Case report

Isolated testicular recurrence of B cell acute lymphoblastic leukaemia in an adult: rare case

Thejus Jayakrishnan ¹ , ¹ Hira Shaikh, ¹ Yazan Samhoury, ² Ariel Sandhu, ³ Salman Fazal ²¹Internal Medicine, Allegheny Health Network, Pittsburgh, Pennsylvania, USA²Medical Oncology, Allegheny Health Network, Pittsburgh, Pennsylvania, USA³Pathology, Allegheny Health Network, Pittsburgh, Pennsylvania, USA

Correspondence to

Dr Thejus Jayakrishnan;
thejus.jayakrishnan@ahn.org

Accepted 16 October 2019

SUMMARY

An 80-year-old man who was previously diagnosed with Philadelphia+ B cell-acute lymphoblastic leukaemia (B-ALL) in remission post-allogeneic matched unrelated donor peripheral blood stem cell transplant. Five years later, he was found to have unilateral testicular relapse of Philadelphia+ B-ALL proven by pathology after radical orchiectomy. Bone marrow aspirate and biopsy did not show evidence of leukaemia. Patient was treated with adjuvant radiation therapy and started on dasatinib 50 mg daily. Given his age and absence of disseminated acutelymphoblastic leukaemia (ALL), no adjuvant chemotherapy was utilised. He is monitored with monthly PCR studies. At 1-year follow-up, no findings suggestive of recurrence of ALL have been identified and the patient is maintained on the dasatinib. Although isolated testicular recurrence is common among paediatric population, it is a rare event among adults as it is considered an immunological sanctuary for cancer cells.

BACKGROUND

Isolated testicular recurrence (ITR) after acute lymphoblastic leukaemia (ALL) is a rare phenomenon. This has been described mainly in paediatric age group where the incidence has been reported to be between 0.5% and 2%.¹ With better understanding of ALL pathology and advancement in molecular testing, treatment and disease course has been changing rapidly. Nevertheless, rare recurrences continue to occur and the ideal form of treatment is still debated. We describe a case of late ITR and multimodality management in an elderly patient with acute lymphocytic leukaemia.

CASE PRESENTATION

An 80-year-old man with history of B cell-acute lymphoblastic leukaemia (B-ALL), coronary artery disease and hypertension presented with left testicular discomfort for 1 month. He denies testicular pain, no associated redness or scrotal changes; he had no fever or chills, and reported no testicular trauma. On physical exam, left testicle was firm and nodular, without redness or tenderness, not enlarged, right testicle was normal. There was no palpable lymphadenopathy or hepatosplenomegaly. Complete blood count (CBC) showed white blood count (WBC) 8000/ μ L with normal differential, haemoglobin 154 g/L and platelets 206×10^9 / μ L. Chemistry was unremarkable. Testicular ultrasound showed a $3.2 \times 2.4 \times 2.9$ cm hypoechoic lesion within the left testicle (figure 1) with increased flow within

the lesion suspicious for malignancy, he underwent left radical orchiectomy and pathology showed a tan-white homogeneous well-circumscribed mass that measured $4 \times 4 \times 3$ cm and grossly appeared to involve the epididymis, located 2 cm from the spermatic cord. Immunohistochemistry of the malignant cells was positive for CD 79, CD10, Bcl2, CD34 and TdT, negative for MUM1, ALK, Bcl6, cyclin D1, CD56. CD20 stained background B cells and CD3 and CD5 stained background T cells. Epstein-Barr virus in situ hybridisation was negative, Mindbomb E3 Ubiquitin Protein Ligase-1 (MIB-1) proliferation index was estimated at 40%. Fluorescent in situ hybridisation (FISH) analysis was positive for BCR/ABL fusion gene (major breakpoint was p210). This was consistent with extramedullary relapse of Philadelphia+ B-ALL (figures 2 and 3). We did not analyse immunoglobulin or T-cell receptor gene rearrangements to assess the clonality further. Bone marrow (BM) aspirate and biopsy did not show evidence of leukaemia with normal male karyotype on chromosomal analysis (Analyte Specific Reagent DNA probes, Abbott Molecular), peripheral blood PCR for BCR/ABL was undetectable. Cerebrospinal fluid analysis was not performed.

