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PICTORIAL ESSAY

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Imaging findings of recurrent acute lymphoblastic leukemia in children and young adults, with emphasis on MRI

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Abstract Acute lymphoblastic leukemia (ALL) is the most common of all childhood malignancies. Current remission rates approach 80%. Recurrent disease can present in a wide variety of ways. MR imaging plays a crucial role in the detection of disease relapse. Because other disorders can mimic recurrence of leukemia, it is important for the radiologist to judge recurrence from non-recurrence accurately in order to avoid unnecessary testing and emotional stress on the patient and family.

Keywords Acute lymphoblastic leukemia · ALL · Magnetic resonance · Childhood leukemia

Introduction

Acute lymphoblastic leukemia (ALL) is the most common of all childhood malignancies [1]. Current remission rates for patients with ALL approach 80% [2, 3]. About 25–30% of patients with ALL experience recurrence of the disease [4]. Relapse of the disease is a major cause of treatment failure and usually occurs within 3 years of treatment [5]. Patients at greatest risk for disease relapse during first remission are those diagnosed with ALL when less than 1 year of age, those with cytogenetic abnormalities, those who do not achieve remission within 28 days of starting induction therapy, and those whose presenting leukocyte count exceeds 1,000,000/mm^3 [6]. Bone-marrow transplantation is most commonly offered to patients who have achieved a second remission [6]. Those who relapse after bone-marrow transplantation usually have a poor prognosis, with the average survival duration of approximately 6–10 months [5]. Treatment of ALL relapse after BMT takes into consideration the patient's age at the time of relapse, interval between BMT and relapse, and the patient's response to previous treatment.

Patients with relapse of leukemia may present with non-specific symptoms such as joint pain or fatigue, or with symptoms reflecting the site of relapse, e.g. blurred vision or seizures [7]. Diagnosis of relapse

includes clinical and laboratory demonstration of peripheral, central nervous system, or marrow disease after induction of remission. Bone marrow aspirate and biopsy are needed for proper immunophenotyping [7]. The bone marrow can remain in morphological remission for months or even years after the patient has developed extramedullary relapse [7]. As MR imaging is a standard method of evaluating many of these symptoms, the diagnosis of relapsed leukemia may first be suggested by the radiologist. Extramedullary relapses typically involve sequestered sites such as the central nervous system (CNS), testes, liver,

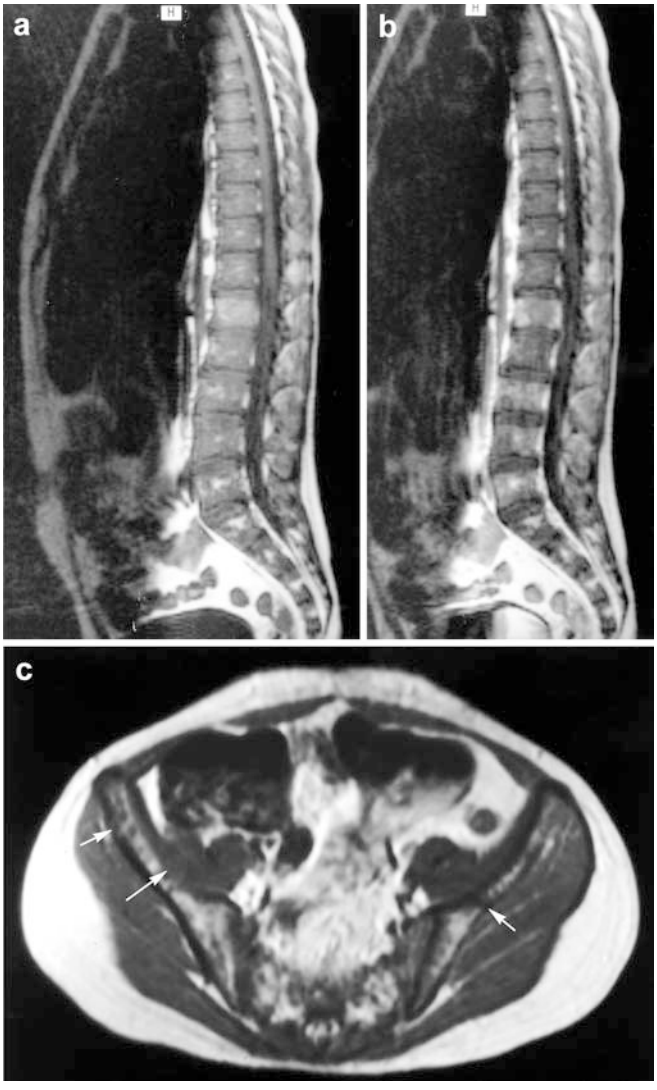


Fig. 1a–c A 12-year-old boy underwent MR imaging of the spine and pelvis to evaluate a 2-week history of increasing back pain while on treatment for acute lymphoblastic leukemia (ALL) relapse. **a** Sagittal non-contrast T_1- and **b** contrast-enhanced T_1-weighted MR of the spine without fat suppression shows abnormal signal of virtually all imaged bones with varying degrees of contrast enhancement at several levels. The normal fatty bone marrow has been replaced by leukemic infiltration. Enhancing lesion conspicuity would be increased with a fat-suppression sequence, but visualization of abnormal fatty changes would be suppressed. **c** Axial proton density imaging of the pelvis shows extensive bone-marrow signal abnormalities in the form of multiple punctate foci that coalesce. Also note interruption of the cortex of the iliac wings indicative of disease (*arrows*). Lumbar spine radiographs (not shown) were normal

