Radiotherapy in Philadelphia chromosome-positive acute lymphoblastic leukemia with pericardial invasion after transplantation: A case report

JING YUAN[1*], YONG ZHANG[2*], HEBING ZHOU[2], SEN WANG[3], QITENG LIU[1] and YUYAN GAO[1]

Departments of [1]Radiotherapy, [2]Hematology and [3]Neurosurgery, Beijing LuHe Hospital, Capital Medical University, Beijing 101100, P.R. China

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Abstract. The present report describes a case of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) with pericardial invasion following bone marrow transplantation. The patient exhibited recurrent pericardial effusion accompanied by wheezing symptoms. Despite undergoing multiple pericardial punctures and drainage procedures, pericardial injections, and systemic treatment, the patient continued to experience recurrent pericardial effusion. Ultimately, the patient underwent whole-heart radiotherapy, resulting in complete resolution of the pericardial effusion. After a follow-up period of 10 months, the pericardial effusion remained well-controlled, and there were no significant impairments in cardiac function. In conclusion, radiotherapy may be considered as a viable treatment option for refractory leukemia cases presenting with pericardial effusion.

Introduction

Adult acute lymphoblastic leukemia (ALL) is one of the most common types of acute leukemia in adults, accounting for 20-30% of adult acute leukemia cases worldwide (1). A previous study indicated a higher morbidity in male patients compared with that in female patients (1.4:1), and a lower morbidity in adults compared with in children (1:3) (1). The rates of complete remission (CR) range between 70 and 90%, with long-term disease-free survival rates ranging between 40 and 50% in ALL cases positive for the Philadelphia chromosome/BCR-ABL fusion gene (2). Cardiac involvement is an uncommon occurrence in patients diagnosed with Philadelphia chromosome-ALL (Ph+ALL) (3). Following cardiac invasion, patients often experience recurrent wheezing symptoms and potential cardiac function impairment, leading to a decreased survival rate. The present report describes the case of a patient admitted with cardiac involvement in Ph+ALL.

Case report

A 48-year-old female patient was admitted to the Beijing LuHe Hospital (Beijing, China) in September 2020 primarily due to a 4-year history of ALL. The patient presented with chest tightness and dyspnea that had occurred for the past 3 days. The patient was initially diagnosed with Ph+ALL in November 2016, and achieved CR following regular chemotherapy [cyclophosphamide (0.8 g day 1), vincristine (4 mg day 2), doxorubicin (80 mg days 3-4), dexamethasone (70 mg days 1-7) and imatinib (600 mg every day), Q4W]. However, in January 2018, relapse was observed in bone marrow morphology, accompanied by pleural invasion, leading to the continuation of chemotherapy (Table I). In March 2018, a left breast mass was detected, and subsequent pathological examination confirmed leukemic infiltration (Fig. 1). Due to the unavailability of total body irradiation (TBI) treatment in the radiation oncology department, and considering the severe bone marrow suppression and rapid disease progression, it was not feasible to refer the patient to an external facility for radiation therapy. Thus, the patient was not selected to undergo TBI despite the presence of extramedullary recurrence. In April 2018, an intensified conditioning regimen (modified BuCY + IDA + VP16; idarubicin 20 mg on days 10 and 9, cytarabine 2 g/m^2 on day 9, daunorubicin 0.8 mg/kg every 6 h on days 8, 7 and 6, cyclophosphamide 1.8 g/m^2 on days 5 and 4, somatostatin 250 mg on day 3, etoposide 60 mg/m^2 on days 4, 3 and 2) was administered, followed by salvage sibling-matched allogeneic hematopoietic stem cell transplantation. A review conducted by PCR (Fig. 2) in July 2018 revealed the presence of the bone marrow BCR/ABL1 fusion gene (Philadelphia chromosome) and a BCR-ABL1/ABL1 ratio of 11.58%. The patient

Correspondence to: Dr Yuyan Gao, Department of Radiotherapy, Beijing LuHe Hospital, Capital Medical University, 82 Xin Hua Nan Lu, Beijing 101100, P.R. China
E-mail: 33639877@qq.com

*Contributed equally

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Table I. Summary of the treatment course of the patient.

