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REVIEW

Imaging findings in recurrent extramedullary leukaemias

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Abstract

Acute leukaemias are relatively common malignancies. Treatment has advanced significantly in the recent past and there has been improved patient survival. This improved initial response is leading to an increasing number of cases of relapse. Extramedullary relapse occurs in a wide variety of locations with varying presentations, imaging findings and differentials. The pathophysiology and clinical course of recurrent extramedullary myeloid and lymphocytic leukaemias are reviewed in this article. The wide variety of imaging findings associated with many important sites of recurrence and the associated differential diagnosis are discussed and illustrated.

Keywords: *Extramedullary leukaemia; extramedullary relapse; computed tomography; magnetic resonance imaging; ultrasonography.*

Introduction

Extramedullary relapse of acute leukaemias are often asymptomatic and can occur at multiple sites simultaneously. They have a variety of imaging appearances, which, with clinical and laboratory data, enables diagnosis of relapsed disease. Recurrence is defined by the detection of marrow or peripheral blood leukaemia cells after attainment of complete remission. The frequency of extramedullary relapse after allogeneic transplant varies from 5 to 12% of all patients with acute leukaemias[1–3]. As a proportion of all relapsed leukaemic disease, extramedullary disease with or without concomitant bone marrow involvement accounts for 27–50% of cases of recurrence[1,2,4]. Extramedullary relapse occurs later than isolated bone marrow relapse and is thought to occur by different pathogenic mechanisms[1,5,6]. Both disease status at haematopoietic stem cell transplant (HSCT) and leukaemia subtype have been found to be significant predictors of extramedullary recurrence but not of bone marrow recurrence alone[1]. It has long been thought that the graft-versus-leukaemia effect from allogenic transplantation would protect against bone marrow and extramedullary relapse, but studies have demonstrated a higher level of graft-versus-host disease in those with extramedullary recurrence. This suggests that the graft exerts a greater effect on maintaining bone marrow remission and that peripheral leukaemic cells may evade detection leading to relapse[6]. As supportive patient care and life expectancy after stem cell transplant progress, it is thought that the incidence of extramedullary relapse is likely to increase[1].

Diagnosis of extramedullary relapse usually only occurs when patients become symptomatic. Relapse may occur at one or multiple sites[1,6–9] and is often followed by the development of disease at other sites including the bone marrow within 1 year[10]. Sanctuary sites are particularly prone to recurrent disease and include the testes, central nervous system and the eye. Recurrence occurs less commonly at other locations including the breast, the paranasal sinuses and gastrointestinal tract[1,6–9]. There are currently no established protocols for surveillance of extramedullary relapse and long-term follow-up with positron emission tomography (PET)/computed tomography (CT), magnetic resonance imaging (MRI) and CT is not routine[6]. Early diagnosis is important as it can allow for possible cure of focal relapses. Clinical and laboratory information are often not diagnostic alone and knowledge of the sites of extramedullary involvement and imaging morphology should aid in establishing a more accurate diagnosis[10].

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Classification

Haematopoietic and lymphoid malignancies include the leukaemias, lymphomas, myeloproliferative neoplasms, plasma cell dyscrasias, histiocytic and dendritic cell neoplasms. They are classified under the WHO classification 2008 according to cell lineage using clinical, morphologic, immunophenotypic and genetic criteria[11].

Lymphoid neoplasms derive from malignant transformation of mature or progenitor B or T cells. Acute lymphoblastic leukaemia and lymphoblastic lymphoma should be considered as different clinical presentations of the same disease. A case is defined as lymphoma if there is a mass lesion, either in the mediastinum or elsewhere, and less than 25% blasts in the bone marrow. It is classified as acute lymphoblastic leukaemia if there are greater than 25% bone marrow blasts, with or without a mass lesion[12].

Myeloid neoplasms are derived from bone marrow progenitor cells that develop into granulocytes (neutrophils, basophils and eosinophils), monocytes, erythrocytes or megakaryocytes[11].

Pathogenesis

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) arises when haematopoietic progenitor cells evade the normal mechanisms that regulate cell growth, differentiation and apoptosis[13,14]. Underlying mechanisms include chromosomal translocations, aberrant expression of proto-oncogenes, and hyperdiploidy[13,14]. These result in proliferation of the genetically altered progenitors and depleted levels of the normal mature cell lines. Examples include the t(9;22) translocation in the BCR-ABL tyrosine kinase fusion protein[15] and the t(12;21) TEL-AML1 translocation, which leads to inhibition of normal stem cell differentiation[16].

