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CASE REPORT
Other

Isolated myocardial relapse of Philadelphia-positive acute lymphoblastic leukaemia causing myocarditis: a case report

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Background Relapse of acute lymphoblastic leukaemia (ALL) causes significant morbidity. Extramedullary relapse is seldom isolated to one site and almost always coexists with extensive marrow disease. Leukaemic infiltration of the myocardium is a well described entity, evident in up to 44% of patients at post-mortem examination; however, ante-mortem diagnosis remains difficult and rare. As a result, myocardial involvement in the absence of any other foci of relapse has only seldom been reported.

Case summary Here, we present an unusual case of isolated gross intracardiac relapse of ALL in a patient presenting with chest pain and fevers. Both cardiac magnetic resonance imaging and endomyocardial biopsy were utilized in the diagnosis and identified leukaemic infiltrate in the absence of peripheral lymphoblasts.

Discussion Despite evidence supporting a positive correlation between peripheral lymphocyte count and myocardial infiltration, our case highlights the rare and hypothesis-driving occurrence of myocardial infiltration with a complete absence of a peripheral lymphoblastosis. The report highlights the utility of modern histopathological and imaging modalities in the diagnosis of isolated myocardial relapse of ALL and provides insight into the aetiologies driving this process.

Keywords Acute lymphoblastic leukaemia • Myocarditis • Myocardium • Case report

Learning points

- Whilst leukaemic infiltration of myocardial cells is relatively common, diagnosis is often only made post-mortem.
- Cardiac magnetic resonance imaging may be a useful tool in the assessment and diagnosis of myocardial leukaemic infiltrate.
- Isolated myocardial relapse of leukaemia is seldom seen but typically heralds fulminant relapse.
- The myocardium may present as a sanctuary site for leukaemic cells.

Introduction

Relapse of acute lymphoblastic leukaemia (ALL) causes significant morbidity, with up to 60% of adult cases failing to be cured.[1] Extramedullary relapse is seldom isolated to one site, and almost always coexists with, or heralds extensive marrow disease.[2] Leukaemic infiltration of the myocardium is a well described entity, being confirmed in up to 44% of patients at post-mortem examination; however, ante-mortem clinical diagnosis remains difficult and rare.[3,4] As a result, myocardial involvement in the absence of any other foci of relapse has only seldom been reported.[5,6] Here, we present an unusual and rare case of isolated gross intracardiac relapse of ALL in a patient presenting with chest pain and fevers.

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Timeline

01/08/2015	Patient completes stem cell transplant and donor lymphocyte infusion with remission of acute lymphoblastic leukaemia
02/03/2016	Patient presents to emergency and is admitted for assessment of central dull chest pain, fevers, and malaise
04/03/2016	Initial diagnostic work-up performed, patient commences steroid treatment for presumed myocarditis
08/03/2016	After failing to respond to IV steroids, cardiac magnetic resonance imaging performed
10/03/2016	Confirmatory diagnostic endomyocardial biopsy performed
25/03/2016	50% blasts seen in peripheral blood. Commences compassionate access tyrosine kinase inhibitor (TKI)
06/04/2016	Fails TKI treatment. Lymphoblast count doubling time of 24 h confirmed
08/04/2016	Patient dies

Case report

A 39-year-old female patient presented to our facility with a 2-day history of fevers, malaise, and central dull chest pain that was neither pleuritic nor altered by position. She had a past history of relapsing Philadelphia-positive ALL for which she had received two consecutive allogeneic stem cell transplants (SCT) from a sibling donor, as well as an infusion of donor lymphocytes. She had no previous history of cardiovascular disease and at the time of presentation had been in remission from her ALL for 6 months. Her post-remission course had been uneventful prior to her emergency presentation.

