

Complete response of myeloid sarcoma with cardiac involvement to radiotherapy

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Abstract: We present a rare case of intracardiac myeloid sarcoma (MS) of acute myeloid leukemia (AML) and who responds completely well to low-dose radiotherapy. This 19-year-old young man initially presented with AML and received standard chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT). However, he developed intracardiac isolated MS relapse with the presentation of exertional dyspnea and superior vena cava (SVC) syndrome 3 years later. He then received radiotherapy with 24 Gy at a 12 daily fractions using forward “field in field” intensity modulated radiotherapy technique. He dramatically had improved clinical symptoms, and complete remission was achieved one month after completing radiotherapy. Our result is in line with anecdotal case reports showed that radiotherapy with 15 Gy in 10 fractions or with 24 Gy in 12 fractions resulted in good response and less toxicity of 2 cases of MS with cardiac involvement. These results indicate that a modest radiotherapy dose, 24 Gy, achieves good local control of MS with cardiac involvement.

Keywords: Heart; myeloid sarcoma; radiotherapy

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Introduction

Myeloid sarcoma (MS), also known as chloroma or granulocytic sarcoma, is a rare hematological phenomenon defined as the aggregation of immature myeloid cells outside the bone marrow. Most cases of MS have been diagnosed in acute myeloid leukemia (AML) patients, with a reported incidence of 2.5–9.1% (1). The incidence of isolated MS relapse after allogeneic hematopoietic stem cell transplantation (HSCT) varied in previous studies, ranging from less than 1% to 12% (2-4). Optimal treatments of MS remained uncertain. Chemotherapy was widely administrated upfront, whereas local radiotherapy was considered part of a combined modality treatment and performed the role of palliative symptoms relief, especially for rapidly progressive lesions (5,6).

Because MS can present at various extra-marrow lesion

sites and result in prominent signs and symptoms, a high degree of awareness is mandatory for physicians caring for AML patients. Common sites of MS include the skin, head and neck, brain and spinal cord, and breasts (6). A cardiac site with MS involvement is extremely rare, and treatment results for cardiac MS have only been addressed by a few studies (7-14). Here, we report that an AML patient with isolated cardiac MS relapse after HSCT was successfully treated using fractionated radiotherapy and review studies on treatment modalities including chemotherapy and radiotherapy and treatment responses and outcomes of MS patients with cardiac involvement.

Case presentation

A 19-year-old man presented with AML, FAB (French-American-British) class M1, in June 2009. Cytogenetic

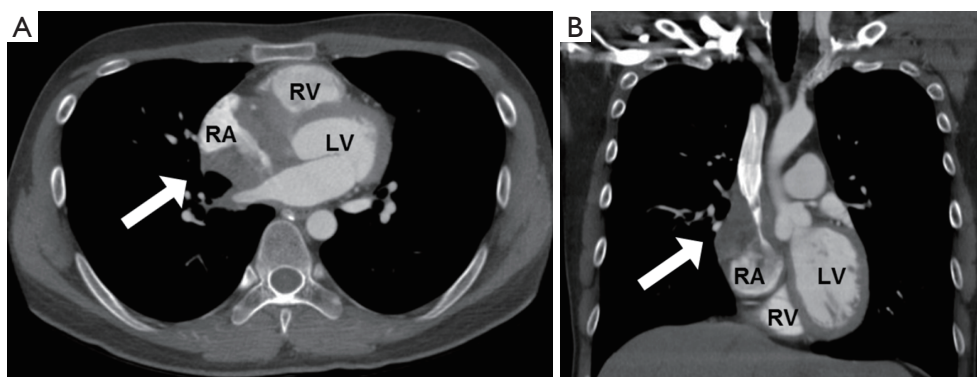


Figure 1 Cardiac computed tomography (CT) scan before radiotherapy displayed on axial (A) and coronal (B) planes. Arrows indicate the intracardiac tumor before radiotherapy. RA, right atrium; RV, right ventricle; LV, left ventricle.

studies revealed a normal karyotype, and a gene mutation screening was negative for nucleophosmin (NPM) and showed FMS-like tyrosine kinase 3. He received induction chemotherapy with idarubicin and cytarabine. However, left eye redness and pain developed after chemotherapy. A funduscopy showed subretinal leukemic cell infiltration, but a cerebrospinal fluid examination was negative for leukemic cells. In addition, he received three cycles of intrathecal chemotherapy with methotrexate, cytarabine, and methylprednisolone and achieved complete remission (CR) in a subsequent bone marrow study. He completed consolidation chemotherapy with idarubicin and high-dose cytarabine without major complications. Matched-unrelated-donor peripheral blood stem cell transplantation was performed smoothly in January 2010.