He was diagnosed with B-ALL 6 years prior to this presentation, when he presented with bronchitis-like symptoms and his CBC showed WBC of 18 000/ μ L with 55% blasts, haemoglobin of 7 g/dL and platelet count 15×10^9 / μ L. BM biopsy and aspirate showed 100% cellularity and demonstrated complete replacement by sheets of blasts with the following immunophenotype: CD34+C-

Figure 1 Longitudinal ultrasound view of the left testis showing the mass concerning for malignancy.

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To cite: Jayakrishnan T, Shaikh H, Samhoury Y, et al. *BMJ Case Rep* 2019;**12**:e232286. doi:10.1136/bcr-2019-232286

Figure 2 Recurrent focus of leukaemia in the mid-spermatic cord at high power, showing a monomorphic population of B-cell blasts with round nuclear outlines, fine vesicular chromatin and small nucleoli. The cells efface and almost completely replace the existing testicular architecture.

D19+CD20 CD10+HLADR+ CD22+CD13+CD33+CD117-CD15-MPO-TDT+ which is consistent with B-ALL, FISH was positive for BCR-ABL fusion gene (in the BM and peripheral blood). Patient was treated with vincristine 2mg followed by dasatinib 70mg -by mouth twice daily along with steroids. He also received intrathecal methotrexate alternated with cytarabine for six treatments. Repeat BM biopsy 1 month after starting treatment did not show any evidence of leukaemia, marrow cellularity was estimated at 40% with 2+ reticulin fibrosis. Cytogenetics were negative for Philadelphia chromosome and PCR was negative for BCR-ABL, consistent with a complete cytogenetic response. He received maintenance chemotherapy with POMP (6 mercaptopurine, methotrexate, vincristine and dexamethasone) for 3 months along with dasatinib, followed by allogeneic matched unrelated donor peripheral blood stem cell transplant using non-myeloablative/reduced intensity conditioning regimen of fludarabine and busulfan (FluBu2). Peripheral blood stem cell transplant was tolerated very well and follow-up BM testing (aspiration and biopsy for 2 years) as well as peripheral blood testing with serial BCR-ABL PCRs showed no evidence of recurrence until current presentation. Post-transplant chimerism

Figure 3 Immunohistochemistry of the testicular section demonstrating relapsed B-cell acute lymphoblastic leukaemia cells staining positive for CD10, CD34 and CD79.

showed consistently 100% donor cells in CD3, CD33/CD66b and CD56.

OUTCOME AND FOLLOW-UP

Patient was treated with adjuvant radiation therapy—26 grey in 13 fractions and he was started on dasatinib 50mg daily. Given his age and lack of evidence of systemic relapse, no adjuvant chemotherapy was utilised and no further BM examinations were performed. He has been monitored with regular blood tests, physical exams and PCRs for BCR-ABL with no evidence suggestive of recurrence. The plan is to continue dasatinib indefinitely or until he develops any systemic illnesses or side effects that would preclude continued administration.

DISCUSSION

ALL is a malignant disorder of lymphoid progenitor cells with estimated worldwide annual incidence of about 1 in 100 000.^{2,3} Average 5-year overall survival in adult patients aged 18–60 years with ALL is 20%–35% despite high complete remission rates (75%–80%).² The major cause of failure of acute lymphocytic leukaemia treatment is relapse. The time to relapse is a strong predictor of long-term survival with further prognosis determined by relapse localisation, response to salvage therapy, performance of stem cell transplant and age.^{4,5} The relapse may happen in the medullary or extramedullary sites. The pattern of relapse varies according to the age and gender of the individual.

A rare but possible site of recurrence, among male patients treated for ALL is testes, with incidence of 0.5%–2% among boys.⁶ The incidence may be higher in certain populations depending on genetic and treatment-related characteristics.⁷ While ITR during complete remission of leukaemia has been reported in children, the reports in adults are rare and may represent first sign of systemic relapse.^{8–10} Studies have shown persistence of isolated microscopic testicular leukaemia after completion of initial treatment which is disconcerting.⁹ The testes is considered an immune sanctuary which likely contributes to its predisposition as a site for extramedullary recurrence after hematopoietic stem cell transplant.^{11,12} Several mechanisms have been proposed to explain this including the immunological tolerance of the testicular microenvironment and the presence of specific growth promoting factors that enhance tumour cell proliferation, such as lymphocyte growth factors (IL like-1).¹³ The physiological pubertal changes resulting in alteration in the permeability of the vascular endothelium and immunosuppressive effect of the testes could be the explanation for the smaller number of testicular relapses in men compared with boys treated for ALL.¹⁴ There is also concern that testes may be a drug sanctuary due to the presence of blood–testes barrier with therapeutic implications.⁷ Therefore, appropriate choice of agents such as methotrexate with efficacious penetration of blood–testes barrier may play a role in preventing ITR.^{15,16}