Acute myeloid leukaemia

The underlying aetiology of acute myeloid leukaemia (AML) remains unknown but is hypothesized to be due a combination of genetic defects giving rise to an acquired proliferative advantage (a Class 1 mutation) and impaired differentiation of a stem cell (a Class 2 mutation)[17,18]. Stem cells may acquire these genetic mutations in response to environmental exposure and genetic damage[17,18]. Proposed genetic mechanisms include RAS cell-surface receptors, tyrosine kinases such as c-KIT and the over-expression of HOX genes or the formation of fusion genes such as t(8;21)[17,19–21]. The inv 16 mutation is associated with a good prognosis in AML but its presence is associated with extramedullary relapse[17,22]. Relapsed extramedullary AML is also known as myeloid sarcoma, granulocytic sarcoma or chloroma[10,17,22].

Clinical course

T-cell ALL

Patients are typically young males who present with a mediastinal mass (50–75%) or cervical, axillary or supraclavicular lymphadenopathy (50%)[23]. Mediastinal masses can lead to symptoms of superior vena cava syndrome, tracheal obstruction, and pericardial effusions. Extranodal disease is less common at initial presentation. 50% have B symptoms (fever, night sweats and weight loss) and up to 80% present with stage III or IV disease[24]. The marrow is often normal at presentation, however approximately 60% will develop bone marrow disease. These patients subsequently have a high incidence of central nervous system (CNS) infiltration and should have cerebrospinal fluid assessed to exclude CNS involvement[24].

B-cell ALL

Patients with B-cell ALL most often present with its leukemic form and symptoms include fatigue, infections and easy bruising due to infiltration of the marrow and resultant anaemia, neutropenia and thrombocytopenia. B symptoms are frequent but often mild. Up to half of adults have hepatomegaly, splenomegaly and lymphadenopathy. Involvement of the CNS is common.

AML

The accumulation of blast cells in the marrow, blood and peripheral tissues impairs the production of red blood cells, platelets and neutrophils and the resultant pancytopenia accounts for the patient's symptoms. Infection with a variety of organisms is the most common sign of marrow failure. Bone pain, due to expansion of the medullary cavity is not common in adults, although when present, it is often in the sternum or long bones. Gum swelling and refractory infections may also be the presenting complaint[17].

Treatments

Treatment of leukaemias consists of induction therapy and post-remission therapy. Complex multiple agent regimens are used with the aim of rapidly restoring bone marrow function, preventing the development of resistant cell lines and treating sanctuary sites such as the CNS as relapse is associated with a poor prognosis. Induction therapy should reduce the leukaemia cell population to below cytologically detectable levels. A substantial cytologically unmeasurable population can remain after initial therapy, which will lead to disease relapse and is countered with post-remission therapy. The choice of post-remission therapy is determined by the patients' risk of relapse and involves consolidation chemotherapy, autologous and allogenic haematopoietic stem cell transplantation. Patients are categorized as low, intermediate

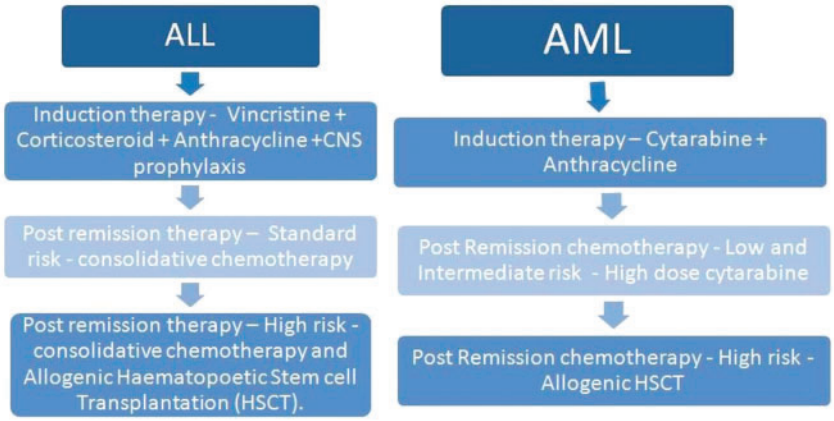

Figure 1 **Basic treatment pathway.**

or high risk of recurrence according to their clinical, cytological and cytogenetic profiles[24–31]. A simplified overview is demonstrated in Fig. 1.

Imaging

Investigation for suspected extramedullary relapse is usually initiated in response to patient symptomatology. Relapse may occur at single or multiple sites and there is a diverse range of clinical presentations according to the size and location of relapse[6,22]. The sanctuary sites of the brain, testis and eye are particularly vulnerable to disease, however any site can be affected[1,6,22]. Philadelphia positive ALL has been found to have the highest rate of extramedullary relapse[1]. CT, magnetic resonance angiography and ultrasonography all have an important role to play in the diagnosis and assessment of recurrence. Radiological findings alone can be non-specific and in the context of previous leukaemia, soft tissue masses include differentials of infection, haemorrhage and secondary neoplasms. Careful consideration of imaging, clinical and laboratory findings can assist radiologists in making accurate early diagnosis enabling appropriate treatment.[6,10,22,32].