He developed multiple, tiny lymphadenopathies in the region of left neck level II in September 2011. The magnetic resonance imaging of head and neck disclosed multiple tiny lymphadenopathies without obvious mass lesions. However, histopathologic examination of core needle biopsy of lymphadenopathies revealed chronic inflammation but negative for malignant cells. The patient subsequently received selective neck dissection of multiple tiny lymphadenopathies for confirming histologic diagnosis because he had AML-free for two years after initial treatment. The pathology of the lymphadenopathies showed MS, in which the tumor cells were positive for myeloperoxidase and CD117 and negative for CD34. He then received chemotherapy with mitoxantrone, etoposide, and intermediate-dose Ara-C and consolidative radiotherapy with 30 Gy in 15 fractions to the left neck level II tumor bed and 24 Gy in 15 fractions to the lymphatic regions of left levels III, IV, and V using a 6-MV photon,

volumetric-modulated arc therapy (VMAT) technique. After the second CR, he received donor lymphocyte infusion in February 2012 but subsequently developed grade I–II grave-versus-host disease (GVHD) of the liver, skin, lungs, oral mucosa, and gastrointestinal tract. The GVHD signs and symptoms were controlled using cyclosporine and steroid. Subsequently, he also developed MS at the left preauricular skin area with parotid involvement. He underwent chemotherapy with FLAG (fludarabine + high-dose cytarabine + G-CSF) regimen followed by local radiotherapy with 30 Gy in 15 fractions to the left parotid gland and skin lesion and achieved CR again.

However, he developed sudden-onset chest tightness in November 2013, and a chest computed tomography (CT) scan disclosed a soft tissue mass along the interatrial groove with an encasement of the right upper pulmonary vein. The positron emission tomography scan revealed a large heterogeneous-intense hypermetabolic area involving the mediastinum and interarterial region (standard uptake value, maximum 8.3) (*Figure S1*). A percutaneous cardiac angiography with an intracardiac echocardiography-guided biopsy showed MS. Because of bronchiolitis obliterans caused by chronic GVHD and active pneumonia, radiotherapy was not suggested. After the pneumonia subsided, he received chemotherapy with azacitidine and achieved partial relief of the symptoms. However, in July 2014, he presented with superior vena cava (SVC) syndrome; a chest X-ray revealed right atrial enlargement (*Figure S2A*), and a cardiac CT scan revealed an enlarged right atrial tumor with venous encasement (*Figure 1*). Because of the SVC syndrome, he received radiotherapy with 24 Gy in 12 fractions. A forward “field in field” intensity-modulated radiation therapy (IMRT) technique