Time	Event	Treatment	Outcome
November 2016	Diagnosis: Philadelphiachromosome-positive acute lymphoblastic leukemia	VDCP + IM consisting of cyclophosphamide (0.8 g day 1), vincristine (4 mg day 2), doxorubicin (80 mg days 3-4), dexamethasone (70 mg days 1-7) and imatinib (600 mg once every day), Q4W	BM: CR
November 2016-January 2018	ph+ALL	Continuation of chemotherapy with the previous regimen (VDCP + IM) for 11 cycles	BM: CR
January 2018	BM morphological relapse and pleural involvement	Cyclophosphamide (1.8 g on days 1 and 2), followed by CAR-T cell infusion (23 ml, totaling $1.71x10^8$ cells) for two cycles	BM: CR; BCR/ABL1 fusion gene, 0.56%
March 2018	Left breast mass, pathological diagnosis: Leukemic infiltration. Marrow morphological relapse	Modified BuCY + IDA + VP16 once, salvage sibling-matched allogeneic hematopoietic stem cell transplantation (counts of peripheral blood stem cells, mononuclear cells: $6.07x10^8$/kg, $CD34^+$: $2.423x10^6$/kg)	BM: CR; BCR/ABL fusion gene, (-)
July 2018	BCR/ABL fusion gene, (+); BCR-ABL1/ABL1, 11.58%	Dasatinib (50 mg; bid); interferon therapy, for 4 months	
October 2018	Chronic graft-versus-host disease of the skin and oral cavity	Prednisone (1 mg/kg/day); methotrexate (7.5 mg/week), for 2 months	BM: CR; BCR/ABL fusion gene, (-)
January 2019	Left breast mass relapse	Dasatinib; interferon therapy, for 4 months	Mass was smaller than before
April 2020	Shortness of breath on exertion. Echocardiogram revealed moderate pericardial effusion	Discontinuation of dasatinib; treatment with prednisone (0.5 mg/kg/day) and diuretics (10 mg/day), for 5 months	Outcomes remained unsatisfactory
September 2020	Increased dyspnea, echocardiography indicated large pericardial effusion. Diagnosis of ALL relapse with involvement of the pericardium	PCC	Pathology indicated primitive cells; flow cytometry revealed 52.37% abnormal primitive B lymphocytes; IGH, (+); BM: CR
September 2020-December 2020	Recurrent pericardial effusion	PCC; intrapericardial injection of dexamethasone (10 mg once); rituximab (375 mg/m^2), for 3 months	Repeated pericardial effusion
December 2020 for 2 weeks	Chest tightness and dyspnea, Echocardiogram showed large pericardial effusion, right atrial compression, bilateral pleural effusion and an abnormal echo of the left parietal pleura	PCC; 4D chemotherapy simulation positioning; radiotherapy (19.8 Gy/1.8 Gy/11 fractions), subsequent maintenance treatment with dasatinib (50 mg; bid), for 6 months	During a 10-month follow-up, the patient did not experience radiation pneumonitis, pericarditis or any impairment in cardiac function
After September 2021	The patient exhibited spinal cord involvement and bone marrow relapse	The patient opted for treatment discontinuation	
October 2021	Patient died of severe pneumonia		

BCR/ABL; BCR-ABL1/ABL1; BCR/ABL1; BM, bone marrow; CAR-T cell, chimeric antigen receptor T cell; CR, complete remission; PCC, pericardiocentesis; Bid, twice a day; 4D, four dimensions; Q4W, every 4 weeks; modified BuCY + IDA + VP16, idarubicin 20 mg on day 10 and 9, cytarabine 2 g/m^2 on day 9, daunorubicin 0.8 mg/kg every 6 h on day 8, 7 and 6, cyclophosphamide 1.8 g/m^2 on day 5 and 4, somatostatin 250 mg on day 3, etoposide 60 mg/m^2 on day 4, 3 and 2.

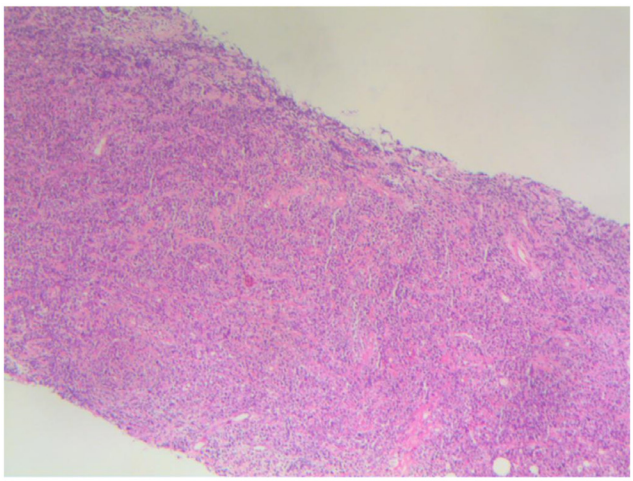

Figure 1. Pathology of breast mass (magnification, x40; H&E staining), indicative of leukemic involvement in the breast.

