year-old boy who had been treated for ALL with irradiation and intrathecal chemotherapy. Several years after remission, he developed seizures. Nonenhanced axial CT scan shows calcifications in the subcortical parenchyma and basal ganglia.

and radiation therapy, is associated with subsequent rapid and progressive clinical deterioration. Extensive areas of white matter necrosis can be seen at neuroimaging, with marked enhancement after contrast medium administration and a tendency toward posterior calcification (13,15).

Mineralizing Microangiopathy.—Radiation therapy produces hyalinization and fibrinoid necrosis of small arteries and arterioles with endothelial proliferation and calcium deposition (1,4). Dystrophic calcifications in the basal ganglia and subcortical white matter were a relatively common finding at cranial CT in children previously treated with radiation therapy and intrathecal methotrexate (Fig 8). Nowadays, with the more conservative protocols, a subtle pattern can be discovered on follow-up MR images, with putaminal increased signal intensity on T1-weighted images due to a surface-relaxation mechanism and decreased signal intensity on T2-weighted



a. **Figure 9.** Subtle mineralizing microangiopathy in a 10-year-old girl who had been treated for ALL with radiation therapy and chemotherapy. Follow-up MR imaging was performed 3 years after treatment. **(a)** Coronal T1-weighted MR image shows subtle hyperintense areas involving the lenticular nuclei. **(b)** Coronal fast spin-echo T2-weighted MR image shows no clear lesion. The patient was asymptomatic; she did not have liver failure and was not receiving parenteral nutrition, conditions that could also produce high signal intensity of the lenticular nucleus on T1-weighted images secondary to manganese deposition.

images (Fig 9). These imaging findings appear 2 or more years after the cranial irradiation, are more common with combined chemotherapy (especially intrathecal) and radiation therapy, and do not clearly correlate with clinical symptoms (16).

Parenchymal Brain Volume Loss.—Children receiving CNS prophylaxis with irradiation or intrathecal chemotherapy may posteriorly develop cerebral volume loss, even when CNS leukemic involvement was not originally present. This finding correlates with posterior neurocognitive deficits, more severe in the youngest group of patients (Fig 10). Although enlarged cerebrospinal fluid spaces usually result from therapy (mainly, corticotherapy), 31% of children with ALL have slightly enlarged ventricles before treatment, probably related to hydrocephalus secondary to primary disease (1,4,12). Nevertheless, when the enlargement does not reverse after remission but instead persists or even increases, it is probably related to cranial irradiation and is responsible for posterior learning problems in up to 80% of survivors (17).

Radiation-induced Cryptic Vascular Malformations.—Children treated with cranial irradiation due to leukemia or CNS primary neoplasms can develop white matter hemorrhagic lesions

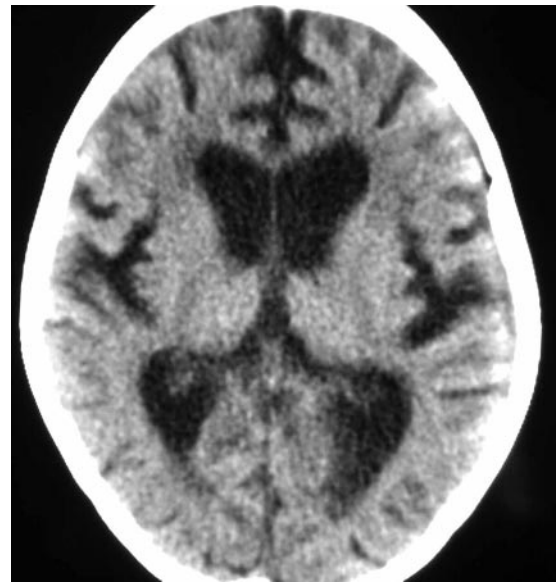
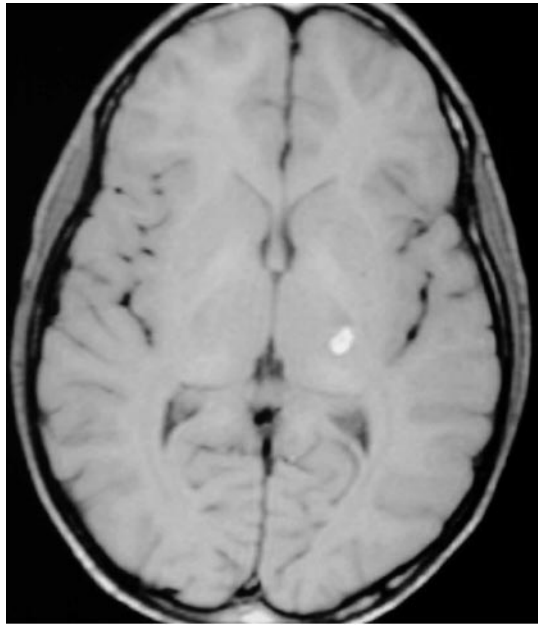
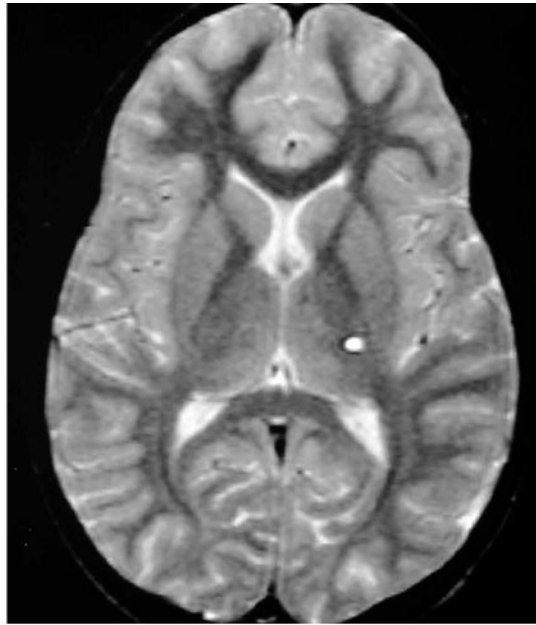


Figure 10. Cerebral parenchymal volume loss in a 5-year-old girl receiving radiation therapy and intrathecal chemotherapy for ALL. Axial CT scan shows that ventricular and subarachnoid spaces are widely dilated. These imaging findings did not reverse at follow-up examinations.

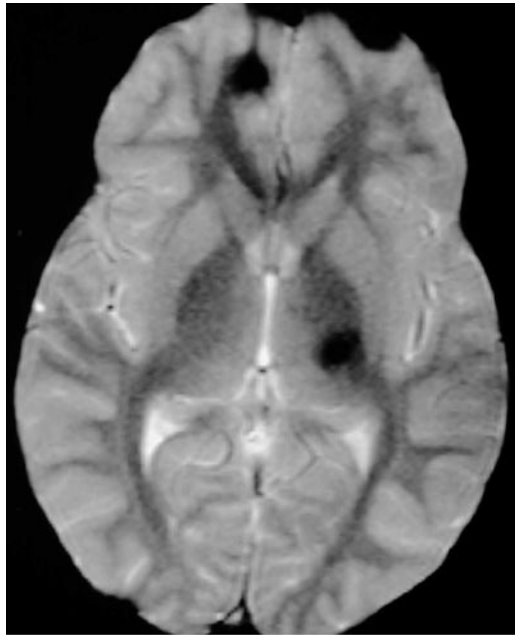
with heterogeneous signal intensity quite similar to that of cryptic malformations or cavernous angiomas on MR images. These features are probably capillary telangiectases secondary to the altered venular endothelium with subsequent venous occlusive disease (18). Gradient-echo



a.



b.



c.