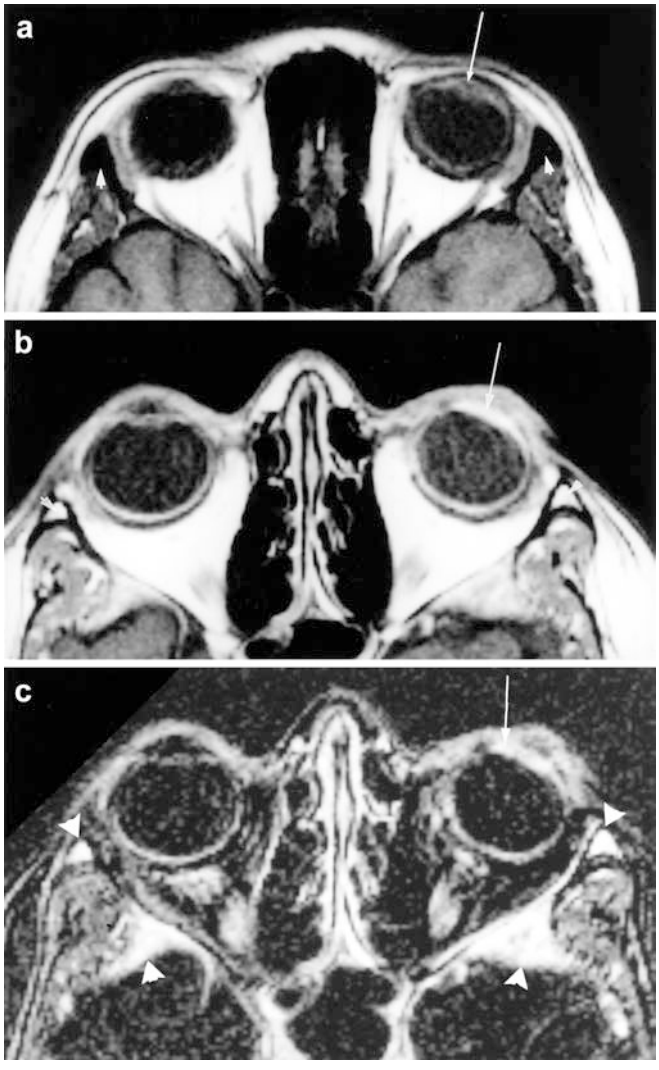


Fig. 2a–c A 14-year-old boy with recurrent ALL and leukemic infiltration of the left anterior chamber; the imaging findings were confirmed by ophthalmologic examination to represent leukemic infiltration of the anterior chamber of the left globe. **a** Pre- and **b** post-contrast enhanced T_1-weighted images demonstrate abnormal thickening and intense enhancement of the curvalinear density of the left anterior chamber corresponding to leukemic infiltration (*arrow*). Also note generalized bone-marrow infiltration evidenced by decreased signal on T_1-weighted sequence and enhancement with contrast administration (*arrowheads*). **c**Subtraction image demonstrates with better conspicuity the abnormal anterior chamber enhancement (arrow) and extensive bone-marrow enhancement

kidneys, spleen, spine, and the eye [1]. This pictorial essay describes the MR appearance of ALL relapse obtained from a single tertiary-care pediatric oncology center. Additional CT and US imaging examples are included where appropriate.

Bone-marrow relapse

The most common site of ALL relapse is the bone marrow. Bone-marrow relapse has been defined as marrow that contains 20% or more blasts [8]. Patients who have bone-marrow relapse present with painful limbs and joints [9]. MR imaging without contrast-enhancement is used to detect bone-marrow infiltration by leukemic cells. Bone-marrow relapse usually has decreased signal on T_1- weighted MR images, increased signal on T_2-weighted sequences, and is enhanced with gadolinium administration [9, 10] (Figs. 1, 2, 3, 4). However, evolving lesions of osteonecrosis (also seen in children under treatment for leukemia) can mimic leukemic relapse by MR [9]. In our (unpublished) experience, osteonecrosis preferentially occurs in weight-bearing joints and in the diaphyses of the long bones, though it may develop in any skeletal site.

Ocular relapse

Nearly all portions of the globe have been reported to be involved by leukemia cells [11] (Fig. 2). Leukemic infiltration of the optic nerve is more common in children with ALL (Fig. 5) than in adults and is found in 13–16% of patients who die from leukemia [7]. If the optic-nerve disease is not diagnosed early, it could result in irreversible vision loss. Because optic-nerve relapse occurs most frequently in patients with a history of ALL, some authors have proposed that follow-up examinations of the optic discs be performed on all patients who have been diagnosed with ALL, whether or not there is a