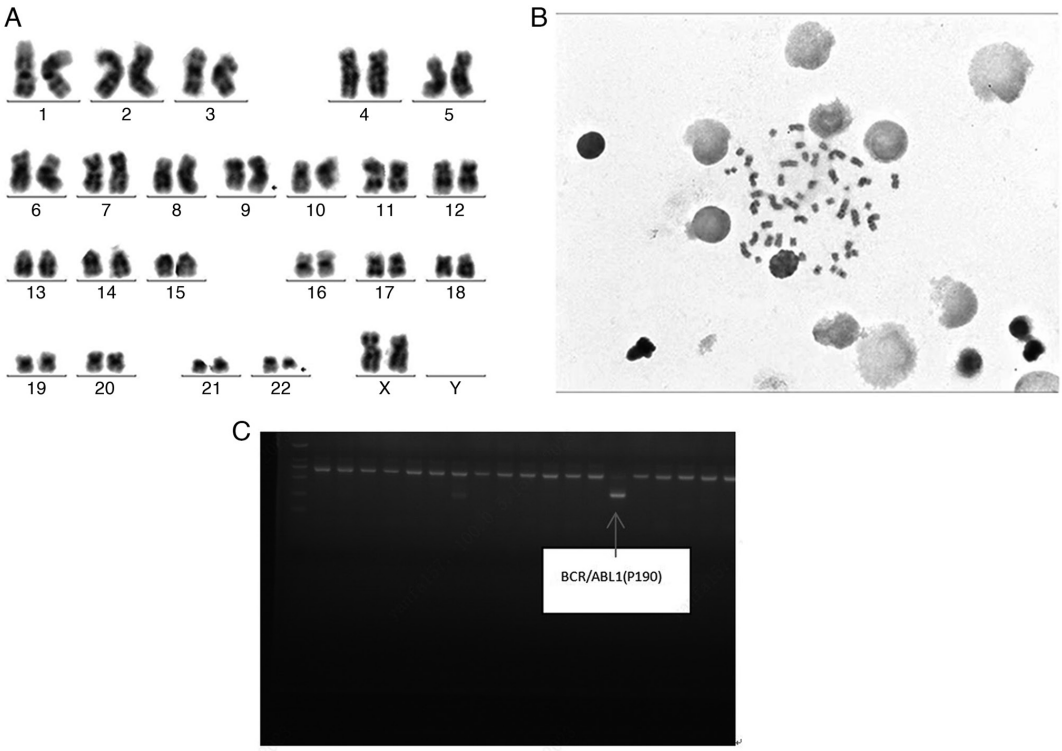

Figure 2. Chromosome and PCR results. (A and B) Chromosome images and (C) fusion gene image. The results indicated the presence of the BCR/ABL fusion gene and the translocation of chromosomes 9 and 22. Therefore, a diagnosis of Philadelphia chromosome-positive acute lymphoblastic leukemia was made.

was prescribed dasatinib (50 mg; twice daily) and interferon therapy. In October 2018, the patient developed chronic skin and oral graft-versus-host disease, which improved with treatment with prednisone (1 mg/kg/day) in combination with methotrexate (7.5 mg/week). In January 2019, a left breast mass was observed. Dasatinib and interferon therapy were continued (Table I), resulting in a reduction of the breast mass.

Since April 2020, the patient complained of intermittent shortness of breath following physical activity. Echocardiography revealed the presence of moderate pericardial effusion, which persisted in multiple subsequent examinations. Considering the possibility of pericardial

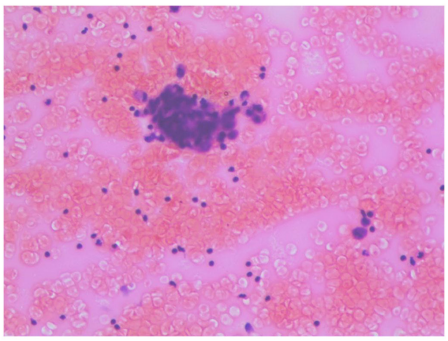

Figure 3. Pathology of pericardial effusion (magnification, x100; H&E staining). Atypical cells were observed.