Figure 11. Radiation-induced cryptic vascular malformations in a 15-year-old boy with headaches who had been treated for ALL. (a, b) Axial T1-weighted (a) and T2-weighted (b) MR images show a hyperintense lesion with a hypointense rim in the left thalamic nucleus. A hypointense lesion in the subcortical white matter of the right frontal region is also seen on the T2-weighted image (b). (c) Axial gradient-echo MR image shows both lesions more clearly. These hemorrhagic lesions were unchanged at follow-up MR imaging examinations.

sequences are particularly useful for their identification because of their greater magnetic susceptibility (Fig 11). The lesions can be isolated or multiple and show calcifications at cranial CT. Patients are usually asymptomatic, although some have headaches, seizures, or focal signs. These lesions, which appear several years after treatment, can have hemorrhagic potential, but surgical removal is justified only in cases of symptomatic hemorrhage (19,20).

Second Neoplasms.—Second neoplasms are relatively rare neoplasms that are mainly related to radiation therapy and have an overall prevalence of 3%–12%. Among the second intracranial tumors, 70% correspond to meningiomas, 20% to gliomas, and 10% to sarcomas. The latency period between treatment and development of these tumors can be variable. Children who underwent cranial irradiation at 5 years of age or younger, those with a genetic predisposition to tumors (bilateral retinoblastoma, type 1 neurofibromatosis), or survivors of bone marrow transplantation have a markedly increased risk. Unfortunately, treatment-induced tumors are more aggressive and highly refractory to therapy (21,22). Secondary meningiomas are also characterized by younger age at presentation, higher male-to-female ratio, and biologically more aggressive variants compared to primary spontaneous meningiomas (Fig 12).

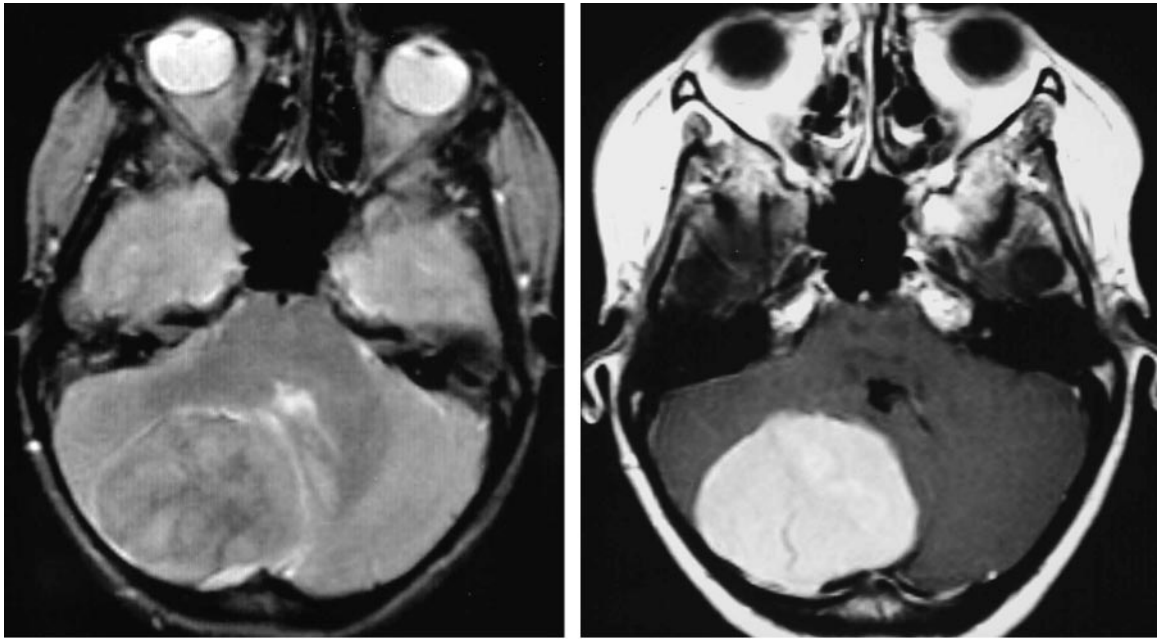


Figure 12. Secondary meningioma in a 17-year-old girl with occipital headaches who underwent therapy for ALL (including cranial irradiation) at the age of 2 years. She was treated for papillary carcinoma of the thyroid 2 years earlier. Axial T2-weighted (**a**) and gadolinium-enhanced T1-weighted (**b**) MR images show an extraaxial mass in the posterior fossa; the mass has slightly low signal intensity on the T2-weighted image (**a**) and demonstrates homogeneous enhancement on the gadolinium-enhanced T1-weighted image (**b**). The tumor was resected, and the histopathologic diagnosis was meningioma with anaplastic foci. Follow-up MR imaging examinations did not demonstrate tumor recurrence.