On assessment she was dehydrated, tachycardic (up to 130 b.p.m.) and hypotensive (90/65 mmHg) with a temperature of 38.5°C. The remainder of the cardiovascular examination was unremarkable. Blood tests demonstrated an elevated C-reactive protein of 72.7 mg/L (<10) and a Troponin T of 2490 ng/L (0–14). Her white cell count was normal (10.4×10^9/L), and peripheral blood film examination did not identify precursor cells. The remainder of her biochemistry was within normal parameters including her haemoglobin, electrolytes, creatinine, and liver function tests. Multiple blood cultures were taken and remained negative. Chest radiography was normal. Electrocardiogram (ECG) demonstrated a sinus tachycardia with new deep T-wave inversion (TWI) in leads V3–V6, not seen on a previous ECG (*Figure 1*). A transthoracic echocardiogram demonstrated mild–moderate left ventricular hypertrophy with anterior and anteroapical hypokinesis and a small circumferential pericardial effusion. The left ventricular size was normal, but systolic function was impaired with a left ventricular ejection fraction of 45%. There was no significant valvular pathology (*Figure 2*). Coronary angiography did not reveal significant obstructive disease.

The patient was resuscitated with IV fluids, given tazocin 4.5 g 6 hourly and commenced on therapy for presumed severe myopericarditis, receiving pulsed 1 g intravenous methylprednisolone daily for 3 days; however, failed to respond with ongoing fevers, tachycardia, and hypotension. Differential diagnoses including infiltrative, tachycardic, and catecholaminergic cardiomyopathies were considered. In the absence of a clear aetiology and given her failure to respond to initial therapy, an urgent cardiac magnetic resonance imaging (CMR) was sought. Cardiac magnetic resonance imaging

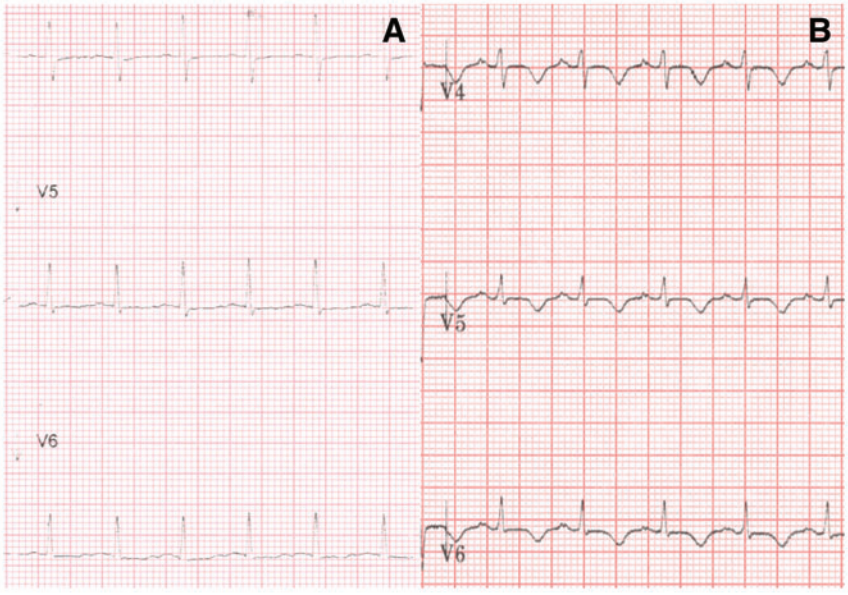

Figure 1 (*A*) Baseline electrocardiogram 6 months prior to admission, (*B*) admission electrocardiogram showing TWI in V4–V6.

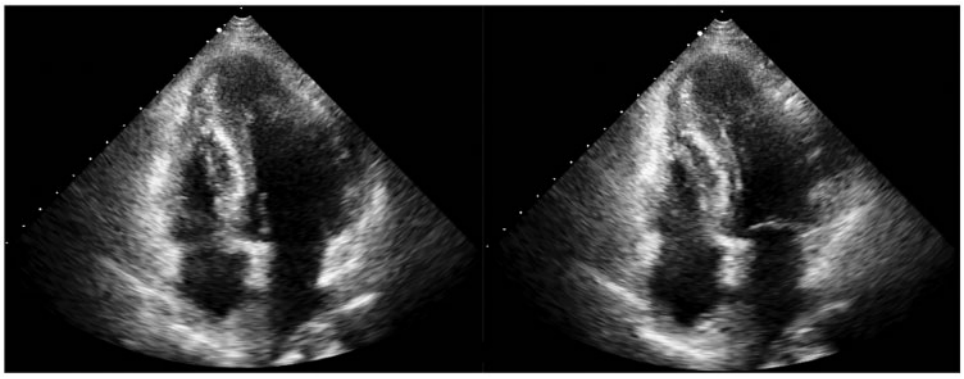

Figure 2 Transthoracic echocardiogram four chamber views: left diastole, right systole.