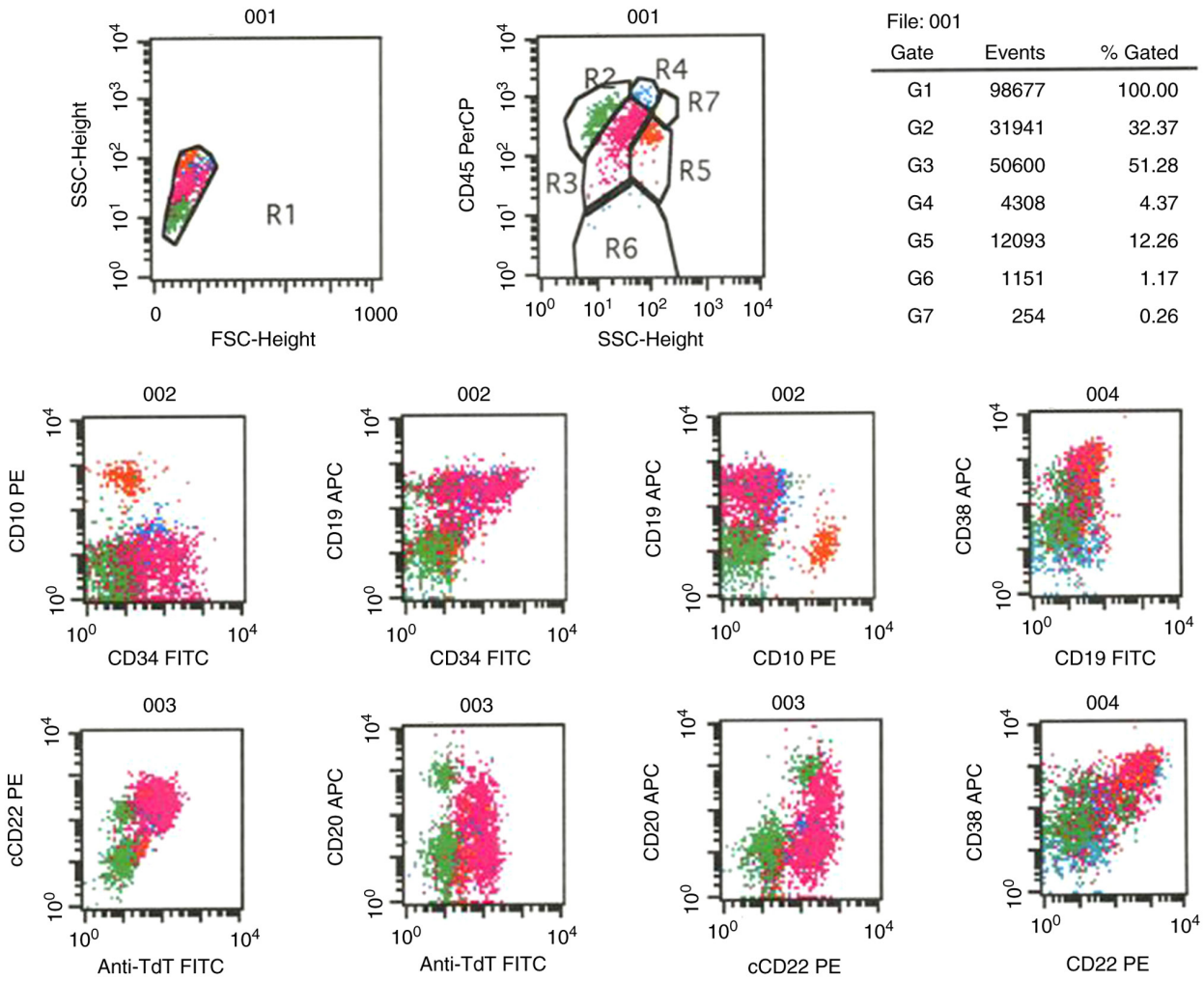

Figure 4. Flow cytometry plots. R1, all cells; R2, lymphocytes; R3, abnormal B blasts; R4, monocytes; R5, granulocytes; R6, nucleated red cells and debris; R7, eosinophils (G1-7 are the same as R1-7). The results indicated that R3 was an abnormal B primitive lymphocyte population, accounting for ~51.28% of cells, and expressing TdT, CD19, cCD22 and CD38, partly expressing CD34 and CD20, but not expressing CD10. Anti-TdT, anti-terminal-deoxynucleotidyl transferase; APC, allophycocyanin; FSC, forward scatter; PE, phycoerythrin; PerCP, peridinin chlorophyll; SSC, side scatter; cCD22, cytoplasmic CD22.