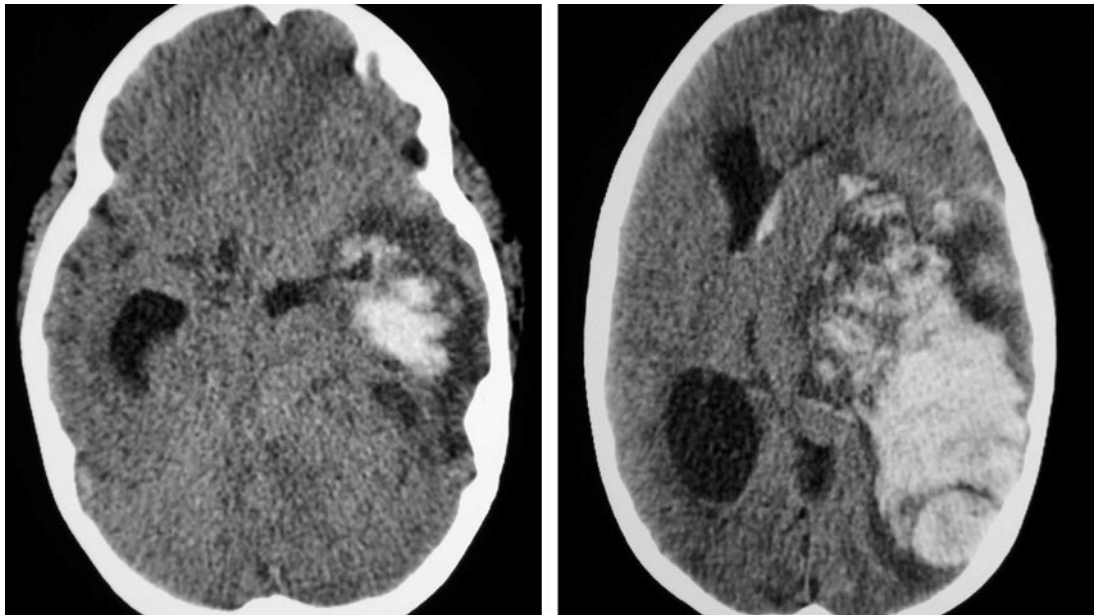
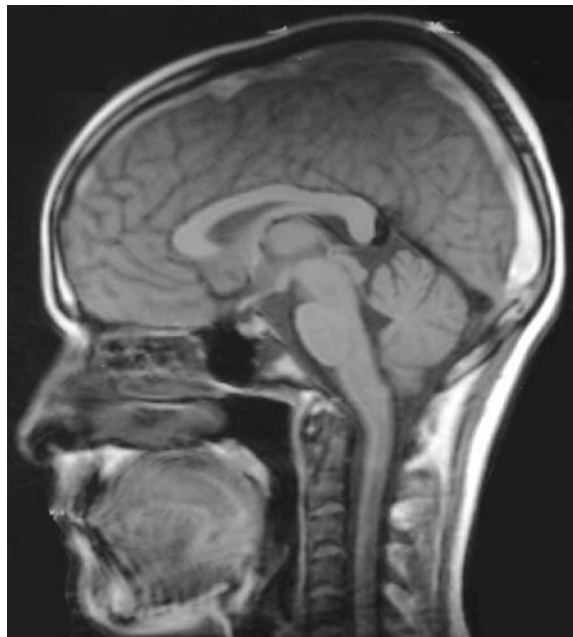
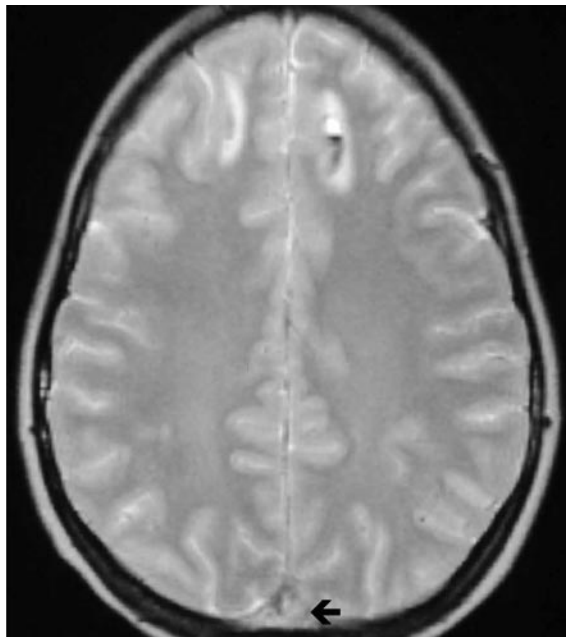


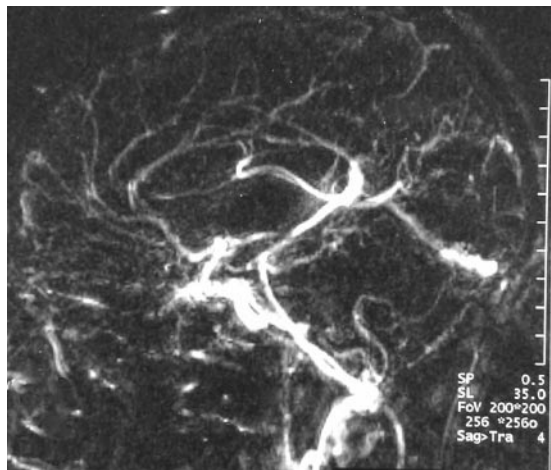
Figure 13. Parenchymal hemorrhage after bone marrow transplantation in a 10-year-old boy with ALL and severe thrombocytopenia who experienced sudden neurologic deterioration. Axial CT scans (**a** obtained at a lower level than **b**) show a huge parenchymal hemorrhage in the left hemisphere with surrounding edema and mass effect. The patient died in the intensive care unit.



a.



b.



c.

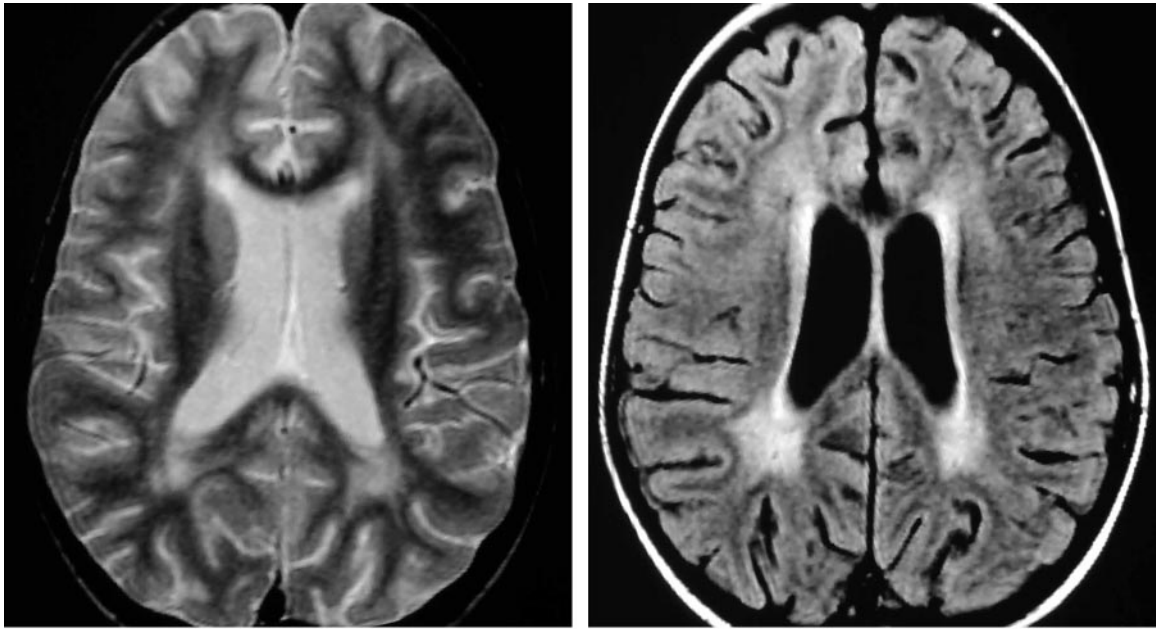
Figure 14. Dural venous thrombosis in a 10-year-old girl with headaches and seizures who had been treated for ALL with L-asparaginase. **(a)** Sagittal T1-weighted MR image shows high signal intensity along the superior sagittal sinus, a finding suggestive of a subacute thrombus. **(b)** Axial T2-weighted MR image shows frontal subcortical hemorrhagic lesions and high signal intensity within the sagittal sinus (arrow), which is suggestive of lack of flow. **(c)** Sagittal phase-contrast MR venogram shows thrombosis involving the superior sagittal sinus. Anticoagulant therapy was started, and follow-up MR imaging showed resolution of the thrombosis.