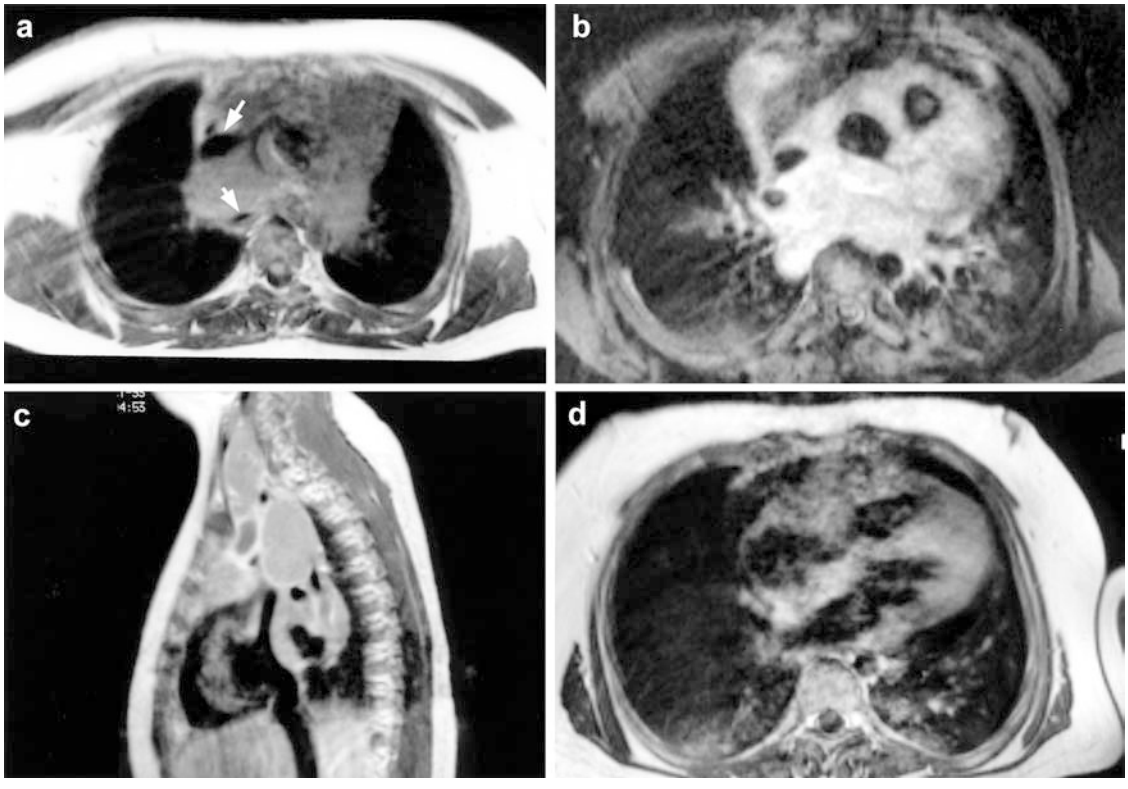


Fig. 3a–d A 14-year-old boy with T-cell ALL having completed therapy 11 months prior to imaging. He presented with cough and low-grade fever unresponsive to antibiotics. The chest radiograph obtained by his local physician reportedly showed cardiomegaly. **a** Axial non-contrast T_1- (650/15) weighted image through the upper chest shows the large intermediate-signal mediastinal mass encasing the ascending aorta and compressing the superior vena cava (*arrow*) and trachea (*short arrow*). **b** Axial T_2-weighted (4500/18) images through the mid-chest demonstrate a large mediastinal mass encasing the superior unit cava and surrounding the roots of the great vessels. There is extension into the retrosternal space and into the subcarinal distribution.**c** Sagittal contrast-enhanced T_1-weighted (787/15) demonstrates extensive adenopathy involving the anterior and middle mediastinum with encasement of great vessels. Note mass effect on the posterior aspect of the right atrium. **d** Axial contrast enhanced T_1-weighted (755/15) demonstrates global myocardial enlargement with homogeneous contrast enhancement

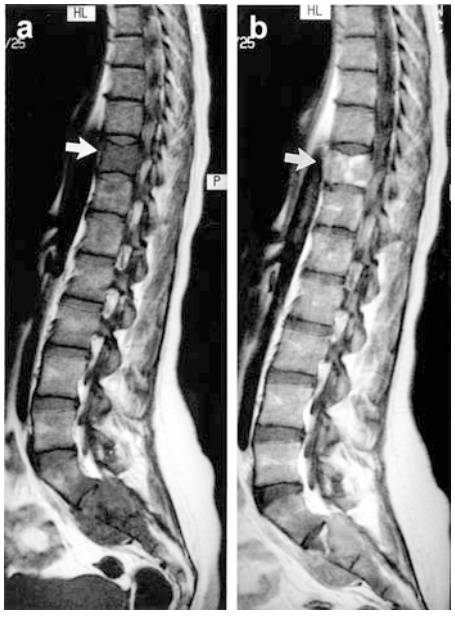


Fig. 4a, b A 25-year-old woman presented with sacral neuropathy 2 years postautologous BMT for relapsed ALL. **a** Sagittal pre- and **b** postcontrast enhanced T_1-weighted (430/15) images of the thoracolumbar spine demonstrates multiple sites of bone metastases. The sites of disease demonstrate decreased signal on T_1, increase signal on T_2 (not shown) and enhanced with intravenous contrast administration. Also note compression fracture of T11 (*arrows*). Note that the sacral mass extends anteriorly from the sacral body as well as posteriorly into the thecal sac

previous history of CNS involvement [7]. However, optic-nerve involvement may occur even in the presence of a normal ophthalmologic examination. Leukemic infiltration of the optic nerve can be detected with MR imaging and should be considered when enhancing optic nerve enlargement is found in a patient previously treated for ALL [7] (Figs. 2, 5, 6) The role of MRI in the routine follow-up of these patients could be considered, but its efficacy as a screening tool has not as yet been determined.

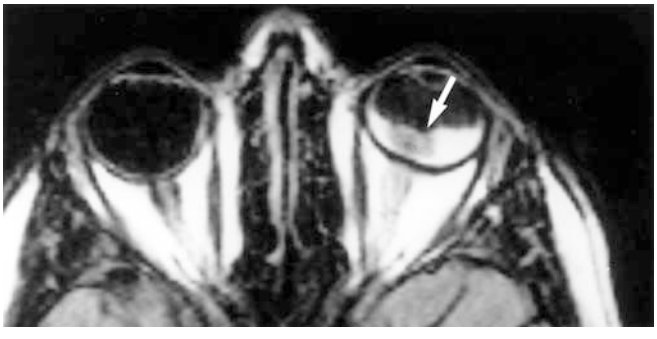


Fig. 5 A 17-year-old boy, 14 months off therapy for ALL, presented with vision loss in the left eye after being hit with a football. Ophthalmologic examination revealed retinal detachment associated with a retinal mass further determined to represent ocular relapse of ALL. Axial postcontrast-enhanced T1-weighted image through the globes demonstrates an enhancing soft-tissue mass (*arrow*) within the fluid of the retinal detachment. Note loss of CSF space of the left optic nerve with enhancement. There is also subtle irregular thickening of the nasal aspect of the retinal surface of the right globe