Nervous system

The CNS and more rarely, the peripheral nervous system, are both sites of extramedullary recurrence. CNS recurrence can be single or multiple and most often occurs as extra-axial masses[11,32,33]. Extra-axial lesions are thought to arise from dural and subarachnoid veins[11,32]. Oedema, mass effect and haemorrhage may also be present. Imaging characteristics on unenhanced CT are lesions that are isodense or hyperdense to cerebral parenchyma. On MRI, they are hypointense or isointense on T1-weighted images, heterogeneously isointense or hyperintense on T2-weighted images and enhance homogenously after gadolinium[32]. The combination of these findings in the context of previous AML may negate the need for biopsy[32,34]. The signal intensity and

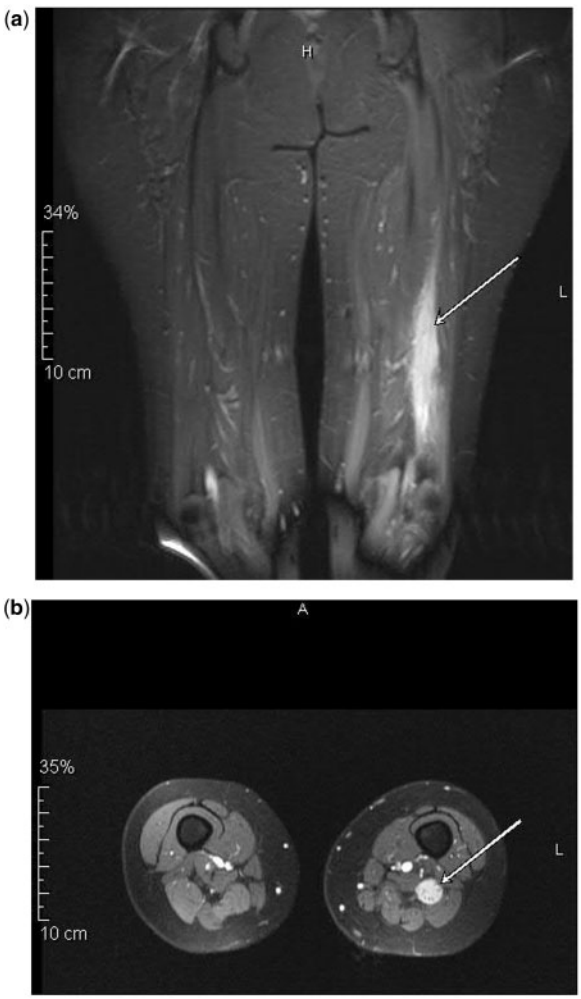

Figure 2 **(a,b) A 25-year-old woman with previous AML after bone marrow transplant presented with left leg pain. Nerve conduction studies were consistent with left sciatic nerve compression. T2-weighted fat-saturated sequences demonstrate an elongated spindle-shaped enhancing soft tissue mass measuring 2 × 2 cm axially and extending 14 cm craniocaudally in the flexor compartment of the thigh. The mass completely resolved after chemotherapy.**

