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Radiotherapy

Role of Radiation Therapy in Management of Isolated Myeloid Sarcoma: Report of a Case and Review of the Literature

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Abstract **Case Report**

Myeloid sarcoma is an infrequent extramedullary tumor originating from immature myeloid cells and is associated with acute non-lymphocytic leukemia or myelodysplastic syndrome. Recent years have seen advancements in the survival rates of leukemia patients, primarily attributed to a deeper comprehension of the genetic underpinnings of the disease and the development of more effective combinations of chemotherapy and targeted therapies. Notably, the ability to achieve lasting control over systemic disease within the blood and bone marrow has markedly contributed to improved survival rates. However, the emergence of extramedullary relapses can present challenging therapeutic situations, where radiation therapy emerges as a crucial intervention. In light of these considerations, we report the case of a 67-year-old patient, with a history of acute leukemia treated in 2019 in remission and who presents an extramedullary blast localization at the level of the left elbow treated locally by radiotherapy and we have conducted a comprehensive literature review aimed at evaluating the potential role of radiotherapy in managing this rare manifestation of leukemia.

Keywords: Myeloid sarcoma-Chloroma- Radiotherapy -acute myeloid leukemia.

INTRODUCTION

Myeloid sarcoma, also referred to as Chloroma, granulocytic sarcoma, or myeloblastoma, is an uncommon solid extramedullary tumor primarily composed of early myeloid precursors. It is frequently associated with acute myeloid leukemia (AML) and other hematological malignancies such as myelodysplastic syndrome or during the accelerated phase of chronic myeloid leukemia [1]. The World Health Organization defines myeloid sarcoma as a tumor mass consisting of myeloid blasts, sometimes with maturation, occurring at a location outside the bone marrow [2]. These occurrences are infrequent, with an incidence of 2.5%-9.1% in AML [3]. Due to their rarity, tendency for misdiagnosis, and variable locations, clinical experience with these tumors is limited.

Extramedullary disease may occur concurrently with or precede bone marrow involvement and can manifest during relapses. In cases where blood or bone marrow is involved, myeloid sarcoma is commonly seen as infiltration of leukemic cells into the skin or gums. Isolated myeloid sarcoma can manifest in various sites including bones, periosteum, soft tissues, lymph nodes, and less frequently in areas like the orbit, intestine, mediastinum, epidural region, uterus, and ovaries [4]. Definitive diagnosis relies on identifying tumor cells as myeloid in nature, achieved through methods like myeloperoxidase or lysozyme staining, flow cytometry, or immunophenotyping from tissue samples.

Treatment approaches encompass systemic therapy, with the addition of radiotherapy and surgery aimed at enhancing local control. The optimal treatment strategy remains uncertain due to the poor prognosis associated with myeloid sarcoma. Multimodality management optimization is crucial. In specific cases, low-dose radiation therapy may be considered, particularly in scenarios where chemotherapy response is insufficient, during recurrences or progression, for isolated chloromas, or in palliative settings requiring symptom relief.

A PubMed database search of existing English literature regarding chloromas revealed few well-described cases. In this context, we present this case and the review of the existing literature to evaluate the role of radiotherapy in managing this rare manifestation of leukemia.

CASE REPORT

We report the case of a 67-year-old patient with a medical history that includes inguinal hernia surgery in 2013, benign prostatic hypertrophy, and non-insulin-dependent diabetes, he was diagnosed with high-risk myelodysplastic syndrome in October 2018, the prognostic score, as indicated by the R-IPSS, was 5.8. Subsequently, in January 2019, the patient exhibited a proliferative disease with bone marrow blasts exceeding 40%. In February 2019, a geno-identical allograft was performed using the patient's brother as the donor, following the KOLB protocol for preparatory conditioning.

Post-transplant, the patient was prescribed Azacitidine due to the elevated risk associated with the disease. Responding to the high risk, the patient received a donor lymphocyte injection (DLI) on July 2019, which unfortunately led to complications involving acute digestive Graft-versus-Host Disease (GvHD). Subsequently, the patient continued Azacitidine treatment post-DLI, with a dosage of 32.5mg/m2.

In April 2023, the patient reported pain in the left elbow, accompanied by an increase in size and limited mobility. Despite this, the patient's overall clinical condition was deemed satisfactory, with a Performance Status (PS) of 1. A clinical examination of the localized area revealed chronic cutaneous GvHD lesions. Notably, the left elbow displayed swelling and reduced flexion movement, without other signs of tumor syndrome. In response, further evaluation was made, including an elbow MRI that highlighted a tumor lesion affecting the lower end of the left humerus, infiltrating the synovium (Image 1). A PET scan confirmed the hypermetabolic nature of the lesion in the left elbow, with no other areas of significant hypermetabolism throughout the explored body (Image 2).

Hematologically, the following results were observed:

- Complete Blood Count (CBC): within normal range.
- Myelogram: revealed diluted marrow with no excessive blasts.
- Bone marrow karyotype: normal.
- Bone marrow phenotyping: 0% blasts.