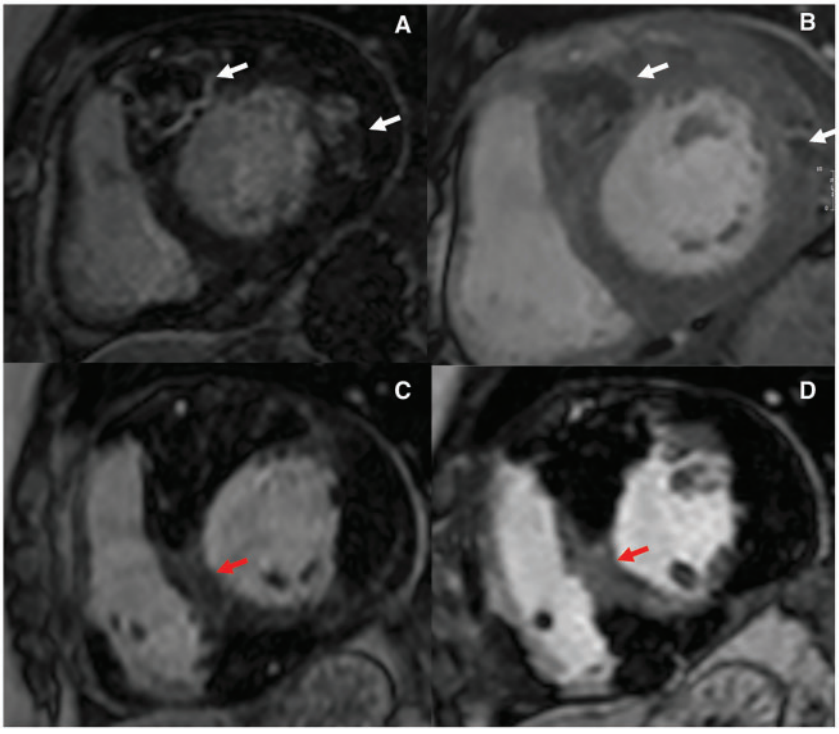

Figure 3 Cardiac magnetic resonance imaging transverse two chamber views: T1 phase sensitive inversion recovery (PSIR) (*A*), T2 bright blood sequence (*B*), and late gadolinium enhancement sequences at the mid-left ventricle (*C*) and apex (*D*). Phase sensitive inversion recovery and bright blood sequences (*A*, *B*) demonstrate increased signal intensity in the basal anteroseptal and anterior walls, the mid-lateral wall, inferior LV–RV junction and the distal interventricular septum consistent with active myocardial inflammation, oedema, and leukaemic infiltrate (white arrows). Late gadolinium images (*C*, *D*) show patchy enhancement consistent with myocarditis/myocardial inflammation (red arrows).

identified severe, patchy increased signal intensity involving the myocardium and pericardium in the basal antero-septum, anterior wall, mid-lateral wall, and the distal interventricular septum on oedema-weighted, and late gadolinium sequences with associated regional wall motion abnormalities consistent with severe myocarditis (*Figure 3*).

She subsequently underwent transjugular endomyocardial biopsy (EMBx). Endomyocardial biopsy revealed a heavy infiltrate of malignant lymphocytes percolating between myocytes (*Figure 4*), with resultant atrophy of the intervening myocardial fibres as well as an accumulation of the malignant cells in a prominent perivascular and pericardial distribution (*Figure 4*), confirming a leukaemic infiltrate in