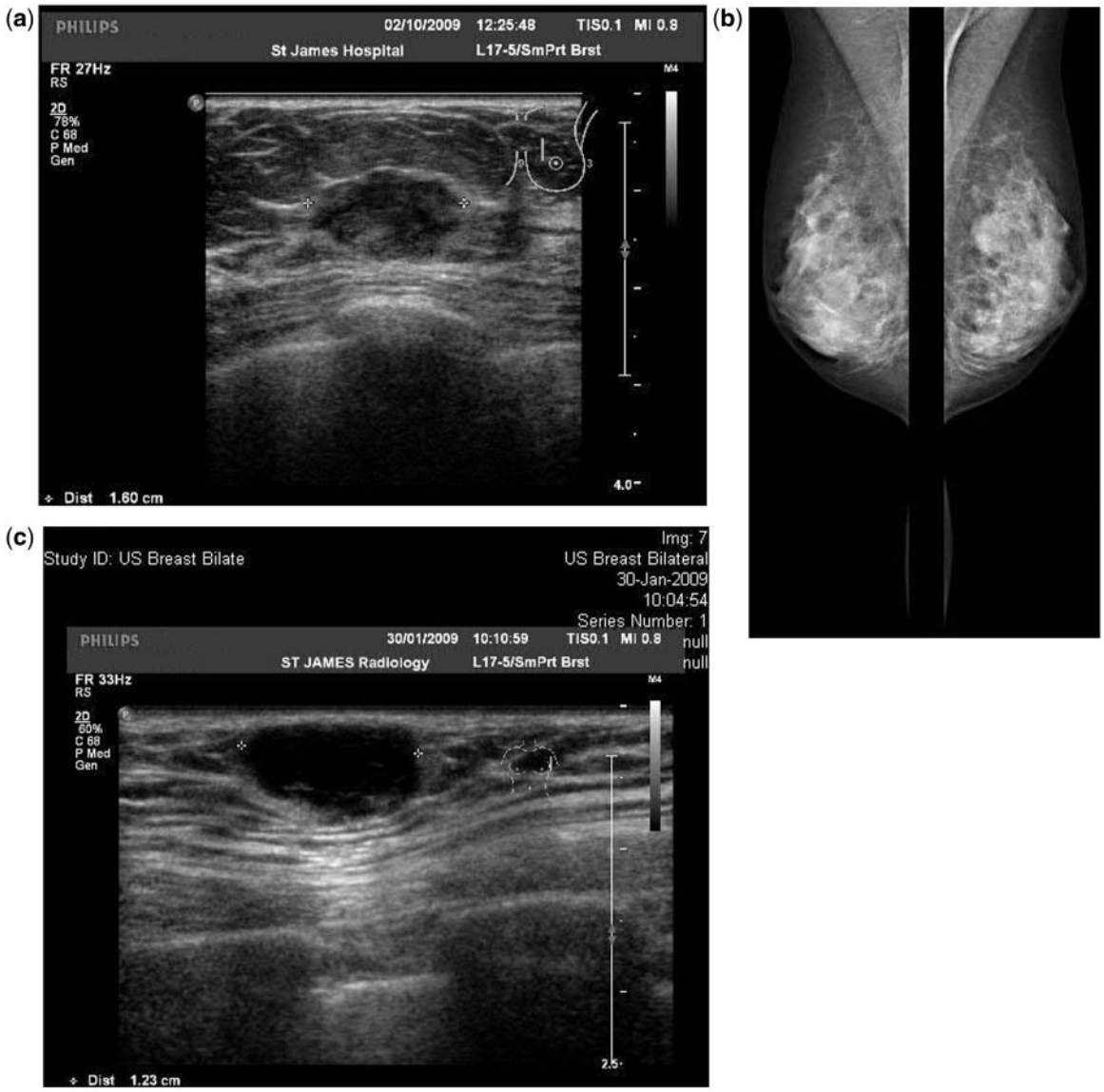

Figure 3 **(a) Breast ultrasonograph of a 41-year-old woman with a history of ALL found on clinical examination to have multiple palpable bilateral breast masses. The ultrasound image demonstrates a heterogeneous hypoechoic mass in the left breast. Similar masses were demonstrated in the right breast. (b) Mammogram on the same patient demonstrates lesions are isodense with surrounding breast parenchyma and not readily appreciable. Subsequent bilateral breast biopsy was positive for extramedullary recurrence of ALL. (c) Breast ultrasonograph of a 25-year-old woman with a previous history of AML. Clinical examination revealed a palpable mass in the left breast. Ultrasonography demonstrated a unilateral well-defined hypoechoic mass with posterior enhancement. Histology confirmed recurrent AML of the breast.**

homogeneous contrast enhancement help with differentiation from haematoma and abscess[32,35].

Peripheral nervous system (Fig. 2A,B) involvement in recurrent extramedullary disease is rarely reported in the literature. Documented presentations include mono- and polyneuropathies and small patient numbers mean that there are currently no definitive imaging findings for this group of patients[36–38].

Breast

Leukaemic infiltrations of the breast (Fig. 3A–D) are reported to account for only 4% of metastatic deposits from primary extra-mammary malignancy[39]. Mammographic appearance is non-specific, usually evident as asymmetry. Ultrasonographic findings consist of ill-defined shadows similar to invasive lobular carcinoma although in comparison with leukaemic masses, an echogenic margin can be seen[40]. Lesions are typically heterogeneous in appearance, with ill-defined margins. Acoustic shadowing may be present or absent[11,41]. Relapse of AML to the breast is more common than ALL, and those cases of ALL breast recurrence that do occur are most often bilateral[41]. Definitive differentiation from other breast lesions is difficult on imaging