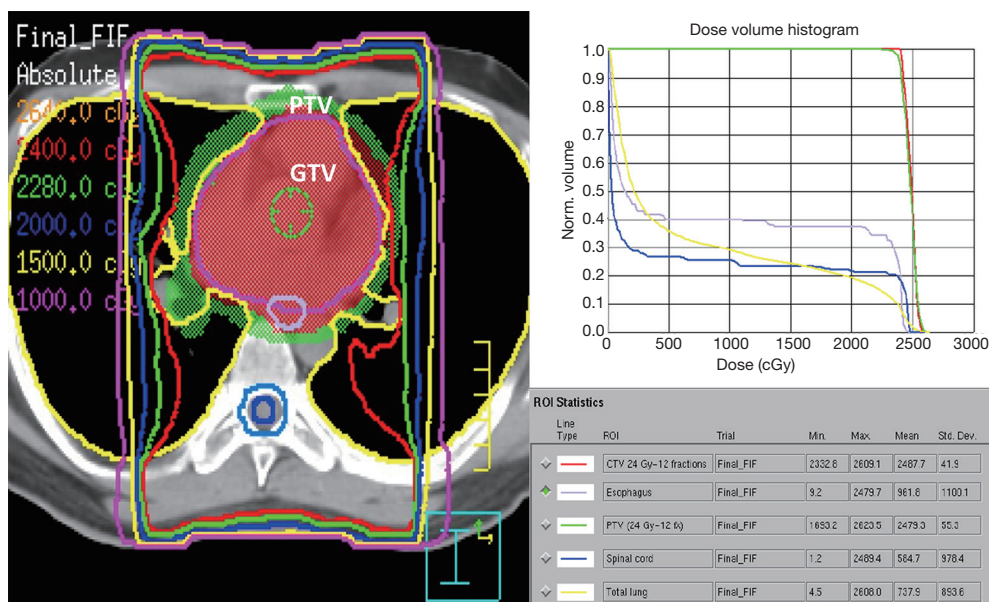


Figure 2 Isodose curves and a dose-volume histogram of the forward intensity-modulated radiation therapy plan using the anterior and posterior fields displayed on the axial plane. GTV, gross target volume; PTV, planning target volume.

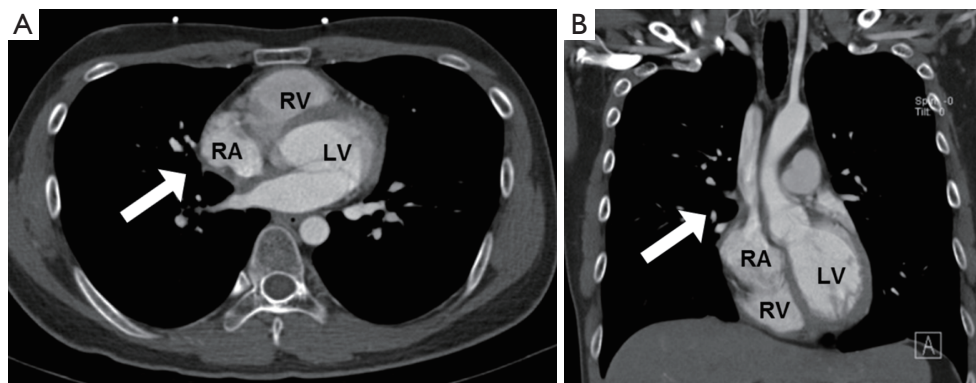


Figure 3 Cardiac computed tomography (CT) scan after radiotherapy displayed on axial (A) and coronal (B) planes. Arrows indicate complete remission of the intracardiac tumor in the postradiotherapy CT scan. RA, right atrium; RV, right ventricle; LV, left ventricle.

with a 10-MV photon was used to treat his entire heart and involved the great vessels with 2 fields in an anterior-posterior direction. The radiotherapy plan is shown in *Figure 2*. The mean lung dose was 7.4 Gy, and the lung V20 (percentage of total lung volume receiving ≥ 20 Gy) was 19%. The maximum spinal cord dose was limited to less than 25 Gy. After the radiotherapy was completed, the SVC syndrome subsided. A follow-up CT 4 weeks after completing radiotherapy demonstrated CR of the MS cardiac tumor (*Figure S2B*, *Figure 3*). He remained MS-free without obvious radiation-related toxicities till the

last follow up in January 2015. However, he died of sepsis-associated respiratory failure in February 2015.

Discussion

An optimal management of MS has not yet to be developed because of the rarity of this phenomenon and heterogeneous presentation. The treatment of choice depends on the status of the underlying disease and also on the MS lesion site. In general, MS emerging at presentation in combination with AML was treated as AML (5). The

Table 1 Review of published case reports of cardiac myeloid sarcoma

Study	Patient	Underlying disease	Timing of MS diagnosis	Treatment	RT dose and fractions	Result
Kara <i>et al.</i> (2005) (7)	28 y/o M	AML, M2	Post HSCT, combined with BM relapse	DLI→C/T (EMA)	–	CR
Kozelj <i>et al.</i> (2008) (8)	52 y/o M	AML t(8;21)	Initial presentation	RT→C/T→HSCT (TBI12Gy)	15 Gy/10 fx	CR
Rigamonti <i>et al.</i> (2009) (9)	52 y/o M	AML 47,X, add (Y) (q12)	Initial presentation	C/T (EMA)	–	Die of tumor emboli
Mignano <i>et al.</i> (2009) (10)	20 y/o M	AML	Post HSCT, isolated MS	RT	24 Gy/12 fx	CR
Tirado <i>et al.</i> (2010) (11)	25 y/o M	APL	Post C/T (CR), Isolated MS	ATRA-ATO	–	CR
Cash <i>et al.</i> (2011) (12)	13 y/o F	AML, M5	Post C/T (CR), isolated MS	C/T→PR→HSCT	–	Die of HSCT
Mawad <i>et al.</i> (2012) (13)	42 y/o M	AML t(8;21)	Initial presentation	C/T	–	CR
Present study	24 y/o M	AML, M1	Post HSCT, isolated MS	C/T→RT	24 Gy/12 fx	CR