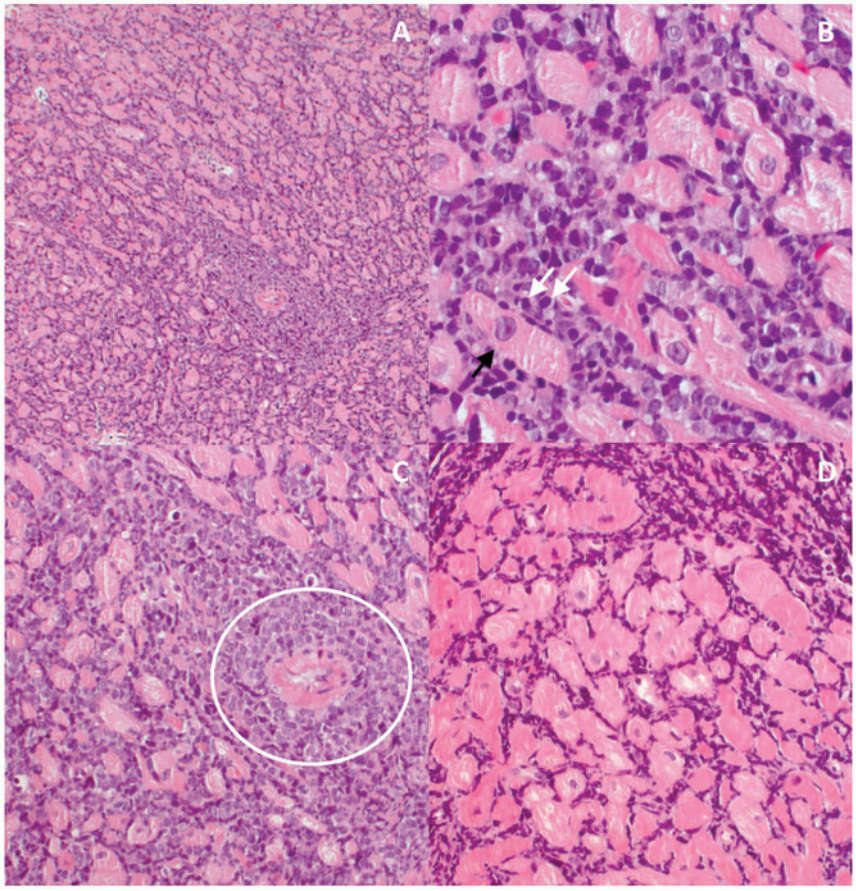

Figure 4 (*A–D*) Myocardial biopsies showed a heavy infiltrate of malignant lymphocytes (white arrows) percolating between myocytes (black arrow) (*A*, *B*), as well as accumulation of the malignant cells in a prominent perivascular (white circle) (*C*) and pericardial distribution (*D*).

the myocardium. The lymphocytes exhibited mild to moderate nuclear pleomorphism with scattered mitoses and hyperchromatic nuclei with increased N:C ratio and stained strongly positively for CD20, CD10, TdT, and PAX5 immunoperoxidase stains (*Figure 5*), confirming the presence of immature lymphoid lineage blood cells. Interphase FISH Probes for BCR/ABL1 [t(9; 22)(q34; q11.2)] revealed a signal pattern consistent with BCR-ABL1 rearrangement in the infiltrating cells (*Figure 6A*) and DXZ1 (X centromere), DYZ1(Yq12) loci-specific probe set confirmed that the majority of the cells contained recipient (XX) origin, with only occasional donor (XY) cells noted (*Figure 6B*). These findings were in keeping with recurrence of the patient's ALL.

Her clinical course was complicated by runs of non-sustained ventricular tachycardia (treated with amiodarone 300 mg orally thrice daily in a weaning regimen and coupled with low-dose bisoprolol 2.5 mg daily, titrated to blood pressure), persistent fevers, and intermittent chest pain with associated changes in serum troponin. Within 2 weeks of confirmation of diagnosis by EMBx the patient had evidence of lymphoblasts (50%) in her peripheral blood. She was commenced on a second-line compassionate-access tyrosine kinase inhibitor, Ponatinib (45 mg orally once daily), as a palliative measure, though she failed to respond and by 4 weeks her blast count was 23.71×10^9/L with a doubling time of under 24 h. She soon thereafter died from fulminant multi-organ failure.