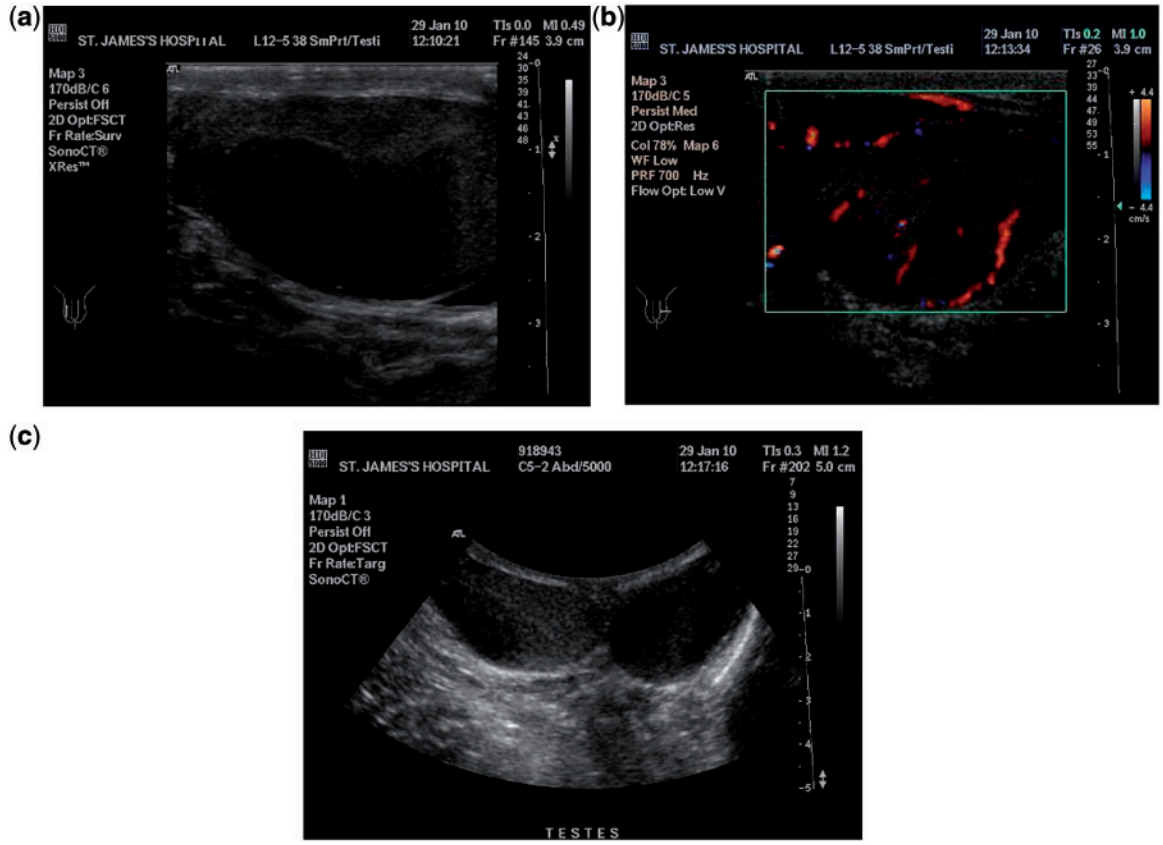

Figure 4 **A 28-year-old man with a previous history of ALL presented 2 years after diagnosis and chemotherapy with subtle induration of the left testicle on clinical examination. (a–c) Ultrasonography demonstrated extensive low attenuation lesions within both testes replacing approximately 50% of the right testicle and 75% of the left with significant associated increased vascularity within the abnormal areas. The findings are consistent with an extramedullary leukemic recurrence.**

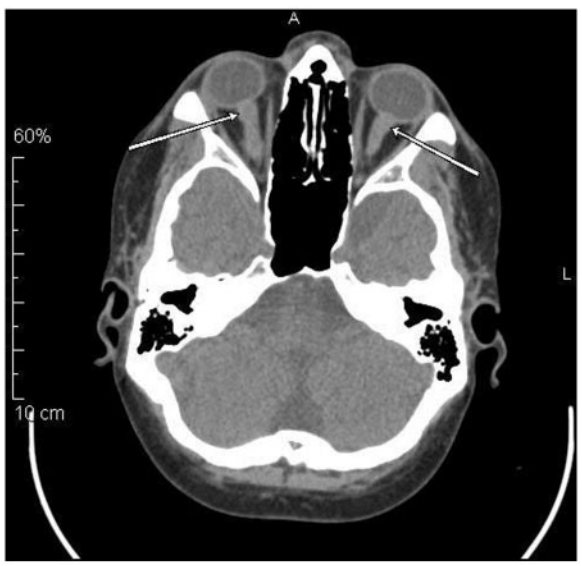

Figure 5 **A 22-year-old man with a background of T-cell ALL presented with bilateral sudden loss of vision. CT showed bilateral nodular enhancing optic nerve lesions consistent with disease recurrence.**

alone although a history of previous leukaemia should increase clinical suspicion for a possible unusual representation.

Testicles

The testicles, being a sanctuary site, are the most common location of extramedullary leukaemic recurrence in males (Fig. 4A–C). It occurs most commonly in the first 2–3 years of the primary disease although recurrence has been reported 19 years after initial diagnosis. In those with testicular recurrence, clinical assessment reveals bilateral involvement in 30% and histology shows bilateral involvement in 80%. Typical ultrasonographic appearances are of enlarged hypervascular testes. They may be of homogeneous echogenicity, especially when small, but often show diffuse or focal hypoechoic lesions replacing normal testicular tissue[11,42,43]. A clinical history of previous leukaemia should raise high clinical suspicion for recurrence, although sonographic appearances can also include differentials of seminomatous tumours, orchitis and testicular abscess[44].