Central nervous system relapse

Leptomeningeal relapse

ALL is the most common pediatric malignancy associated with leptomeningeal disease [12]. Leptomeningeal metastases, though rare overall, may occur either at the time of diagnosis of ALL with an overall risk of about 3% (range, 1.3–7.6%) or at the time of relapse with an overall risk of about 15% (range 8–20%) [13]. The like-

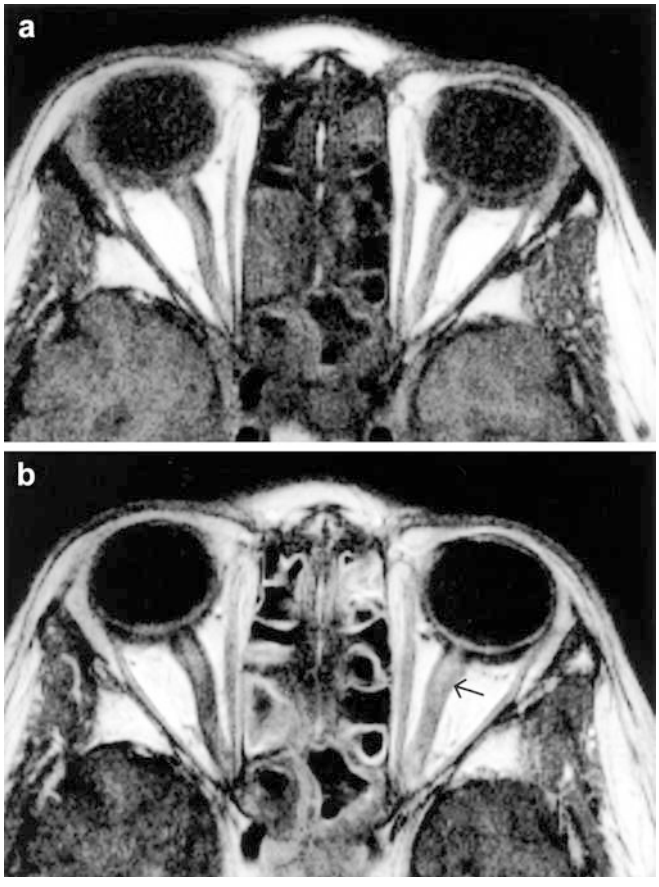


Fig. 6a, b An 8-year-old male complained of blurred peripheral vision while on continuation therapy for ALL. Clinical examination revealed retinal lesions suspicious for tumor. **a** Axial noncontrast T_1-weighted image through the orbits demonstrates mildly enlarged optic nerves that diffusely enhance with **b** intravenous administration of gadolinium (*arrow*). These findings are consistent with leukemic infiltration of the optic nerves