The recurrence usually presents as a palpable mass and radical orchiectomy is performed for both diagnostic and therapeutic purpose. Role of mutational profiling has been studied based on the fact that the testicular relapse could either be directly evolved from the leukaemic clone at initial diagnosis that survived chemotherapy or a common ancestral clone that arose independently.⁶ We did not pursue analyses of immunoglobulin or T-cell receptor gene rearrangements to elucidate this but could be considered in similar cases. It is also important to differentiate relapse from primary testicular tumours such as spermatocytic seminoma in elderly patients. Current treatment modalities for patients with ITR include orchiectomy, local

irradiation, systemic chemotherapy or a combination of these modalities.^{12 17} Successful management with orchiectomy alone has been reported although not widely accepted.¹⁸ In terms of utilisation of radiation therapy, although the event-free survival (EFS) was similar among patients who received radiation therapy compared with those who did not, the overall survival tends to be better among those who received radiation therapy.¹⁹ Systemic submicroscopic disease has been identified in patients presenting with apparent ITR and is the rationale for intensified systemic treatment.²⁰ Novel therapies such as chimeric Ag receptor-modified T cell therapy has been shown to successfully treat ITR with minimal side effects and could be investigated further.¹² There are proposals to omit radiation therapy as systemic therapy becomes more effective but it remains to be further validated.³ Although we chose dasatinib therapy in the present case following radiation, there are no data about its ability to penetrate blood–testis barrier and therefore continued vigilance during follow-up is absolutely important.

With appropriate treatment, patients who develop overt testicular leukaemia do attain clinical remission quite frequently.⁹ There are no large-scale long-term studies available on adults with ITR. However, among children with ITR, the overall 5-year survival has been reported to be around 73%.¹⁹ At least among young patients, the overall 4-year EFS with late testicular relapse (≥ 6 -month off-therapy) is around 84%. The rate is lower for those with occult testicular relapse (around 53%) or early relapse.²¹ This is because early ITR may represent high probability of systemic disease compared with late presentation that could be managed locally.²²

As the case points out, diagnosis and treatment of isolated testicular relapse of ALL can be very challenging given the rarity of this entity, and lack of data and experience in adult population. The case is also unique in terms of the prolonged interval between initial treatment and relapse which we hope would be a favourable factor for the patient. We limited adjuvant therapy to radiation and dasatinib without further chemotherapy due to patient's age and comorbidities which allowed him to enjoy his lifestyle without major treatment-related morbidity.

Learning points

- Our case adds to the sparse literature on isolated testicular relapse in adult acutelymphoblastic leukaemia patients and highlights the challenges haematologists may encounter in similar cases.
- As populations become older and survive cancer longer, these unusual recurrences may be identified more frequently.
- Long-term outcomes as well as patient and treatment characteristics associated with isolated testicular recurrence in adults is not well understood, and requires multimodality approach for management.

Contributors Each author meets all the following four criteria: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs

Thejus Jayakrishnan <http://orcid.org/0000-0002-3636-0353>

REFERENCES

- 1 Barredo JC, Hastings C, Lu X, *et al*. Isolated late testicular relapse of B-cell acute lymphoblastic leukemia treated with intensive systemic chemotherapy and response-based testicular radiation: a children's Oncology Group study. *Pediatr Blood Cancer* 2018;65:e26928.
- 2 Abbasi S, Maleha F, Shobaki M. Acute lymphoblastic leukemia experience: epidemiology and outcome of two different regimens. *Mediterr J Hematol Infect Dis* 2013;5:e2013024.
- 3 Pui C-H. Is testicular irradiation necessary for patients with acute lymphoblastic leukemia and testicular relapse? *Pediatr Blood Cancer* 2018;65:e26977.
- 4 Gökbuget N, Stanze D, Beck J, *et al*. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood* 2012;120:2032–41.
- 5 Nguyen K, Devidas M, Cheng S-C, *et al*. Factors influencing survival after relapse from acute lymphoblastic leukemia: a children's Oncology Group study. *Leukemia* 2008;22:2142–50.
- 6 Ding L-W, Sun Q-Y, Mayakonda A, *et al*. Mutational profiling of acute lymphoblastic leukemia with testicular relapse. *J Hematol Oncol* 2017;10.
- 7 Kulkarni KP, Marwaha RK, Trehan A, *et al*. Testicular relapse in childhood acute lymphoblastic leukemia: the challenges and lessons. *Indian J Cancer* 2010;47:134–8.
- 8 Vukelja SJ, Swanson SJ, Knight RD, *et al*. Testicular relapse in adult acute lymphocytic leukemia: a case report and literature review. *Med Pediatr Oncol* 1989;17:170–3.
- 9 Li CK, Shing MM, Chik KW, *et al*. Isolated testicular relapse after bone marrow transplant with total body irradiation and testicular boost in acute lymphoblastic leukemia. *Bone Marrow Transplant* 1998;22:397–9.
- 10 Forrest DL, Dalal BI, Naiman SC, *et al*. Testicular relapse of acute promyelocytic leukemia after allogeneic BMT. *Bone Marrow Transplant* 1997;20:689–90.
- 11 X-D M, Kong J, Zhao T, *et al*. Extramedullary relapse of acute leukemia after haploidentical hematopoietic stem cell transplantation: incidence, risk factors, treatment, and clinical outcomes. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant* 2014;20:2023–8.
- 12 Yu J, Hu Y, Pu C, *et al*. Successful chimeric Ag receptor modified T cell therapy for isolated testicular relapse after hematopoietic cell transplantation in an acute lymphoblastic leukemia patient. *Bone Marrow Transplant* 2017;52:1065–7.
- 13 Ritzén EM. Testicular relapse of acute lymphoblastic leukemia (all). *J Reprod Immunol* 1990;18:117–21.
- 14 Jahnukainen K, Morris I, Roe S, *et al*. A rodent model for testicular involvement in acute lymphoblastic leukaemia. *Br J Cancer* 1993;67:885–92.
- 15 Dördelmann M, Reiter A, Zimmermann M, *et al*. Intermediate dose methotrexate is as effective as high dose methotrexate in preventing isolated testicular relapse in childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 1998;20:444–50.
- 16 Shama G, Bhagwat R, Pai SK, *et al*. Isolated testicular relapse in acute lymphoblastic leukemia - effective treatment with the modified CCG-112 protocol. *Indian J Cancer* 2005;42:65–9.
- 17 Tomberli B, Cappelli F, Perfetto F, *et al*. Abrupt onset of refractory heart failure associated with light-chain amyloidosis in hypertrophic cardiomyopathy. *JAMA Cardiol* 2017;2:94–7.
- 18 Kodama Y, Okamoto Y, Ijichi O, *et al*. Continued complete remission without systemic therapy for isolated testicular relapse after bone marrow transplantation in a boy with acute lymphoblastic leukemia. *Pediatr Transplant* 2009;13:769–72.
- 19 Thacker LR, McCune TR, Harland RC. Kidney sharing by centers of the south-eastern organ procurement Foundation. *Clin Transpl* 1996;129–37.
- 20 Arima K, Hasegawa D, Ogawa C, *et al*. Detection of submicroscopic disease in the bone marrow and unaffected testis of a child with T-cell acute lymphoblastic leukemia who experienced "isolated" testicular relapse. *Int J Hematol* 2009;90:370–3.
- 21 Wofford MM, Smith SD, Shuster JJ, *et al*. Treatment of occult or late overt testicular relapse in children with acute lymphoblastic leukemia: a pediatric Oncology Group study. *Journal of Clinical Oncology* 1992;10:624–30.
- 22 Uderzo C, Grazia Zurlo M, Adamoli L, *et al*. Treatment of isolated testicular relapse in childhood acute lymphoblastic leukemia: an Italian multicenter study. Associazione Italiana Ematologia ED Oncologia Pediatrica. *Journal of Clinical Oncology* 1990;8:672–7.

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