y/o, year-old; AML, acute myeloid leukemia; MS, myeloid sarcoma; M, male; F, female; RT, radiotherapy; C/T, chemotherapy; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; CR, complete response; PR, partial response; EMA, etoposide, mitoxantrone, Ara-C; fx, fractions; DLI, donor lymphocyte infusion; BM, bone marrow; APL, acute promyelocytic leukemia; ATRA-ATO, all-trans retinoic acid; ATO, arsenic trioxide.

presence of MS was considered a poor prognostic factor for survival in some series (15). Nevertheless, the outcome of an MS relapse after transplantation seemed to be associated with a superior survival outcome (4,16). Chemotherapy is typically applied as a first-line treatment; however, there is no standard regimen for MS relapse. Donor lymphocyte infusion (17) and azacitidine (18) have been proposed as showing potential benefit on relapsed MS and AML. In our case, both donor lymphocyte infusion and azacitidine were used to achieve a short period free of progression.

Generally, radiotherapy serves as a palliation or consolidation treatment for MS, which we recently demonstrated in 20 patients receiving radiotherapy for MS lesions (in 43 radiotherapy courses) (6). The median radiotherapy dose of 20 Gy (range, 6–35 Gy), administered in 1.5–3.5 Gy fractions, provided a 63% CR rate, indicating that a modest RT dose (20–30 Gy) achieves strong local control of MS. Hall *et al.* also showed that approximately 50% of patients had subjectively complete symptomatic improvement without significant acute toxicities after palliative radiotherapy with a median dose of 24 Gy (19). However, when radiotherapy is used to treat cardiac involvement of MS, several concerns arise. The organ

motion of the heart makes it difficult to define a tumor location precisely. Possible toxicity to the lungs, heart, and spinal cord should be considered because some of these patients have received HSCT or have impaired heart and lung function. Because modest radiotherapy doses of 20–30 Gy results in a favorable CR rate for MS, we treated our patient with 24 Gy in 12 fractions to the entire heart, using a forward “field in field” IMRT technique. The studied patient experienced a substantial improvement of symptoms during radiotherapy and had no acute lung and heart toxicity at presentation. In addition, we reviewed published case reports addressing cardiac MS and treatment outcomes (Table 1). Most cases received chemotherapy as a primary treatment and a possible HSCT if there was no history of previous transplantation. Radiotherapy was employed in two cases. One of them received 15 Gy in 10 fractions for cardiac MS followed by chemotherapy and an HSCT conditioning regimen with a total body irradiation of 12 Gy (8); the other received local radiotherapy to the heart using 24 Gy in 12 fractions, with a complete radiographic and clinical response and no acute toxicity being reported (10).