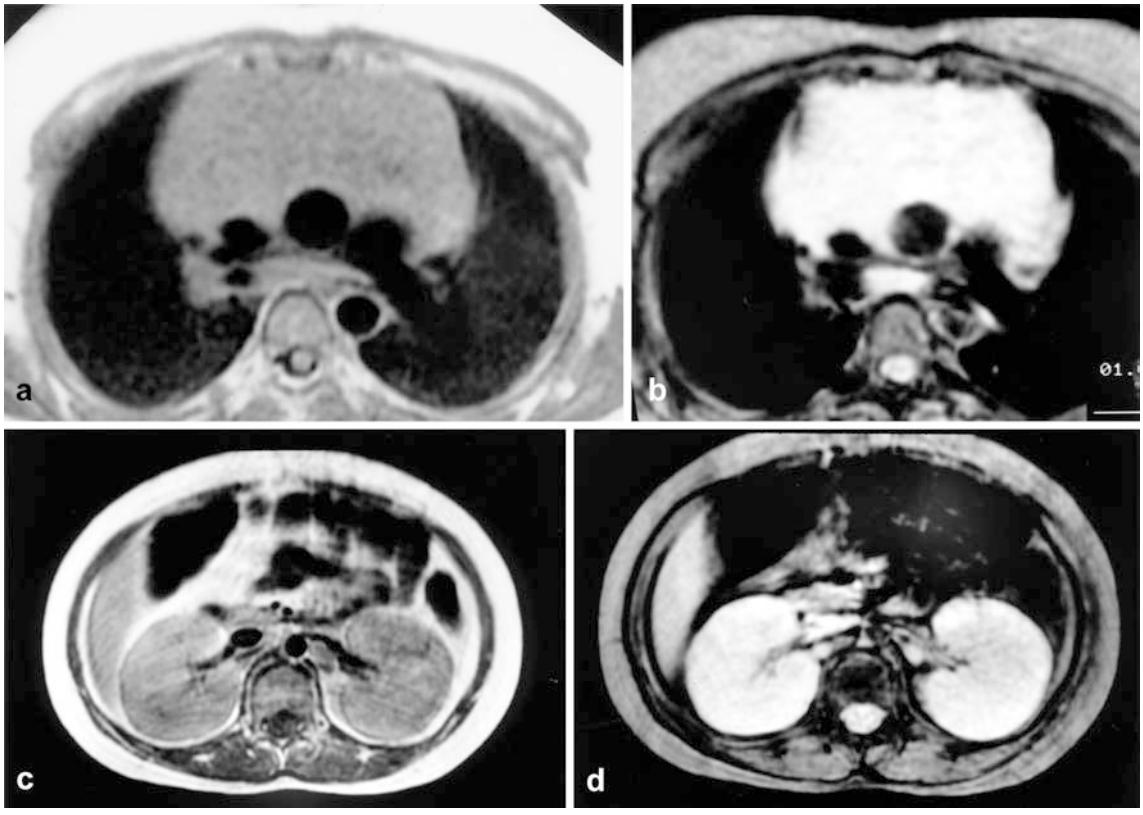


Fig. 7a–d This 10-year-old girl underwent MR imaging of the chest prior to referral to our institution because of a mediastinal mass noted on chest radiography. **a** Axial non-contrast T1- and **b** T2-weighted MR images of the chest demonstrate a diffusely enlarged thymus with homogeneous signal intensity. Note encasement of great vessels and extension into the middle mediastinum. The thymus is larger than normally seen for a child of this age and has convex lateral margins. There is also mild airway compression. These factors suggest an infiltrative process of the thymus.**c** Axial non-contrast T_1- and **d** T_2-weighted MR images of the abdomen demonstrate diffusely enlarged kidneys with homogeneous signal (intermediate signal on T_1- and increased signal on T_2-weighted sequences)

lihood of developing leptomeningeal relapse in children seems to correlate with the children's initial clinical presentation: high peripheral leukocyte count, young age at diagnosis, T-cell disease, thrombocytopenia, lymphadenopathy, hepatosplenomegaly [14]. Clinical presentations of leptomeningeal disease include headache, cauda equina syndrome, cranial neuropathy, ataxia, and myelopathy [13]. The MR appearance of leptomeningeal metastasis includes subarachnoid nodule(s), cord widening, and epidural cord compression [13].

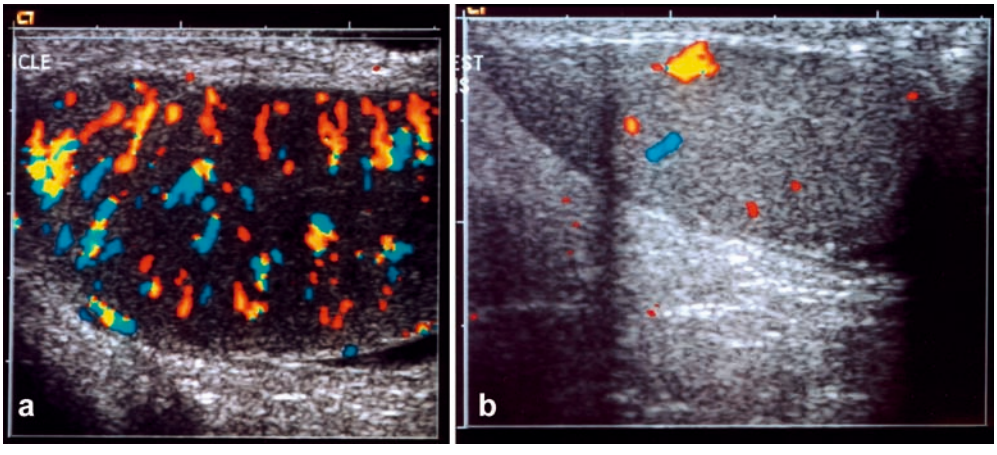


Fig. 8a, b This 17-year-old boy was diagnosed with low-risk ALL when 2 years old. Unilateral testicular enlargement was noted on a routine physical examination. Histologic examination of a right testicular biopsy revealed lymphoblastic infiltrate. Longitudinal images of the right (**a**) and left (**b**) testicles demonstrate an enlarged, hypoechoic and hypervascular right testes; these findings are charatceristic of testicular leukemia

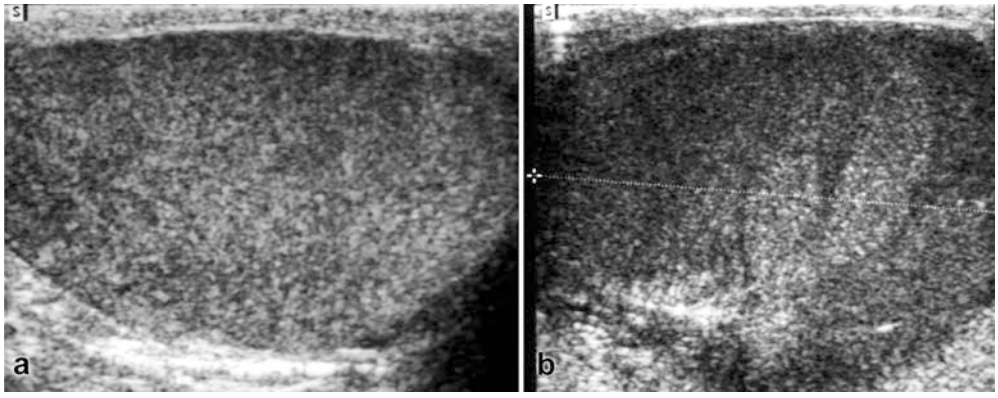
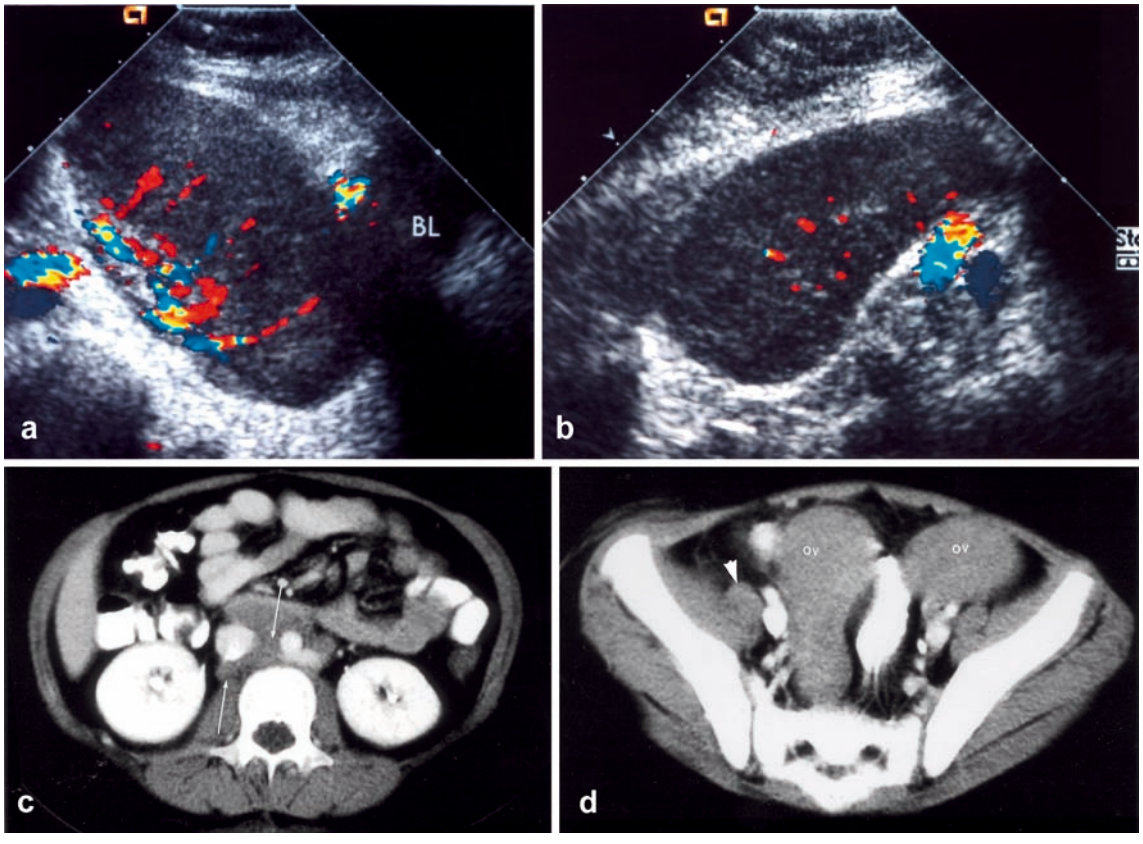