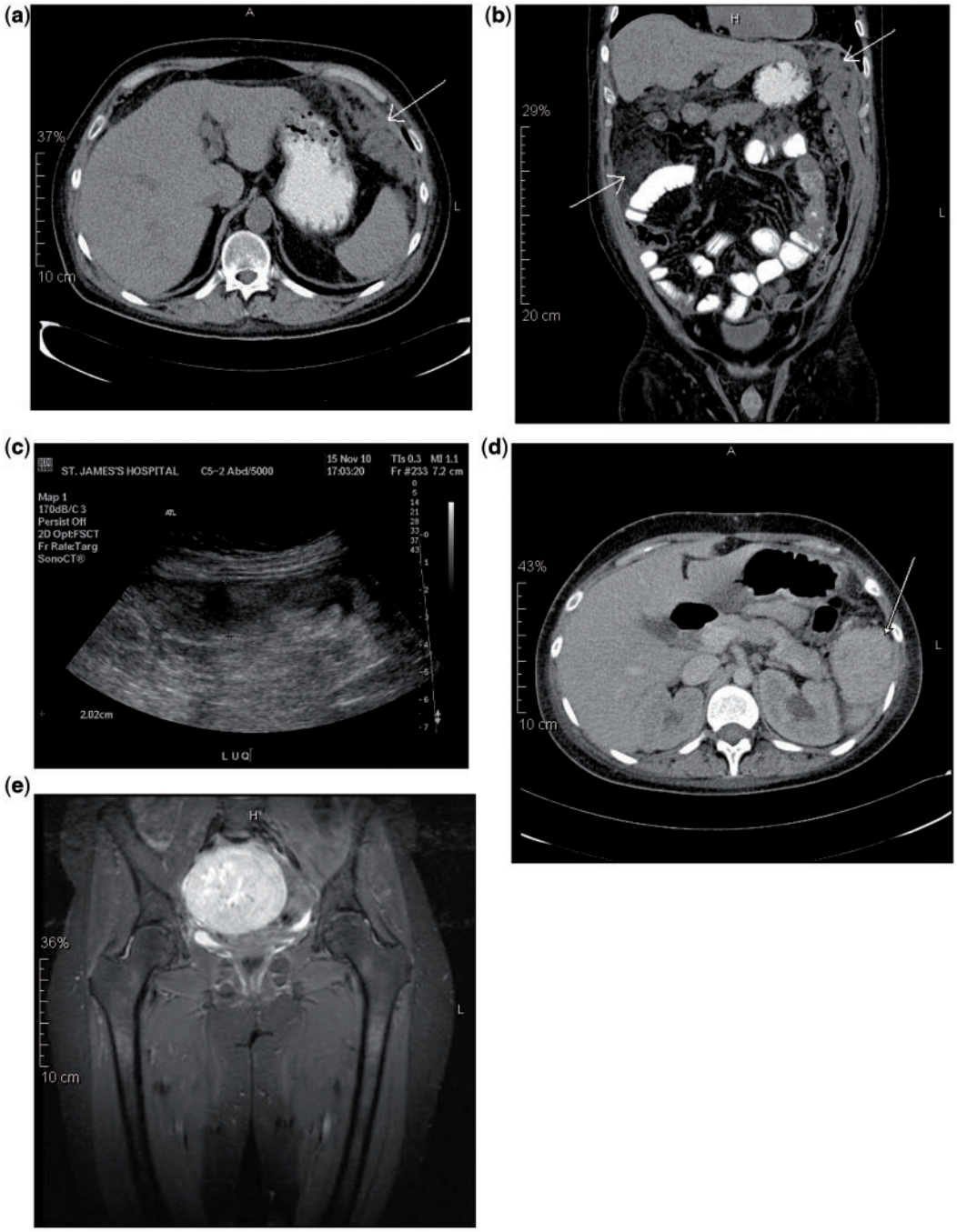

Figure 6 **A 44-year-old man with a previous history of B-cell ALL. The patient had a complicated course after a successful bone marrow transplant. He developed obstructive hydrocephalous secondary to subarachnoid haemorrhage for which 2 ventriculoperitoneal shunts were placed. At the same presentation, his lumbar puncture demonstrated immature lymphocytes consistent with CNS recurrence of his ALL; this was successfully treated. Two years later, the patient represented with a palpable left upper quadrant mass. (a) Axial and (b0 coronal CT images demonstrate an irregular soft tissue mass in the left upper quadrant with diffuse mesenteric infiltration. (c) A hypoechoic soft tissue mass on ultrasonography, which on biopsy, proved to recurrent extramedullary B-cell ALL. Clinically, it was hypothesized that this peritoneal recurrence was iatrogenic, likely secondary to placement of the ventriculoperitoneal shunt. (d,e) A 26-year-old woman with previously treated AML. The patient represented with abdominal discomfort particularly in the pelvis and left upper quadrant. CT demonstrated a left upper quadrant mass and a second mass in the pelvis that was causing bilateral hydronephrosis. MRI of the pelvis demonstrated a well-defined heterogeneous mass within the pelvis that enhanced markedly after contrast. CT-guided biopsies of pelvic and right upper quadrant masses confirmed granulocytic sarcoma.**