Chemotherapy and Bone Marrow Transplantation

Hemorrhage.—In patients with hematologic malignancies, hemorrhage can also occur during chemotherapy or bone marrow transplantation (Fig 13). The effect of some chemotherapeutic agents such as L-asparaginase aggravates the underlying thrombocytopenia and the anomalous production or breakdown of coagulation factors with subsequent bleeding diathesis (23). Leukemic patients may also develop disseminated intravascular coagulation with resulting hypofibrinogenemia and a pattern of multiple small hemorrhages in the subcortical white matter. Subdural or subarachnoid extraaxial hemorrhage is less common than intraaxial. Leukemic patients and oncologic patients in general are also at increased risk for cerebral hemorrhagic infarction, although

the pathogenic mechanism is often sinovenous thrombosis (2,4,15).

Dural Venous Thrombosis.—Sinovenous occlusion is now reported more frequently in oncologic pediatric patients, particularly in leukemia. Contributing factors include CNS infiltration, leukostasis, and chemotherapeutic agents such as L-asparaginase and vincristine. Up to 2% of patients treated with L-asparaginase develop hemorrhagic or nonhemorrhagic infarcts, usually secondary to sinovenous occlusion (24,25). Transient protein S deficiency induced by L-asparaginase has been advocated as a causal mechanism (26). Diagnosis requires a high index of suspicion, and radiologists should look for subtle signs at CT such as venous infarcts, abnormal sinus high attenuation on precontrast scans, and abnormal central sinus low attenuation (“empty delta sign”) on postcontrast scans (27–30). MR imaging with flow-sensitive gradient-echo techniques or MR venography can easily show the lack of flow void in the affected dural sinuses (Fig 14).



a.

b.

Figure 15. Pure methotrexate leukoencephalopathy in a 6-year-old boy who had been treated for ALL only with chemotherapy (intravenous and intrathecal methotrexate therapy). He developed progressive neurologic deterioration with motor dysfunction and lethargy. Axial T2-weighted (**a**) and fluid-attenuated inversion-recovery (**b**) MR images show hyperintense symmetrical lesions involving the periventricular white matter. The patient's condition improved, but he was lost to further MR imaging follow-up.

White Matter Disease.—Chemotherapeutic agents, particularly methotrexate, cisplatin, arabinosylcytosine, carmustine, and thiotepa, occasionally cause cerebral white matter anomalies. These abnormalities, which can be asymptomatic or symptomatic, transient or permanent, are characterized by diffuse, symmetrical involvement of central and periventricular white matter, usually with relative preservation of subcortical fibers (12,13). Treatment exclusively with high-dose chemotherapy in leukemic patients, usually consisting of both intravenous and intrathecal methotrexate, can cause acute or subacute transient benign neurotoxic effects (Fig 15) or rarely more severe encephalopathy with permanent neurologic deficits (7,31). More significant alteration of

intellectual performance after cranial irradiation than after intrathecal methotrexate therapy has been reported in children with ALL, although neurologic sequelae can be seen in both groups (17).

Reversible Posterior Leukoencephalopathy Syndrome.—The term *reversible posterior leukoencephalopathy syndrome* refers to reversible acute neurologic complications in pediatric patients under treatment for myeloproliferative disorders, occurring with immunosuppressor medication, mainly cyclosporine. The clinical syndrome was first described as acute neurologic changes in the setting of sudden or prolonged arterial hypertension that overcomes the autoregulatory capacity of the cerebral vasculature (32,33). The relative paucity of sympathetic innervation in the posterior circulation may account for the preponderance of posterior cerebral changes. Neurologic

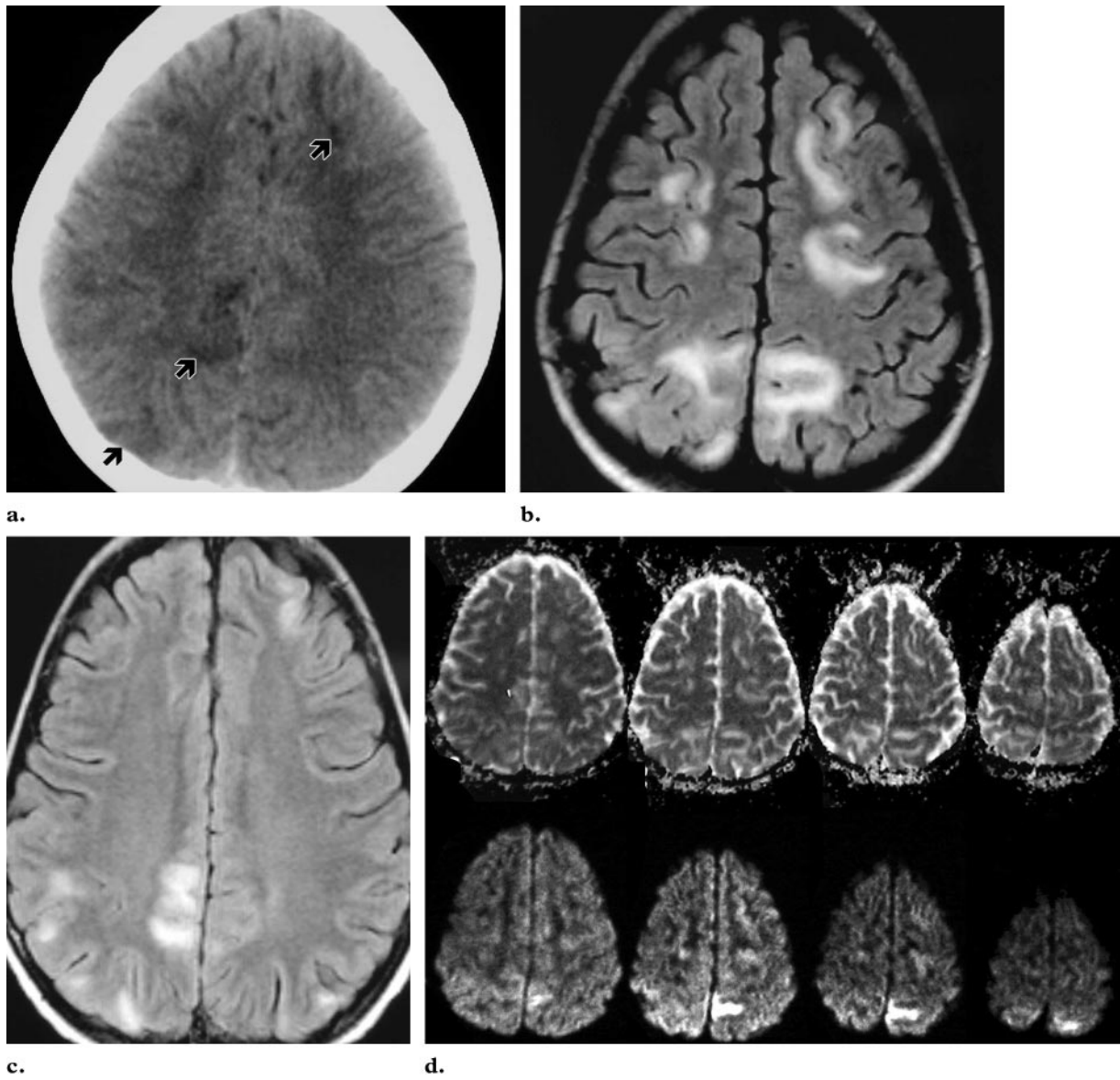


Figure 16. Reversible posterior leukoencephalopathy in a 12-year-old boy with ALL and a bone marrow transplant who presented with visual disturbances and seizures. The clinical symptoms coincided with arterial hypertension. **(a)** Axial CT scan shows hypoattenuating cortical-subcortical lesions in the parietal lobes (arrows). **(b, c)** Axial fluid-attenuated inversion-recovery MR images (**b** obtained at a lower level than **c**) show the lesions more clearly. **(d)** Axial isotropic diffusion-weighted MR images show an elevated apparent diffusion coefficient in regions with the corresponding signal intensity abnormality on T2-weighted images. The patient recovered from the neurologic symptoms after blood pressure was controlled, and follow-up MR imaging demonstrated complete resolution of the lesions.