Fig. 9a, b A 12-year-old boy who returned with bilateral testicular enlargement 4 years after completing therapy for ALL. Histologic examination material obtained from biopsy of both testes revealed bilateral leukemic infiltrates of the testes. Longitudinal images of the right (**a**) and left (**b**) testicles demonstrate bilaterally symmetrical enlargement but asymmetrical echotexture. The left testicle has considerably greater inhomogeneous echo pattern than the right

Intraspinal mass

Leptomeningeal disease is relatively common in patients with acute leukemia, but an intraspinal mass as a site of relapse is rare [15, 16, 17]. (Figs. 1, 4) Such sites of recurrence may present with focal pain and/or neuro-

Fig. 10a–d A 10-year-old girl initially attained complete remission after 2 months of therapy. Ten months after completion of therapy, she presented with jaundice. An abdominal US was obtained for evaluation of hyperbilirubinemia. Bone-marrow aspirates performed during evaluation were consistent with relapse of ALL. Longitudinal US images of the pelvis demonstrate large bilateral (**a** right and **b** left) hypervascular ovarian masses; normal ovaries could not be discerned. **c** Axial contrast-enhanced abdominal-pelvic CT image demonstrates extensive paracaval adenopathy (*arrow*) and right iliac adenopathy (*arrowhead*) **d** in association with marked enlargement of the ovaries (*ov*). A hypodense area within the right ovary (not shown) was interpreted as indicative of necrosis



logic deficit. MR imaging readily demonstrates the intraspinal mass.

Mediastinal relapse

About 15% of patients with ALL have mediastinal masses at diagnosis [18] that are characteristically bulky and lie in the anterior mediastinum. They may extend into the middle or posterior mediastinum (Fig. 3). Leukemic infiltration of the mediastinum can result in thymic enlargement at relapse as well as at initial presentation [18, 19]. (Fig. 7).

Differentiation between post-therapy thymic rebound and thymic relapse of disease may be difficult. Radionuclide imaging with gallium-67, thallium-201, and/or 18-fluorodeoxyglucose (FDG) and MR imaging has been reported to be helpful in distinguishing between these two entities [20, 21, 22, 23, 24, 25]. Absence of gallium and/or thallium avidity suggests a quiescent process [20]. Though gallium avidity strongly suggests disease acitivity, such avidity may be falsely positive in up to 43% of cases [26]. More recently, thallium-201 has been shown to be 100% sensitive in patients with Hodgkin's disease at diagnosis [21]; its sensitivity in diagnosing relapsed ALL has not been studied. MR has a 100% sensitivity, 73% specificity, 35% positive predictive value, and 100% negative predictive value in detecting mediastinal disease [27]. Disease recurrence may be suspected when thymic signal is inhomogeneous (areas of decreased signal on T_1- and increased signal on T_2-weighted sequences) [20].

Cardiac relapse

Leukemic involvement occurs in 37% of 420 autopsy cases in the myocardium and 13% in the pericardium [28]. Involvement of the heart by malignant tumors occurs via three modes: retrograde involvement along lymphatic channels, direct extension, and hematogenous dissemination [29]. Cardiac involvement has rarely been reported as the presenting sign of leukemia [30], and most cases of cardiac involvement are asymptomatic [30, 31]. (Fig. 3). Cardiac valve involvement has been reported in chronic adult T-cell leukemia [32].