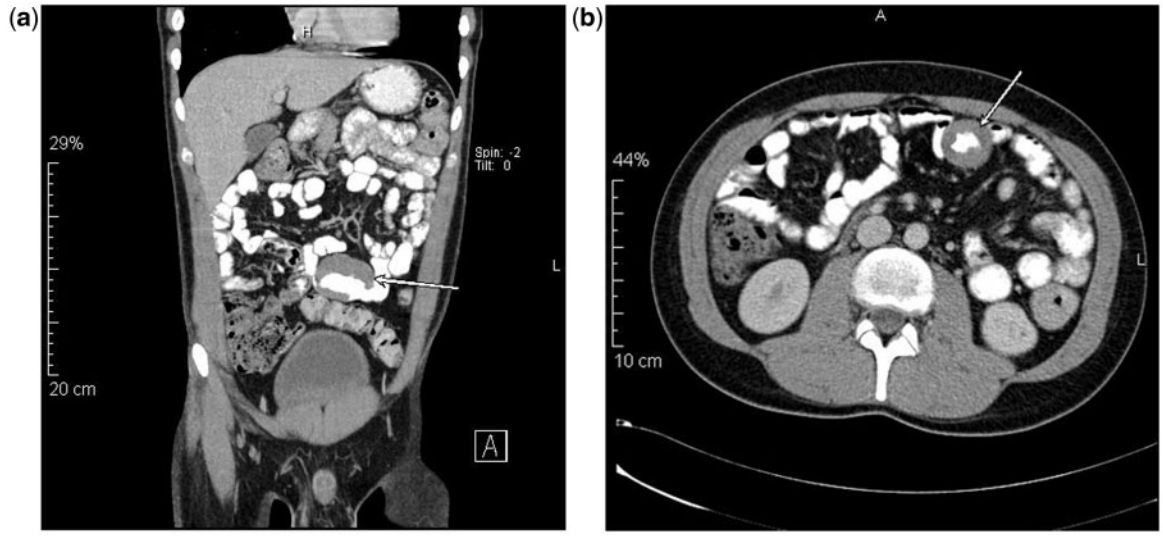

Figure 7 **(a,b) A 28-year-old man in remission from B-cell ALL with clinically palpable supraclavicular lymph nodes. CT demonstrated a 12-cm length of proximal jejunum with tumour invasion, aneurysmal dilatation and without obstruction. The patient subsequently had an excellent response to chemotherapy.**

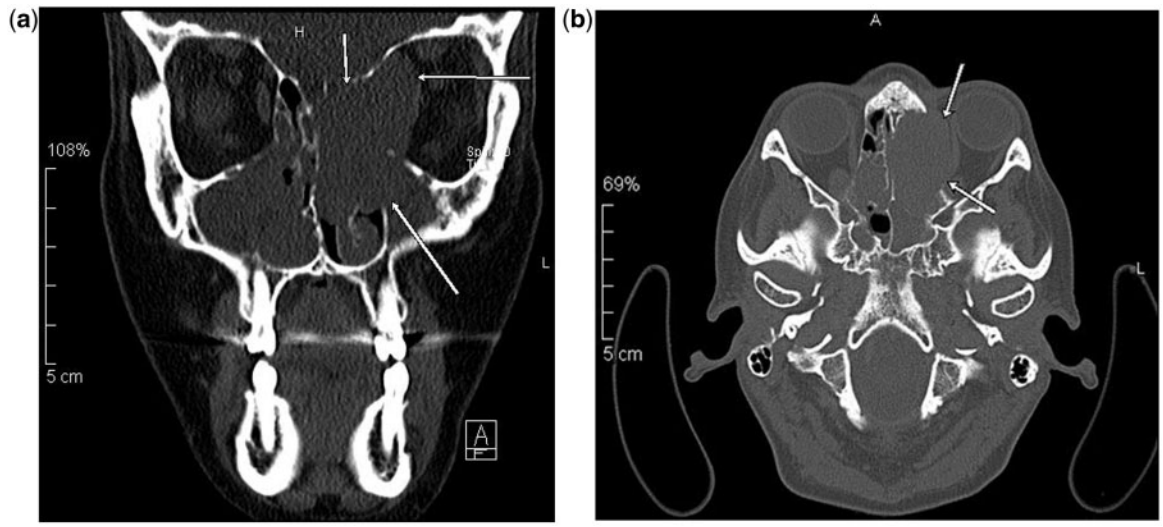

Figure 8 **(a,b) A 41-year-old woman with a history of ALL found on clinical examination to have painless proptosis of the right eye. CT of the brain shows a sinus mass that has eroded through the lamina papyracea and cribriform plate. It is displacing the ocular muscles and optic nerve. Imaging of the orbits after intensive chemotherapy demonstrated complete resolution of the infiltrative lesion.**

Orbit and optic nerve

Orbital involvement of relapsed disease is common and often presents as painless proptosis (Fig. 5). It is usually identified as a homogeneous mass, may be bilateral and can involve bony erosion, most often of the medial orbital wall. It may also arise outside the orbit and invade into it from the adjacent structures[32,43,45].