Discussion

Involvement of the myocardium by leukaemic cells is an entity that has been well established since the 1940s and is usually an incidental finding at autopsy.[4] In one of the largest post-mortem studies of hearts from children with leukaemia, Sumners *et al.* reported that 44% of hearts had at least one myocardial area of leukaemic involvement. Factors that have been postulated to influence the occurrence of cardiac involvement include duration of disease, degree of lymphocytosis, and subtype of malignancy, though there are likely many other mediators yet to be identified. The occurrence of isolated myocardial ALL relapse is very rare, and to the best of our knowledge, isolated myocardial relapse following SCT has only been reported in one patient.[7]

Despite evidence to support a positive correlation between peripheral lymphocyte count and myocardial infiltration,[4] our case

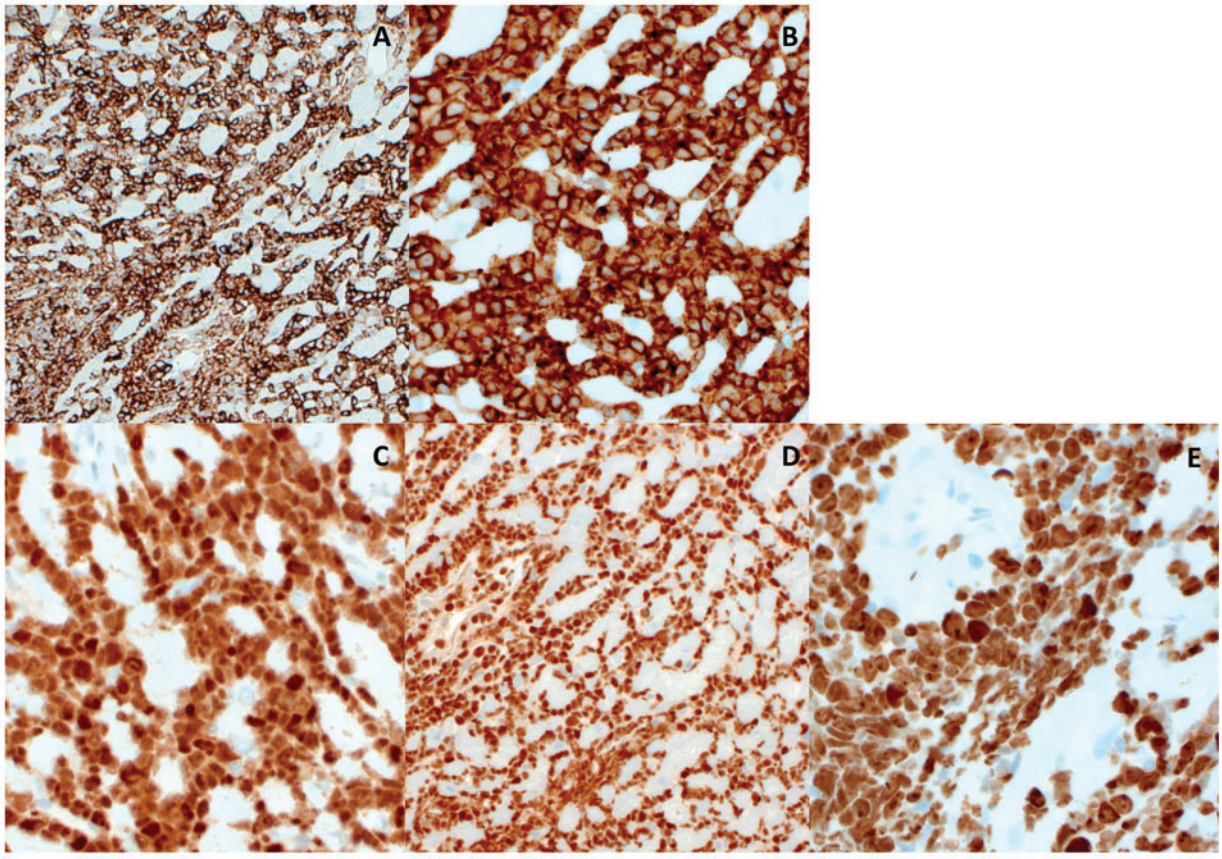

Figure 5 (*A–E*) Immunoperoxidase stains revealed strong positive staining of malignant cells for CD20 (*A*, membranous staining), CD10 (*B*, membranous staining), TdT (*C*, nuclear staining), and PAX5 (*D*, nuclear staining) with a Ki67 proliferative index of 80–90% (*E*).