manifestations include headache, nausea, vomiting, seizures, visual changes, confusion, and coma. CT and MR imaging show subcortical white matter edema, predominantly in the posterior temporal, parietal, and occipital areas, although more severe cases can also affect the basal ganglia, cerebellar hemispheres, and brainstem (Figs 16, 17). Characteristically, these affected

areas usually have increased or facilitated diffusion at diffusion-weighted MR imaging because of the absence of cytotoxic edema. Prompt control of blood pressure and withdrawal of the immunosuppressive drug often result in complete

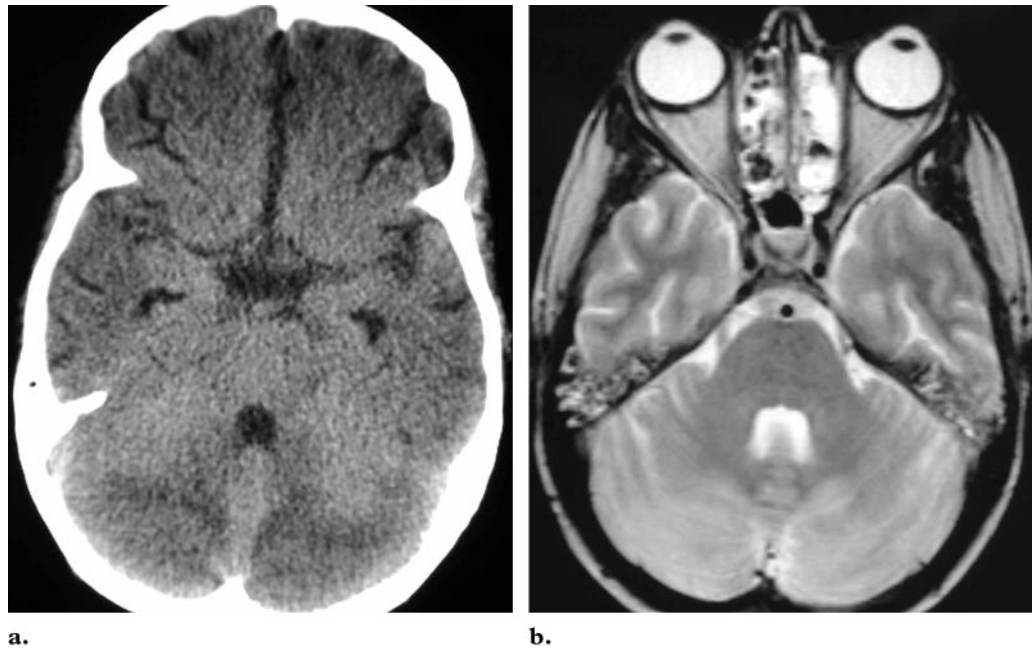


Figure 17. Reversible posterior leukoencephalopathy with cerebellar involvement in a 10-year-old boy with ALL and a bone marrow transplant who presented with posterior headaches and cerebellar signs. **(a)** Axial CT scan shows symmetrical hypoattenuating cerebellar lesions. **(b)** Axial T2-weighted MR image obtained 24 hours later shows improvement of the lesions.

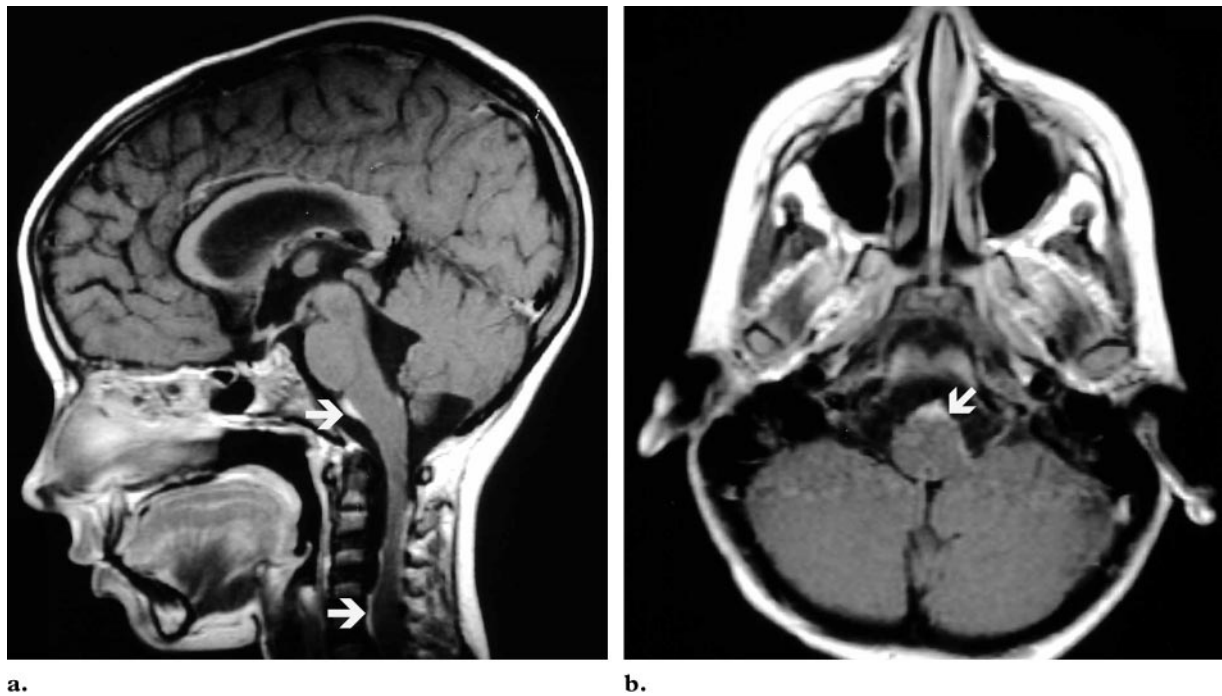
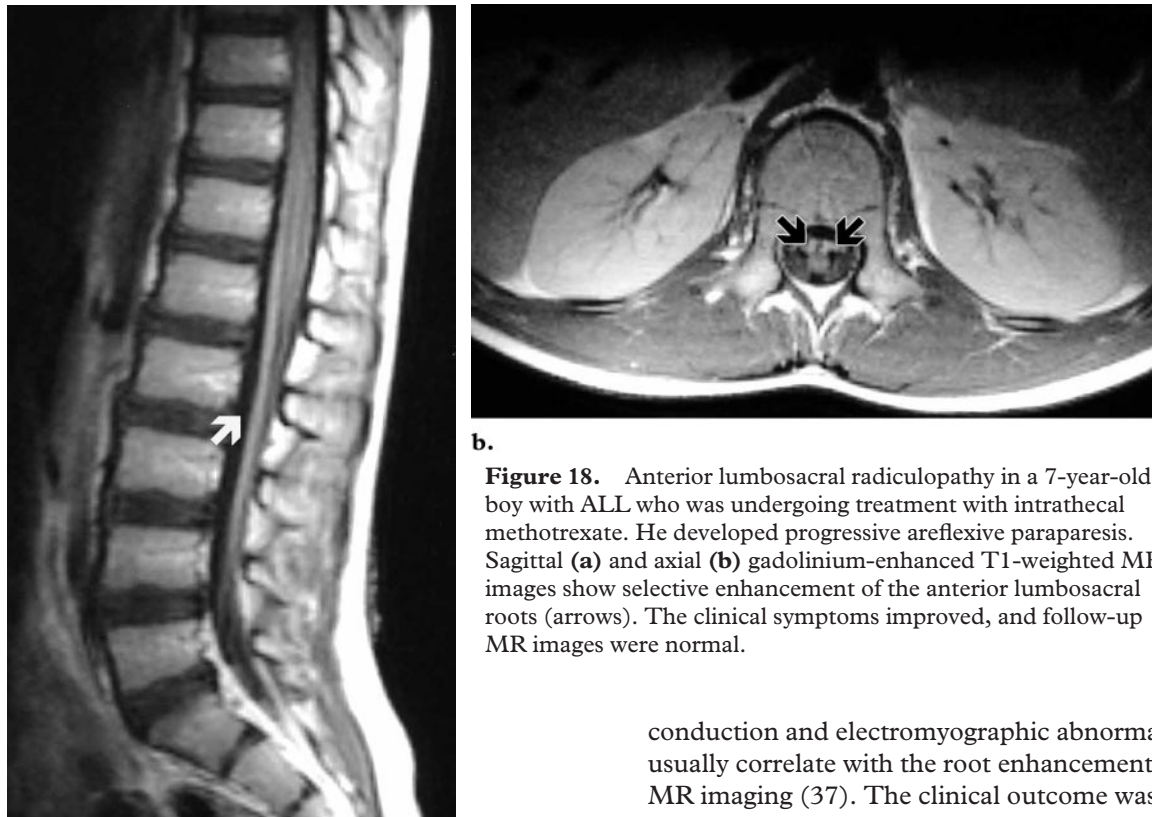