Renal relapse

Isolated renal relapse of ALL occurs very rarely [33, 34, 35]. Renal involvement by ALL at presentation or relapse may be inconspicuous or heralded by acute renal failure often with hyperuricemia [33, 34]. Leukemic infiltration of the kidneys is typically characterized by nephromegaly and, though usually bilateral, may rarely be unilateral or focal [34]. The kidneys may be symmetrically enlarged by imaging (Fig. 7) [33, 34]. By ultrasound, the involved kidney typically demonstrates heterogeneous echogenicity, but hypoechoic multifocal lesions have also been described [34]. Because of the rarity of unilateral or focal renal leukemia and the lack of specificity of imaging findings, such involvement requires biopsy to rule out other renal malignancy such as Wilms' tumor and renal cell carcinoma [34].

Testicular relapse

The testicle is the most common site of extramedullary relapse of leukemia in males [4, 35] and the third-most-common site of relapse of ALL in boys [36]. With contemporary therapy regimens, testicular relapse occurs in

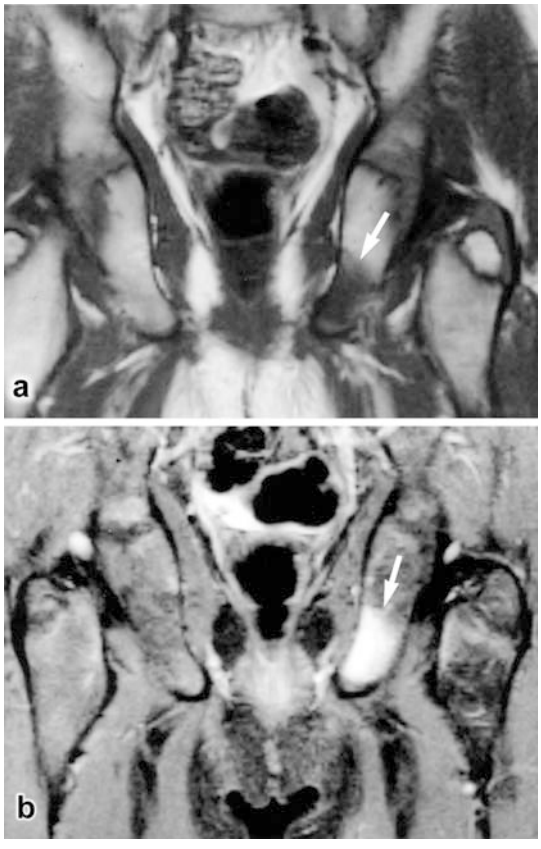


Fig. 11a–d A 6-year-old boy was undergoing induction chemotherapy for ALL and underwent his second protocol-driven MR imaging of the hips and knees for osteonecrosis. This new focus of abnormal marrow signal is consistent with evolving osteonecrosis of the left ischium. Such a finding can prompt concern for recurrent disease and potentially prompt bone-marrow aspiration and biopsy. He is well 2 years later. **a** Coronal non-contrast T_1-weighted and **b** STIR imaging through the demonstrate a new 2.5-cm focus of abnormal signal that is dark on T_1-weighted and bright on STIR sequences involving the left inferior ischium (*arrows*)

less than 5% of patients [36]. It most often occurs within 2–3 years from completion of chemotherapy [3, 37], although it has been reported as late as almost 19 years from treatment completion [36]. About one-third of patients with testicular relapse have clinical involvement of both testes, but up to 80% of cases demonstrate bilateral involvement histologically [36, 38]. Because of their anatomic location, US is typically the imaging method of choice for evaluatng the testicles. Involved testes may have normal echogenicity, but may be enlarged [36]. Alternatively, the testes may have hypoechoic areas. Hypervascularity is typical of leukemic involvement (Figs. 8, 9).

Ovarian relapse

Ovarian relapse has rarely been reported in pediatric ALL and may occur in the absence of bone-marrow relapse or in combination with relapse in other extramedullary sites [35, 39]. This site of recurrent disease has more commonly been reported with acute myelogenous leukemia (AML) where ovarian chloroma may also occur. Large ovarian masses owing to leukemic infiltration have been reported. Autopsy reports of leukemic infiltration of the ovary have varied from 3.2 to 36% [35]. Pelvic masses are typically first evaluated with US (Fig. 10). Such masses appear ultrasonographically as solid echogenic masses that may be hypervascular. By CT, they may appear as solid masses, isodense with adenopathy.

In conclusion, it is important for radiologists to be familiar with MR findings of ALL relapse in order to expedite and appropriately direct patient care. Because other disorders can mimic recurrence of leukemia (Fig. 11), radiologists must be able to distinguish recurrence from non-recurrence accurately in order to avoid unnecessary testing and emotional stress on the patient and family. MR imaging plays a crucial role in the detection of disease relapse.