Following thorough deliberation in a multidisciplinary consultation meeting, the diagnosis of chloroma was retained without recourse to a biopsy and the consensus was to administer radiotherapy to the elbow at a dose of 36 Gy, followed by a chemotherapy regimen involving Venetoclax and Azacitidine.

Radiotherapy (RT) was provided using 6 MV linear accelerator photons with arctherapy technique (4 half arch) and the target volumes included the gross tumour volume contoured after registration with MRI and PET scanner, the clinical target volume was the GTV (gross tumor volume) plus 10 mm margin, and to generate the PTV (planning target volume) a margin of 1cm was taken (Image 3). The prescribed dose of 36 Gy (dose-per-fraction of 2 Gy) was decided. At the end of the radiotherapy there was a total disappearance of pain swelling with normal mobility of the elbow, RT was well tolerated and the only side effect seen during follow-up was mild dry desquamation within the treatment field, then the patient was referd to his hematologist to poursuit chemotherapy with Venetoclax and Azacitidine. To date our patient is in good local and systemic control.

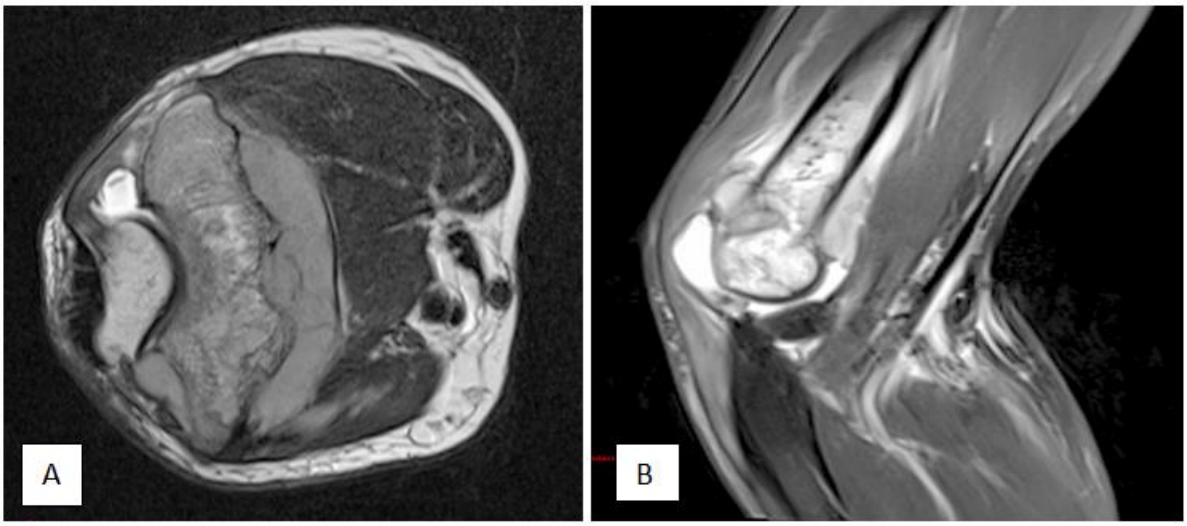

Image 1: MRI that highlighted a tumor lesion affecting the lower end of the left humerus, infiltrating the synovium; A: Axial image in T1 sequence. B: Sagittal image in STIR sequence

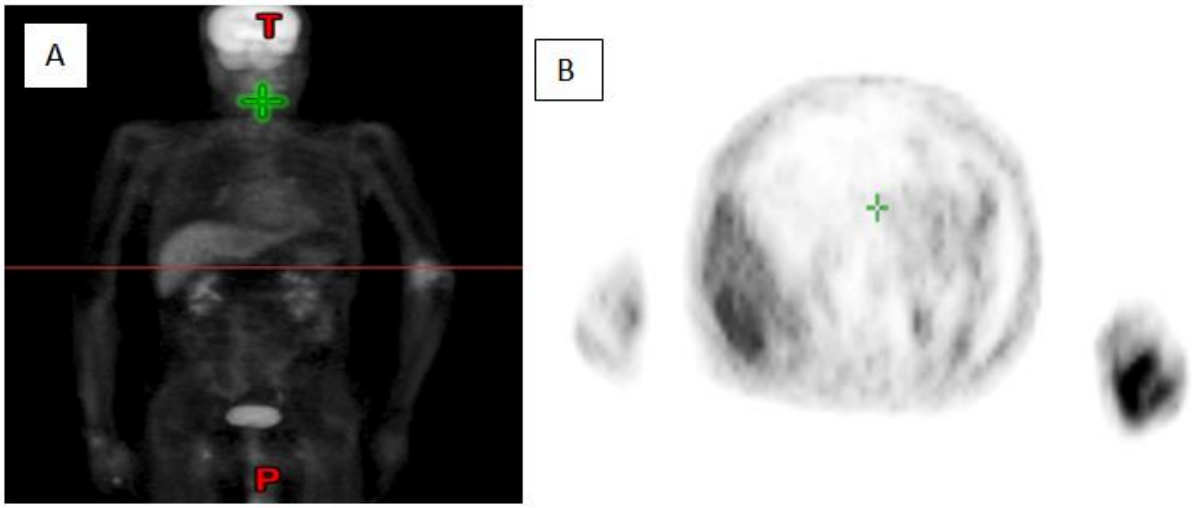

Image 2: 18 FDG positron emission tomography of our patient showing myeloid sarcoma at the left elbow; A: Whole body topogram. B: Axial image