Figure 19. Fungal meningitis in an 8-year-old girl being treated for a cervicothoracic neuroblastoma. She later developed acute myelogenous leukemia and during chemotherapy and bone marrow transplantation presented with persistent headaches and fever. Sagittal **(a)** and axial **(b)** gadolinium-enhanced cranial T1-weighted MR images show nodular enhancing leptomenigeal lesions along the brainstem and spinal cord (arrows). A very rare opportunistic fungus (*Pseudallescheria Boydii*) was identified at cerebrospinal fluid culture, and antifungal therapy was intensified with administration via an Ommaya reservoir. However, the patient developed hydrocephalus and eventually died.



a.

b.

Figure 18. Anterior lumbosacral radiculopathy in a 7-year-old boy who was undergoing treatment with intrathecal methotrexate. He developed progressive areflexive paraparesis. Sagittal (a) and axial (b) gadolinium-enhanced T1-weighted MR images show selective enhancement of the anterior lumbosacral roots (arrows). The clinical symptoms improved, and follow-up MR images were normal.

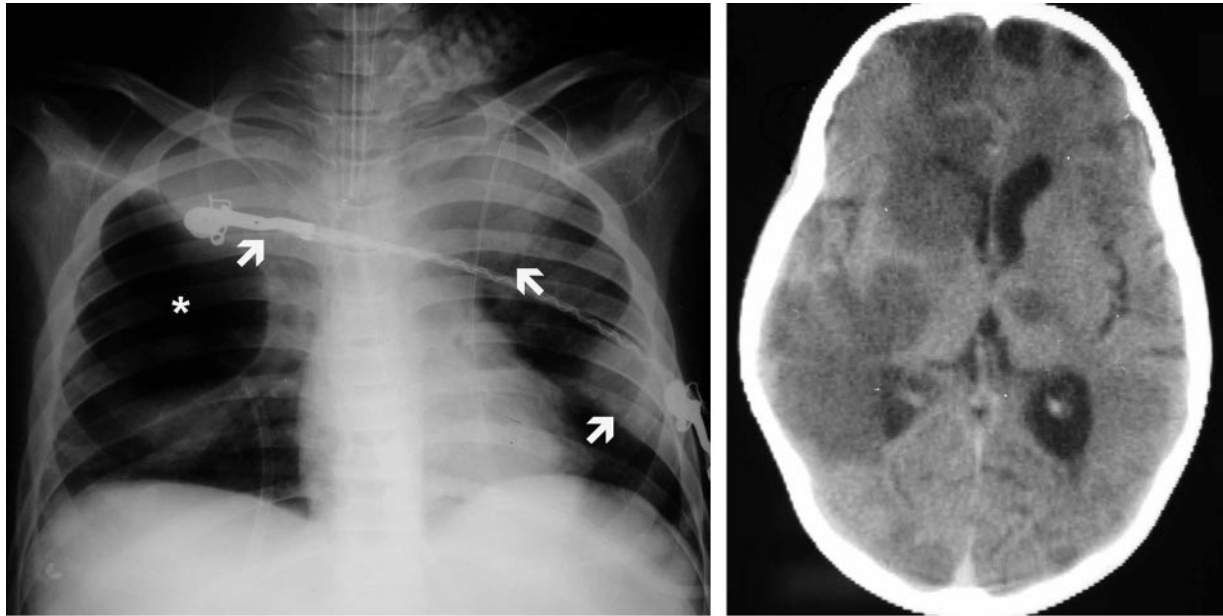
neurologic recovery with resolution of the neuroimaging abnormalities. Nevertheless, if left untreated, arterial hypertension can lead to progressive neurologic deterioration with infarction or hemorrhage and possible irreversible neurologic deficit (34). In these cases, the presence of cytotoxic edema due to cerebral vasospasm and cerebral ischemia can result in decreased water mobility at diffusion MR imaging (35).

Anterior Lumbosacral Radiculopathy.—Intrathecal methotrexate administration can produce anterior lumbosacral radiculopathy attributed to direct toxic effects on the spinal cord. The clinical picture was similar in the three patients seen in our hospital and consisted of progressive, flaccid weakness of the lower extremities without sensory deficit. All of these patients showed enhancement of the anterior lumbosacral nerve roots on gadolinium-enhanced MR images (Fig 18). It has been suggested that this finding is related either to a susceptibility of the anterior roots to the toxic effect of methotrexate or to a gravity-dependent increased concentration of the drug around these roots, although a selective autoimmune process cannot be excluded (36). Nerve

conduction and electromyographic abnormalities usually correlate with the root enhancement at MR imaging (37). The clinical outcome was dissimilar in our three patients, with posterior recovery in one patient, partial recovery in another, and persistent paraplegia in the third. Spinal MR imaging allows quick differential diagnosis between this anterior toxic radiculopathy and the potential epidural-subdural hematoma occurring after lumbar puncture secondary to thrombocytopenia.