References

1. Margolin JF, Steuber CP, Poplack DG (2001) Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 4th edn. Lippincott, Philadelphia, pp 489–544
2. Haddy TB, Mosher RB, Reaman GH (2001) Osteoporosis in survivors of acute lymphoblastic leukemia. Oncologist 6:278–285
3. Rivera GK, Raomondi SC, Hancock ML, et al (1991) Improved outcome in childhood acute lymphoblastic leukemia with reinforced early treatment and rotational combination chemotherapy. Lancet 337:61–66
4. Henze G, Fengler R, Hartmann R, et al (1991) Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85): A Relapse Study of the BFM Group. Blood 78:1166–1172
5. Frassoni F, Barrett AJ, Ernst P, et al (1988) Relapse after allogeneic bone marrow transplantation for acute leukaemia: a survey by the E.B.M.T. of 117 cases. Br J Haematol 70:317–320
6. Sanders JE (1997) Bone marrow transplantation for pediatric malignancies. Pediatr Clin N Am 44:1005–1020
7. Madani A, Christophe C, Ferster A, et al (2000) Peri-optic nerve infiltration during leukaemic relapse: MRI diagnosis. Pediatr Radiol 30:30–32
8. Behrendt H, Leeuwen EF, Schuwirth C, et al (1990) Bone marrow relapse occurring at first relapse in children with acute lymphoblastic leukemia. Med Pediatr Oncol 18:190–196
9. Amano Y, Takaura J, Kumazaki T (1997) Case report: the MRI diagnosis of bone marrow infraction in a child with leukaemia. Clin Radiol 52:560–561
10. Jensen KE, Sorensen PG, Thomsen C, et al (1990) Magnetic resonance imaging of the bone marrow in patients with acute leukemia during and after chemotherapy. Acta Radiol 31:361–369
11. Sahdev I, Weinblatt ME, Lester H, et al (1993) Primary ocular recurrence of leukemia following bone marrow transplant. Pediatr Hematol Oncol 10:279–282
12. Huang LT, Hsiao CC, Went HH, et al (1996) Neurologic complications of pediatric systemic malignancies. J Formos Med Assoc 95:209–212
13. Chamberlain MC (1997) Pediatric leptomeningeal metastases: outcome following combined therapy. J Child Neurol 12:53–59
14. Bleyer WA, Byrne TN (1988) Leptomeningeal cancer in leukemia and solid tumors. Curr Probl Cancer 12:181–238
15. Hwang W-L, Gau J-P, Hu H-T, et al (1994) Isolated extramedullary relaps of acute lymphoblastic leukemia presenting as an intraspinal mass. Acta Haematol 91:46–48
16. Krepler P, Jentzsch K, Mayer-Obiditsch J (1975) Lymphoblastic extramedullary spinal tumor during remission of acute lymphoblastic leukemia. Acta Neuropathol 6[Suppl]:213–215
17. Bunin N, Rivera G, Goode F, et al (1987) Ocular relapse in the anterior chamber in childhood acute lymphoblastic leukemia. J Clin Oncol 5:299–303
18. Merten D (1992) Diagnostic imaging of mediastinal masses in children. AJR 158:825–832
19. Molina PL, Siegal MJ, Glazer HS (1990) Thymic masses on MR imaging. AJR 155:495–500
20. Kaste SC (2001) Lymphoma—Controversies in imaging the chest. In: Lucaya J, Strife JL (eds) Pediatric chest imaging. Chest imaging in infants and children. Springer, Heidelberg, pp 209–223
21. Fletcher BD, Kauffman WM, Kaste SC, et al (1995) Use of Tl-201 to detect untreated pediatric Hodgkin disease. Radiology 196:851–855
22. Fletcher BD, Xiong X, Kauffman WM, et al (1998) Hodgkin disease: use of Tl-201 to monitor mediastinal involvement after treatment. Radiology 209:471–475

23. Nadel HR (1993) Thallium-201 for oncologic imaging in children. Semin Nucl Med 23:243–254
24. Siegel MJ, Glazer HS, Wiener JI, et al (1989) Normal and abnormal thymus in childhood: MR imaging. Radiology 172:367–371
25. Boothroyd AE, Hall-Craggs MA, Dicks-Mireaux C, et al (1992) The magnetic resonance appearances of the normal thymus in children. Clin Radiol 45:378–381
26. Brisse H, Pacquement H, Burdairon E, et al (1998) Outcome of residual mediastinal masses of thoracic lymphomas in children: impact on management and radiological follow-up strategy. Pediatr Radiol 28:444–450
27. Elkowitz SS, Leonidas JC, Lopez M, et al (1993) Comparison of CT and MRI in the evaluation of therapeutic response in thoracic Hodgkin disease. Pediatr Radiol 23:301–304
28. Kulkarni AG, Patil AP, Desai SR (1991) Pericardial Involvement as a presenting feature of acute myeloblastic leukemia. J Assoc Physicians India 40:345–46
29. Iemura A, Yano H, Kojiro M, et al (1991) Massive cardiac involvement of adult T-Cell leukemia/lymphoma. Arch Pathol Lab Med 115:1052-54
30. Handa R, Bhatia S, Wali JP, et al (1997) Acute leukemia presenting as pericardial effusion—a case report. Singapore Med J 38:491–492
31. Furihata M, Ido E, Iwata J, et al (1998) Adult T cell leukemia/lymphoma with massive involvement of cardiac muscle and valves. Pathol Int 48:221–224
32. Takata J, Taguchi H, Miyoshi I, et al (1998) Cardiac valve invasion in chronic adult T cell leukemia. Heart 80:311–12
33. Jones DP, Stapleton FB, Dalwinsky D, et al (1990) Renal dysfunction and hyperuricemia at presentation and relapse of acute lymphoblastic leukemia. Med Pediatr Oncol 18:283–286
34. Kebaili K, Manel AM, Chapelon C, et al (2000) Renal enlargement as presentation of isolated renal relapse in childhood leukemia. J Pediatr Hematol Oncol 22:454–45
35. Chu J-Y, Cradock TV, Danis RK, et al (1981) Ovarian tumor as manifestation of relapse in acute lymphoblastic leukemia. Cancer 48:377–379
36. Franck P, Duffner U, Schulze-Seeman W, et al (1998) Testicular relapse after 13 years of complete remission of acute lymphoblastic leukemia. Urol Int 60:239–241
37. Rivera GK, Pui C-H, Hancock ML, et al (1992) Update of St. Jude Study XI for childhood acute lymphoblastic leukemia. Leukemia 6[Suppl 2]:153–156
38. Pui CH, Dahl GV, Bowman WP, et al (1985) Elective testicular biopsy during chemotherapy for childhood leukemia is of no clinical value. Lancet III:410–412
39. Cecalupo AJ, Frankel LS, Sullivan MP (1979) Pelvic and ovarian extramedullary leukemic relapse in young girls. Proc Am Assoc Cancer Res 20:365