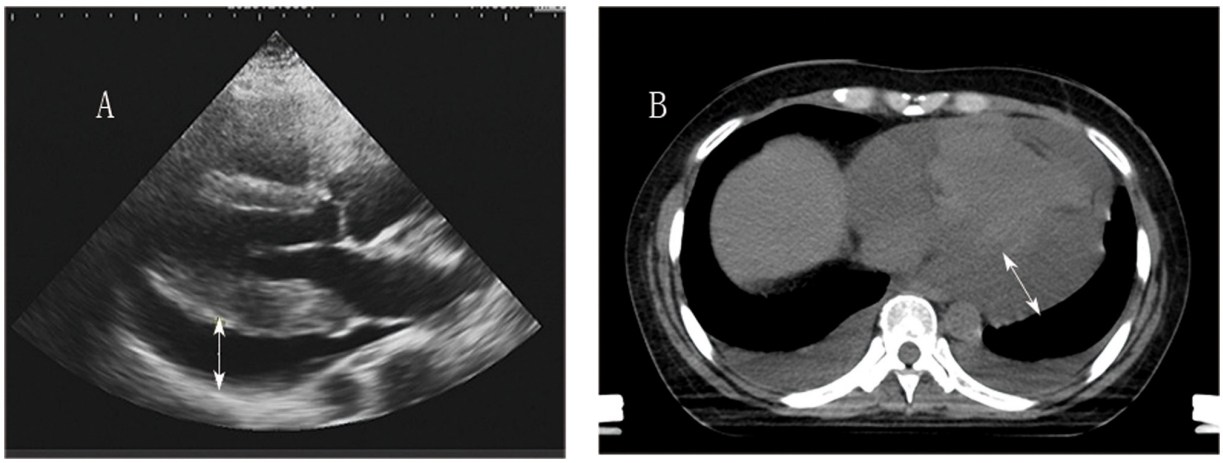

Figure 5. Pericardial effusion. (A) Echocardiography prior to radiotherapy indicated pericardial effusion (arrow) (December 2020). (B) Chest CT before radiotherapy revealed pericardial and bilateral thoracic low-density fluid, i.e., pericardial effusion (arrow) (December 2020).

effusion as a side effect of dasatinib, the medication was discontinued. Prednisone (0.5 mg/kg/day) and diuretics (10 mg/day) were administered for 4 months; however, there was no significant improvement in symptoms. The condition of the patient deteriorated in mid-September 2020, with echocardiography indicating a large pericardial effusion.

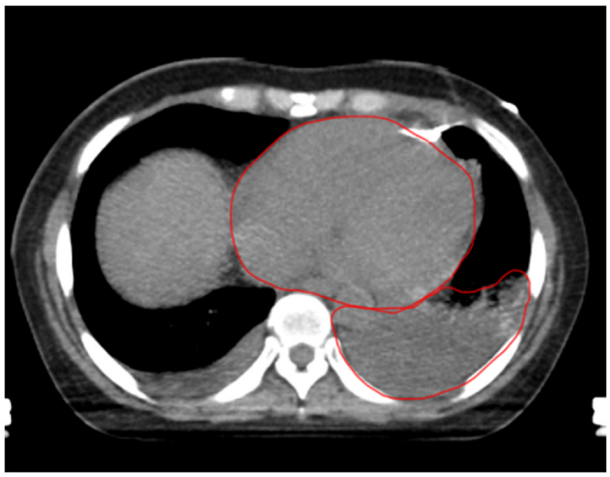

Figure 6. Radiotherapy. Both red areas indicate the radiotherapy target, including the whole heart and pleural effusion (December 2020).

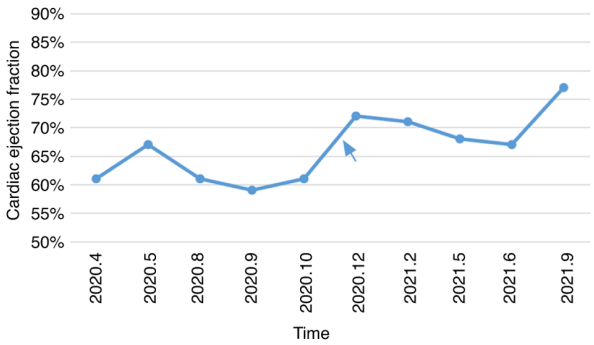

Figure 7. Changes in the left ventricular EF, the radiotherapy time point is marked with an arrow. EF, ejection fraction.