Involvement of the optic nerve is more common in those with a history of ALL and occurs more often in children than adults. It can lead to irreversible vision loss and can occur in the presence of a normal ophthalmologic examination. Suspicious imaging findings are evident on CT as enlarged optic nerves; in addition, MRI demonstrates post-contrast enhancement[43,45]. As a result of the often clinically occult nature of optic nerve disease, some authors have proposed that MRI of the orbits may have a role as part of the routine follow-up of such patients[43]. The differential for those with orbital and optic nerve lesions includes gliomas, meningiomas, orbital pseudotumour and rhabdomyosarcoma.

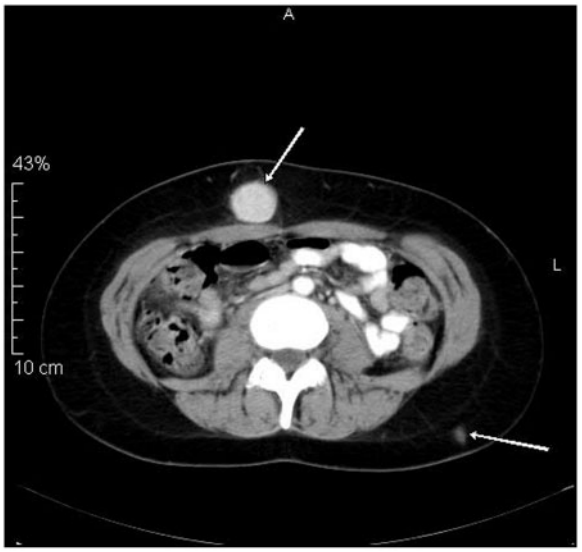

Figure 9 **A 26-year-old woman with a previous history of AML whose treatment included bone marrow transplantation. Clinical examination showed a palpable abdominal mass. CT of the abdomen demonstrated a large subcutaneous deposit. Ultrasound-guided biopsy confirmed granulocytic sarcoma. A small second focus of increased attenuation in the left flank was also felt likely to represent a second focus of recurrence; this was not biopsied at the time, however.**

Peritoneal disease

Leukemic infiltration of the peritoneum is a rare occurrence and can mimic peritoneal carcinomatosis in appearance (Fig. 6A–F). Its appearance on CT is nonspecific and may demonstrate focal soft tissue masses or diffuse peritoneal infiltration with irregular thickening of the peritoneum and often ascites[11,46]. The non-specific nature of these findings and the rarity of leukaemic recurrence in the peritoneum require the exclusion of a separate malignant process.

Gastrointestinal tract

The presentation of gastrointestinal recurrence is nonspecific and can mimic graft-versus-host disease[47]. It can occur in the stomach, small bowel or colon (Fig. 7A,B). There are a variety of different findings within the gastrointestinal tract and infiltration can be mass-like, nodular, ulcerated, polypoid or plaque-like[11,47,48]. Segmental bowel wall thickening occurs usually without stenosis and it is not possible to distinguish these on imaging alone from primary non-Hodgkin lymphoma or adenocarcinoma[10].

Sinuses

Involvement of the paranasal sinuses in recurrent extramedullary disease is uncommon (Fig. 8A,B). It can present with unilateral sinus symptoms or symptoms secondary to extension of the tumour into the adjacent orbits. CT findings typically show a soft tissue mass, which, in the presence of associated bony destruction or extension into adjacent cavities, is highly suspicious for disease[49]. Differentials include malignant neoplasms such as squamous cell carcinoma, lymphoma and rhabdomyosarcoma, traumatic haematomas and benign polypoid lesions.

Skin

Extramedullary recurrence of the skin is termed leukaemia cutis and occurs in approximately 3% of patients with AML; it has been rarely reported in ALL. It may occur in the epidermis, dermis or subcutis (Fig. 9)[22]. It can appear as ill-defined nodules or may be infiltrative in appearance[11,22]. It is most commonly found in the lower extremities; the upper extremities, the back and trunk are progressively less frequent sites of occurrence[22]. The differential for their appearance includes inflammatory, infectious and malignant conditions and the incidence may be overestimated as a result because biopsy is not always performed[11,22].

Conclusion

Recurrent extramedullary leukaemias are likely to become increasingly common with improving therapeutics. They produce significant variation in imaging appearance at different sites of recurrence and on different imaging modalities. There should be a low threshold for suspicion in those with supportive clinical and laboratory data. Knowledge of the imaging features of these diseases enables the radiologist to narrow the differential and optimize detection of early recurrence to improve patient care. Standardized protocols for imaging those at risk of recurrence are not yet widespread but are likely to become established with improved therapies and patient life expectancy.

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