Infectious Complications

Infectious complications are one of the most significant causes of morbidity and death in the pediatric cancer patient. Both the underlying malignancy (leukemia or lymphoma) and the antineoplastic therapy can cause immunosuppression. The risk of infection increases as a function of the degree and duration of granulocytopenia. Fungi are the most frequent causal microorganisms (Fig 19) and typically affect patients having absolute granulocytic counts of less than $100/\text{mm}^3$ for more than 2 weeks (4,15). Additional risk factors for disseminated fungal disease include prolonged hospitalization, administration of broad-spectrum antibiotics, chemotherapy- or radiation therapy-induced mucosal damage, and steroid administration. *Candida* and *Aspergillus* species are the organisms most frequently identified (38–42).



a.

b.

Figure 20. Invasive thoracic and cerebral aspergillosis in a very neutropenic patient being treated with intensive chemotherapy and bone marrow transplantation. The invasive pulmonary aspergillosis required treatment in the intensive care unit. **(a)** Chest radiograph shows bilateral pulmonary infiltrates (arrows) with a huge bulla on the right side (*). **(b)** Axial cranial CT scan shows large hypoattenuating areas that correspond to invasive aspergillosis with secondary infarcts. Postmortem examination demonstrated aspergillosis in multiple locations.

Aspergillus disseminates to the CNS hematogenously, most commonly from the lung, causing infectious vasculopathy leading to acute infarction or hemorrhage, or extends into surrounding tissue as infectious cerebritis or abscess. In neutropenic patients, fungal sinusitis, usually aspergillosis or mucormycosis, may manifest only as mild rhinorrhea or facial pain and quickly progress to rhinocerebral syndrome with invasion of the CNS via the cribriform plate (5). Three imaging patterns have been described in neutropenic patients with cerebral invasive aspergillosis (40): (a) cortical-subcortical hypoattenuating areas on CT scans (Fig 20) or hyperintense areas on T2-weighted images, (b) multiple ring-enhancing lesions, and (c) dural enhancement adjacent to sinonasal disease (Fig 21). In our experience, subtle or minimal peripheral enhancement is more common in leukemic patients than a well-defined ring pattern because edema and enhancement capacity are dependent on lymphocyte and total leukocyte counts.

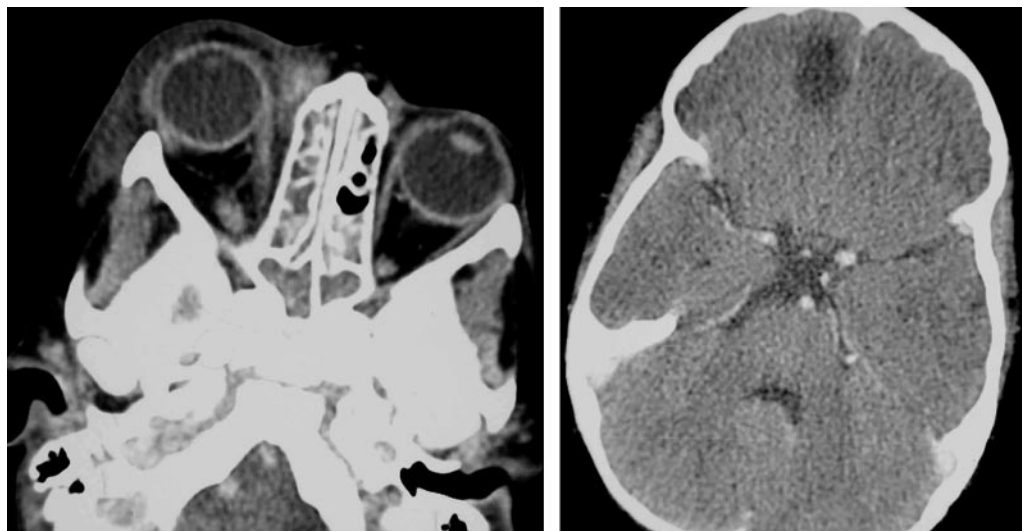
Candidiasis can also be seen in immunocompromised patients; however, in our experience, it

is rather uncommon beyond the neonatal period. It appears at imaging as numerous ring-enhancing microabscesses less than 3 mm in diameter at the gray-white matter junction, basal nuclei, and cerebellum. The predilection of *Candida* for vascular structures may cause vasculitis, intraparenchymal hemorrhage, mycotic aneurysms, and thrombosis of small vessels with secondary infarction (43).

Conclusions

Many pathologic conditions affect the CNS in pediatric patients with oncohematologic processes. These pathologic conditions are related to the primary disease, the various antineoplastic therapies required for its treatment (radiation therapy, chemotherapy, and bone marrow transplantation), or infectious complications. Use of modern imaging techniques facilitates prompt diagnosis, which is essential for early therapy and increased overall survival.

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a.

b.

Figure 21. Invasive paranasal and cerebral aspergillosis in an 11-year-old boy with ALL and a bone marrow transplant who was severely neutropenic. He presented with fever, frontal headaches, and right proptosis. **(a)** Axial CT scan shows extensive ethmoidal and sphenoidal disease with right pre- and postseptal orbital cellulitis. Sinus aspergillosis was diagnosed, and intensive antifungal therapy was administered. The patient's condition quickly deteriorated in the course of 1 week, with severe headaches. **(b)** Axial contrast-enhanced cranial CT scan shows a hypoattenuating area in the olfactory right frontal lobe. The patient's neurologic status deteriorated, and he died in a few days.