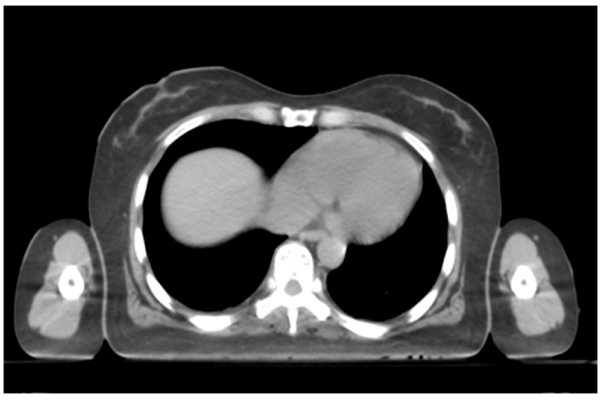

Figure 8. At 10 months of follow-up after radiotherapy, chest CT indicated no pericardial effusion (September 2021).

Pericardiocentesis (PCC) was performed to drain the pericardial effusion. Pathological analysis of the pericardial effusion revealed the presence of primitive cells (Fig. 3), and flow cytometry demonstrated 51.28% abnormal primitive B lymphocytes (Fig. 4). It was revealed that abnormal primitive B cells, under certain circumstances, may express terminal-deoxynucleotidyl transferase, and are not associated with graft-versus-leukemia effects. PCR results showed that the quantitative percentage of the positive BCR-ABL1 fusion gene in the pericardial effusion was 17.704%, with positive IGH gene rearrangement (Fig. 2C). Bone marrow morphology analysis indicated a CR, with the presence of residual, leukemia immune cells and a neoplasm negative for the BCR-ABL1 fusion gene (BCR-ABL1 <10-4). Pericardial biopsy was not performed for this patient due to the following reasons: Firstly, the Beijing LuHe Hospital does not perform pericardial biopsies. Secondly, there is a high risk associated with myocardial biopsies. Additionally, the patient did not undergo a positron emission tomography (PET)/CT scan because our hospital did not offer PET imaging at that time, and the patient could not afford the related expenses. Following the diagnosis of ALL relapse with involvement of the pericardium, the patient underwent PCC and received intrapericardial injections of dexamethasone and rituximab; however, the pericardial effusion recurred. In December 2020, the patient was readmitted to the Beijing LuHe Hospital due to chest tightness and dyspnea. A transthoracic echocardiogram revealed a large pericardial effusion, compression of the right atrium, bilateral pleural effusion and an abnormal echo in the left parietal pleura (Fig. 5). Following the diagnosis of leukemia with pericardial and pleural invasion, the patient underwent pericardial catheter drainage and received local radiotherapy in the pericardium at a dose of 19.8 Gy/1.8 Gy/11 fractions in December 2020 (Fig. 6). During and after radiotherapy, cardiac function was monitored using myocardial enzymes, B-type natriuretic peptide and ejection fraction values, and no cardiac dysfunction was observed (Fig. 7). Follow-up chest CT scans revealed the absence of radiation-induced pneumonia in the patient. Subsequently, the patient received dasatinib (50 mg; bid) and did not experience any recurrence of pericardial effusion, radiation pneumonitis, or pericarditis, nor any impairment in cardiac function during a 10-month follow-up period until September 2021 (Figs. 8 and 9). The patient exhibited spinal cord involvement and bone marrow relapse after September 2021. Follow-up visits were conducted once a month until the patient died in October 2021 due to severe pneumonia. The course of treatment of the patient is summarized in Table I.

Discussion

ALL is a malignant blood disease characterized by abnormal proliferation, aggregation and infiltration of primary and juvenile lymphocytes, leading to impaired normal hematopoiesis (1). While extramedullary organ involvement is common in ALL, affecting the liver, spleen, lymph glands, central nervous system and testes, cardiac infiltration is infrequent in clinical presentations of leukemia (4-6) but more commonly observed during autopsies (7-9). The cardiac infiltration rate is ~30% in postmortem examinations of patients with leukemia and 50% in patients with ALL (9). The diagnosis of leukemia with extramedullary invasion poses significant difficulties due to the following reasons: i) Low incidence of cardiac metastasis, ii) difficulty in obtaining cardiac biopsy for pathological examination.