In our previously published data (6), patients who

received radiotherapy after HSCT had a higher CR rate compared with those who underwent RT prior to HSCT (CR rate 100% vs. 50%, $P=0.05$). Radiation-induced graft-versus-leukemia effect may contribute to the favorable results of radiotherapy and may explain why our current case was alive 3 years after MS (20). In this study, we present a case of isolated intracardiac MS successfully treated by low-dose, fractionated radiotherapy. Based on our case and other case reports, cardiac involvement of MS can be treated safely with local radiotherapy with a favorable response. However, the addition of chemotherapy after radiotherapy for MS is warranted because of possible systemic failure and new MS merged outside the radiotherapy field following local treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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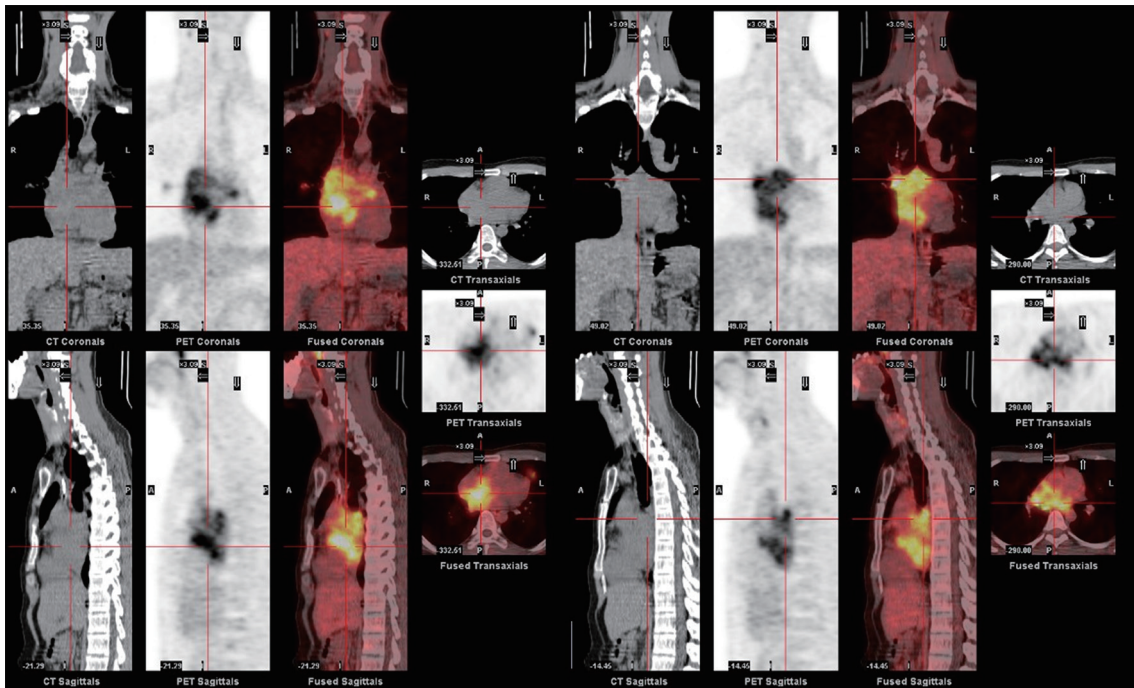


Figure S1 Preradiotherapy positron emission tomography scan image showing a hypermetabolic area involving the mediastinum and interarterial region with a maximal standard uptake value of 8.3.

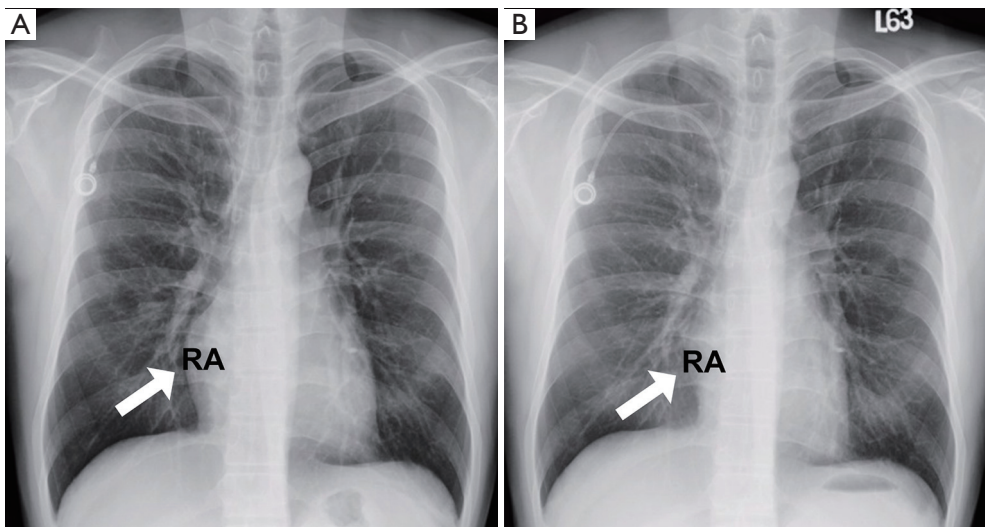


Figure S2 Chest X-ray before (A) and after (B) radiotherapy. An enlarged atrium on the preradiotherapy CXR (white arrow) no longer exists in the postradiotherapy chest X-ray.