References

1. Parker BR. Leukemia and lymphoma in childhood. *Radiol Clin North Am* 1997; 35:1495–1516.
2. Ginsberg LE, Leeds EN. Neuroradiology of leukemia. *AJR Am J Roentgenol* 1995; 165:525–534.
3. Jäger HR, Williams EJ, Savage DG, et al. Assessment of brain changes with registered MR before and after bone marrow transplantation for chronic myeloid leukemia. *AJNR Am J Neuroradiol* 1996; 17:1275–1282.
4. Chen C, Zimmerman RA, Faro S, et al. Childhood leukemia: CNS abnormalities during and after treatment. *AJNR Am J Neuroradiol* 1996; 17:295–310.
5. Kaste SC, Rodriguez-Galindo C, Furman WL, Langston J, Thompson SJ. Imaging aspects of neurologic emergencies in children treated for non-CNS malignancies. *Pediatr Radiol* 2000; 30:558–565.
6. Kingma A, Tamminga RY, Kamps WA, Le Coultré R, Saan RJ. Cerebrovascular complications of L-asparaginase therapy in children with leukemia: aphasia and other neuropsychological deficits. *Pediatr Hematol Oncol* 1993; 10:303–309.
7. Shuper A, Stark B, Kornreich L, et al. Methotrexate treatment protocols and the CNS: significant cure with significant neurotoxicity. *J Child Neurol* 2000; 15:573–580.
8. Paige ML, Bernstein JR. Transcalvarial primary lymphoma of bone: a report of two cases. *Neuroradiology* 1995; 37:456–458.
9. Guerhazi A, Feger C, Rousselot P, et al. Granulocytic sarcoma (chloroma): imaging findings in adults and children. *AJR Am J Roentgenol* 2002; 178:319–325.
10. Tomura N, Hirano H, Kato K, et al. CNS involvement of leukemia and systemic lymphoma in children: CT and MR findings. *No To Shinkei* 1997; 49:993–1000. [Japanese]
11. Madani A, Christophe C, Ferster A, Dan B. Peri-optic nerve infiltration during leukaemic relapse: MRI diagnosis. *Pediatr Radiol* 2000; 30:30–32.
12. Ball WS Jr, Prenger EC, Ballard ET. Neurotoxicity of radio/chemotherapy in children: pathologic and MR evaluation. *AJNR Am J Neuroradiol* 1992; 13:761–776.
13. Barkovich AJ. *Pediatric neuroimaging*. 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2000.
14. Edwards-Brown MK, Jakacki RI. Imaging the CNS effects of radiation and chemotherapy of pediatric tumors. *Neuroimaging Clin North Am* 1999; 9:177–193.
15. Parisi MT, Fahmy JL, Kaminsky CK, Malogolowkin MH. Complications of cancer therapy in children: a radiologist's guide. *RadioGraphics* 1999; 19:283–297.
16. Shanley DJ. Mineralizing microangiopathy: CT and MRI. *Neuroradiology* 1995; 37:331–333.
17. Bernaldez-Rios R, Villasis-Keever MA, Beltrán-Adame G, et al. Neurological and psychological sequelae in children with acute lymphoblastic leukemia who had received radiotherapy and intrathecal methotrexate. *Gac Med Mex* 1998; 134:153–159. [Spanish]

18. Maeder P, Gudinchet F, Meuli R, Tribolet N. Development of a cavernous malformation of the brain. *AJNR Am J Neuroradiol* 1998; 19:1141–1145.
19. Gaensler EH, Dillon WP, Edwards MSB, Larson DA, Rosenau W, Wilson CB. Radiation-induced telangiectasia in the brain simulates cryptic vascular malformation at MR imaging. *Radiology* 1994; 193:629–636.
20. Poussaint TY, Siffert J, Barnes PD, et al. Hemorrhagic vasculopathy after treatment of CNS neoplasm in childhood: diagnosis and follow-up. *AJNR Am J Neuroradiol* 1995; 16:693–699.
21. Choi D, Seex K. Intracranial meningioma following childhood irradiation for leukaemia. *Br J Haematol* 2000; 108:665.
22. Wishio S, Morioka T, Inamura T, et al. Radiation-induced brain tumours: potential late complications of radiation therapy for brain tumours. *Acta Neurochirurg* 1998; 140:763–770.
23. Feinberg WM, Swenson MR. Cerebrovascular complications of L-asparaginase therapy. *Neurology* 1988; 38:127–133.
24. Ho CL, Chen CY, Chen YC, Chao TY. Cerebral dural sinus thrombosis in acute lymphoblastic leukemia with early diagnosis by fast fluid-attenuated inversion recovery (FLAIR) MR image: a case report and review of the literature. *Ann Hematol* 2000; 79:90–94.
25. Fleischhack G, Solymosi L, Reiter A, Bender-Gotze C, Eberl W, Bode U. Imaging methods in diagnosis of cerebrovascular complications with L-asparaginase therapy. *Klin Padiatr* 1994; 206:334–341.
26. Millot F, Traore P, Boinot C, et al. Homonymous lateral hemianopsia revealing cerebral thrombophlebitis: role of a deficiency of protein S induced by L-asparaginase. *Presse Med* 2001; 309:855–857. [French]
27. Schick RM, Jolesz F, Barnes PD, Macklis JD. MR diagnosis of dural venous sinus thrombosis complicating L-asparaginase therapy. *Comput Med Imaging Graph* 1989; 13:319–327.
28. Meininger V, James JM, Rio B, Zittoun R. Dural venous sinus occlusions in hemopathies. *Rev Neurol* 1985; 141:228–233.
29. Steinherz PG, Miller LP, Ghavimi F, Allen JC, Miller DR. Dural sinus thrombosis in children with acute lymphoblastic leukemia. *JAMA* 1981; 246:2837–2839.
30. Lockman LA, Mastri A, Priest JR, Nesbit M. Dural venous sinus thrombosis in acute lymphoblastic leukemia. *Pediatrics* 1980; 66:943–947.
31. Lovblad K, Kelkar P, Ozdoba C, Ramelli G, Remonda L, Schroth G. Pure methotrexate encephalopathy presenting with seizures: CT and MR features. *Pediatr Radiol* 1998; 28:86–91.
32. Jones BV, Egelhoff JC, Petterson J. Hypertensive encephalopathy in children. *AJNR Am J Neuroradiol* 1997; 18:101–106.
33. Cooney MJ, Bradley WG, Symko SC, Patel ST, Groncy PK. Hypertensive encephalopathy in children treated for myeloproliferative disorders: report of three cases. *Radiology* 2000; 214:711–716.
34. Antunes NL, Small TN, George D, Boulard F, Lis E. Posterior leukoencephalopathy syndrome may not be reversible. *Pediatr Neurol* 1999; 20:241–243.
35. Mukherjee P, McKinstry RC. Reversible posterior leukoencephalopathy syndrome: evaluation with diffusion-tensor MR imaging. *Radiology* 2001; 219:756–765.
36. Koh S, Nelson M, Kovanlikaya A, Chen LS. Anterior lumbosacral radiculopathy after intrathecal methotrexate treatment. *Pediatr Neurol* 1999; 21:576–578.
37. Anderson SC, Baquis GD, Jackson A, Monteleone P, Kirkwood JR. Ventral polyradiculopathy with pediatric acute lymphocytic leukemia. *Muscle Nerve* 2002; 25:106–110.
38. Sparano JA, Gucalp R, Llena JF, Moser FG, Wiernik PH. Cerebral infection complicating systemic aspergillosis in acute leukemia: clinical and radiographic presentation. *J Neurooncol* 1992; 13:91–100.
39. Talbot GH, Huang A, Provencher M. Invasive aspergillus rhinosinusitis in patients with acute leukemia. *Rev Infect Dis* 1991; 13:219–232.
40. Ashdown BC, Tien RD, Felsberg GJ. Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: CT and MR imaging findings. *AJR Am J Roentgenol* 1994; 162:155–159.
41. Dietrich U, Hettmann M, Maschke M, Doerfler A, Schwechheimer K, Forsting M. Cerebral aspergillosis: comparison of radiological and neuropathologic findings in patients with bone marrow transplantation. *Eur Radiol* 2001; 11:1242–1249.
42. Miaux Y, Ribaud P, Williams M, et al. MR of cerebral aspergillosis in patients who have had bone marrow transplantation. *AJNR Am J Neuroradiol* 1995; 16:555–562.
43. Lai PH, Lin SM, Pan HB, Yang CF. Disseminated miliary cerebral candidiasis. *AJNR Am J Neuroradiol* 1997; 18:1303–1306.