Pericardial invasion in leukemia often presents with recurrent pericardial effusion, wheezing and reduced cardiac

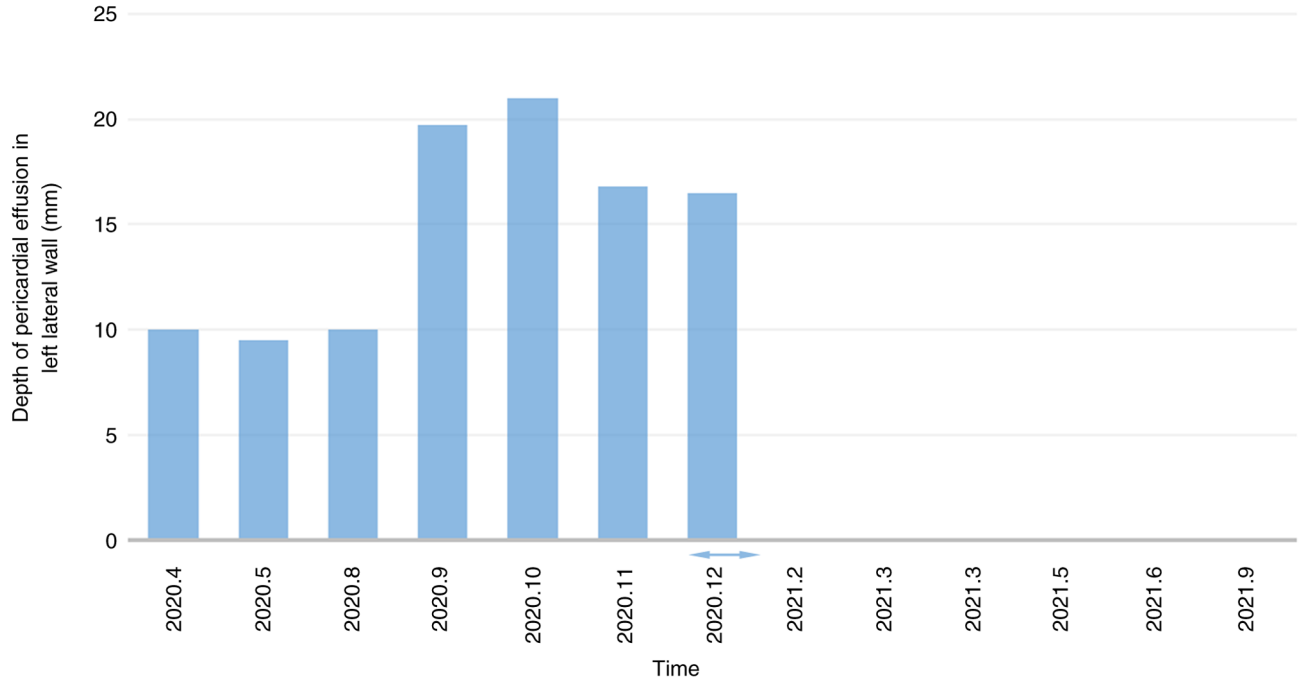

Figure 9. Bar chart of changes in pericardial effusion in the patient, the duration of radiotherapy is indicated by the double ended arrow.

function. In a specific case, a patient with unexplained heart failure was ultimately diagnosed with ALL through cardiac MRI and combined PET/CT imaging. These diagnostic methods revealed hypermetabolism in the right ventricle, atrium and entire bone marrow (6). When the patient of this case first developed pericardial effusion, the possibility of it being an adverse effect of dasatinib treatment was considered. At that time, the treatment approach involved discontinuation of dasatinib and administration of steroids; however, this proved to be ineffective. Subsequently, the recurrence of pericardial effusion was confirmed to be due to extramedullary involvement of ALL based on pathological findings. In the Beijing LuHe Hospital, such cases were previously uncommon in Ph+ALL but had been encountered in chronic myelogenous leukemia. However, in these patients, after discontinuation of therapy and targeted steroid treatment, resolution of the pericardial effusion was observed.