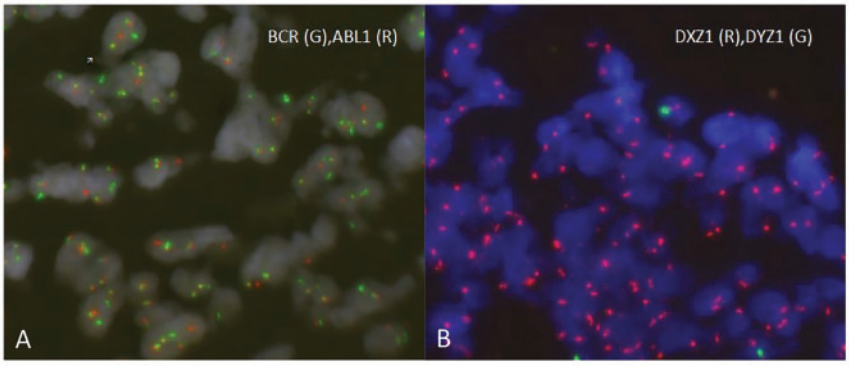

Figure 6 (*A*) Interphase FISH Probes for BCR/ABL1 [t(9; 22)(q34; q11.2)] dual colour dual fusion translocation probe set (Vysis) reveal a signal pattern consistent with BCR-ABL1 rearrangement in the majority of infiltrating atypical cells with most cells showing abnormal probe pattern. Normal cells should contain two green (BCR), two red (ABL1), and no fusion signals. In these abnormal cells, the yellow dots represent the fusion gene and most cells show abnormal pattern that can be as simple as nuclei that have one red, one green, and two fusion signals with a balanced t(9; 22) up to nuclei that have varying supernumerary red, green, yellow or a combination thereof. (*B*) DXZ1 (X centromere), DYZ1(Yq12) loci-specific probe set (Vysis) reveals the majority of cells contain DXZ1 (red) signals with only rare cells containing additional DYZ1 (green) signal, confirming that the majority of the cells are the patient's own XX cells and not the donor XY cells.

highlights the interesting occurrence of myocardial infiltration with a complete absence of a peripheral lymphoblastosis. This has been reported in only two other patients.[6,7] We propose one possible mechanism is our patient's history of multiple relapses, which may have led to significant net cardiac exposure by leukaemic cells over time, leading to greater likelihood of infiltration. Similarly, it has been hypothesized that atypical extramedullary sites may represent sanctuary sites for the conditioning chemoradiotherapy.[8] Further to this, it is possible that the graft-vs.-leukaemia (GVL) phenomenon may be less potent in peripheral tissues compared to bone marrow. This may leave the myocardium with unchecked exposure to seeded malignant cells, due to either an absence of GVL effector cells or an inherently unsuitable molecular environment for these cells to function.[9]

Although EMBx is generally an accepted requirement for the diagnosis of myocardial involvement by leukaemic cells, multiple imaging modalities, particularly CMR, may play an increasing role in the diagnostic work up.[6,10] Hori *et al.*[7] hinged their diagnosis of myocardial relapse on combined CT, MRI, and gallium scintigraphy findings in the absence of a tissue specimen, and this guided at least temporarily successful treatment. Similarly, Baritussio *et al.*[11] presented a case of disseminated ALL in which the CMR features showed infiltration in a pattern and distribution similar to our case. Nevertheless, there remains a paucity of data with respect to reliable imaging findings that may assist in the prediction of cardiac involvement, and our case is the only one in the literature to utilize CMR in the diagnosis of isolated myocardial relapse of ALL.

With ongoing improvements in the management of leukaemia, the incidence of myocardial involvement causing clinical disease may increase due to the mechanisms aforementioned. As such, consideration around the surveillance for recurrence in known sanctuary sites may be warranted in the correct clinical context. Our paper may encourage clinicians to consider using advanced imaging techniques in the early assessment of patients at-risk of cardiac involvement. Further case reports and observational data, particularly utilizing CMR will help to identify imaging indicators of leukaemic involvement of the myocardium.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that consent was obtained posthumously via patients next of kin.

Conflict of interest: none declared.

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