A definitive diagnosis of pericardial invasion in ALL was made in this case based on the following reasons: Firstly, the history of the patient indicated extramedullary invasion of leukemia. Secondly, recurrent wheezing symptoms were observed. Thirdly, imaging findings consistently suggested recurrent pericardial effusion that was unresponsive to medication. Lastly, cytology, flow cytometry and genetic testing of the pericardial effusion supported the diagnosis (Figs. 1 and 2). According to the National Comprehensive Cancer Network (NCCN) guidelines, the following treatment options are recommended for relapsed/refractory Ph+ALL: Tyrosine kinase inhibitor (TKI) and multiagent therapy/corticosteroid/blinatumomab/inotuzumab ozogamicin, or brexucabtagene autoleucel (following therapy that has included TKIs) (3). However, at the time, non-TKI targeted agents were not available in China, and the patient faced financial constraints. Therefore, following the relapse of the patient, TKI (dasatinib) therapy was chosen. In this particular case, despite the administration of pericardial injections of dexamethasone and rituximab, the patient experienced recurrent pericardial effusion. Symptom relief could only be achieved through PCC and drainage, as medical treatment failed to effectively control the condition. Given the limited efficacy of medication, local radiotherapy was considered as an alternative option for symptom control.

In another study, radiotherapy was employed in 38 cases of cardiac and pericardial metastases, with a radiation dose ranging between 25 and 35 Gy over a period of 3-4 weeks. Among these cases, six individuals with leukemia and lymphoma received radiotherapy at doses of 15-20 Gy over 1.5-2 weeks, resulting in continuous CR lasting for 2-4 months, with a clinical improvement rate of 60% (6). However, in a further study, 2 cases of leukemia with cardiac infiltration experienced recurrent and uncontrollable heart failure within 6 months, leading to death (10,11).

In cases of central nervous system invasion, the NCCN guidelines recommend lumbar puncture, intrathecal injection or a combination of these procedures, along with whole-brain and spinal cord radiotherapy, at doses 18 Gy/1.8-2 Gy. However, the total doses should be adjusted to 24 Gy/2.0 Gy in testicular invasion (1). A retrospective study (12) focusing on 38 cases of chloroma has highlighted the role of radiotherapy in controlling local disease and alleviating symptoms with no significant reported cytotoxicity during extramedullary progression, bone marrow relapse or when rapid relief was needed. The doses should be at least 20 Gy, and the usage of 24 Gy/12 times is recommended (12). For ALL cases with cutaneous involvement, local radiotherapy has demonstrated favorable outcomes when administered at a recommended dose of 24 Gy/12 fractions (13). In situations where the clinical condition does not permit a dose of 24 Gy, a dose range of 6-20 Gy can be considered (14,15). Furthermore, among 15 cases of leukemia cutis, 50% achieved CR when treated with medium doses of radiotherapy ranging between 6 and 24 Gy, and the 1-year

local control rate was 33%. It is important to note that patients who experienced a relapse of cutaneous involvement either had active bone marrow disease during radiotherapy or experienced marrow recurrence shortly after treatment. The median survival time after radiotherapy was 5 months, with a range of 0.5-136 months (14).

Leukemia arises from abnormal proliferation of immature and undifferentiated progenitor cells, which are known to be responsive to radiotherapy. The treatment approach in this particular case was determined by considering the radiation doses employed in other cases of leukemia with extramedullary invasion (3,12-15). Specifically, the patient underwent continuous pericardial drainage followed by radiotherapy targeting the entire pericardium, left pleura and pleural effusion. The radiation was administered using 6 MV X-ray irradiation at a dose of 19.8 Gy delivered over 1.8 Gy per fraction for a total of 11 treatments. During the 10-month follow-up period, the patient exhibited well-controlled pericardial effusion without any apparent cardiac function impairment. This treatment approach demonstrated superior results compared with previously documented methods (14).

In conclusion, in general, radiotherapy represents a potential treatment modality for patients experiencing refractory leukemic pericardial effusion. Radiotherapy can be considered for cases involving extramedullary progressive solitary lesions in leukemia, poor response to chemotherapy or isolated relapse following hematopoietic stem cell transplantation, or for symptomatic relief. In such situations, a low-dose radiation therapy regimen (ranging between 6 and 24 Gy) can be explored as a viable option.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JY was responsible for collecting clinical, imaging and pathological data of the patient and was responsible for the conception, design, content and writing of the manuscript. YZ contributed to collection of clinical and imaging data. YG analyzed and interpreted data related to radiotherapy and helped revise the manuscript. HZ analyzed and interpreted data related to chemotherapy. SW and QL analyzed and interpreted imaging data. JY and YZ confirm the authenticity of all the raw data. All authors agreed to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent for publication has been obtained from the son of the patient. All identifying information has been removed or anonymized to ensure confidentiality.

Competing interests

The authors declare that they have no competing interests.

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