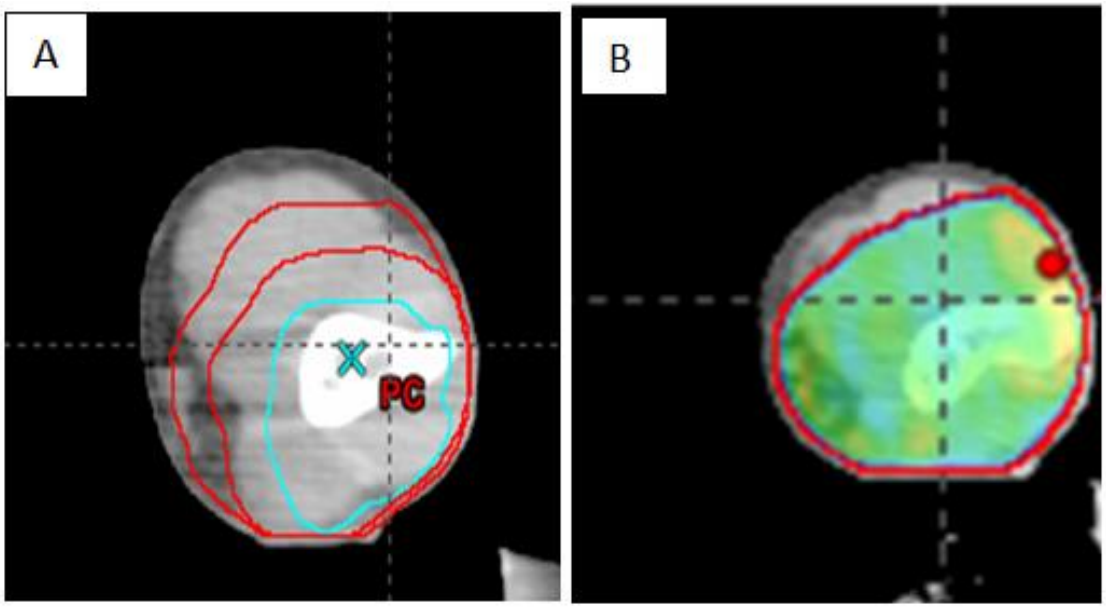

Image 3: Axial image of the dosimetric scanner showing: A: Target volumes, Cyan: GTV, red: CTV, orange PTV. B: Isodose 95%

Table 1: Table summarizing the clinical and therapeutic characteristics as well as the response after radiotherapy of the three large series of patients treated for myeloid sarcoma

Study	Cases	Location	Primary cancer or relapse of hemopathy	Dose (Gy)	Fractions (Gy)	Therapeutic response
Chak *et al.*, 1983 [10]	33	Bone (33%), soft tissue (32%), lymphadenopathy (11%), spinal cord (7%), brain (6%), other (11%)	unspecified	<10 Gy: 31% 10 Gy–19,99 Gy : 39 %	0,2–5	< 10 Gy: complete response 18% 10 Gy–19.99 Gy: complete response 43%
Bakst *et al.*, 2012 [11]	22	Cervicofacial (58%), extremity (13%), spine (17%), abdomen (12%)	primary cancer (18%), relapse (unspecified)	BED médiane 20 (6–36)	2 (1,5–4)	Complete response (97%)
Chen *et al.*, 2013 [17]	20	Skin (53.5%), breast (9.3%), brain (9.3%), spinal cord (7%), bone (7%) other (13.8%)	Primary cancer (45%), relapse (55%)	BED médiane 20 (6,5–35,9)	2 (1,5–3,5)	Complete response (63%)

DISCUSSION

The extramedullary manifestations of acute leukemia present a complex array of clinically significant occurrences, often creating challenging therapeutic scenarios. Chloroma, also recognized as granulocytic sarcoma or myeloid sarcoma, constitutes a rare extramedullary tumor composed of immature myeloid cells. While chloroma primarily arises in the context of acute myeloid leukemia (AML), it can also manifest in association with chronic myeloid leukemia during its accelerated phase, myelodysplastic syndrome, and, in rare instances, even without marrow involvement.

Histology

Histological sections of chloroma typically reveal infiltrating myeloid cells at various maturation stages, displaying granulocytic or monocytic maturation patterns, akin to what is observed in acute myeloid leukemia (AML). Employing techniques such as immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH), and other molecular methods has demonstrated an enhancement in diagnostic precision.

Immunohistochemistry is a common approach for confirming the diagnosis, and it doesn't necessitate the use of fresh tissue. It's advisable to employ a comprehensive antibody panel for this purpose. In the past, staining for myeloperoxidase (MPO) was employed to aid in distinguishing lesions from lymphomas. MPO is expressed in up to 66-96% of myeloid sarcoma cases and contributes to its green hue when exposed to air, which led to its historical designation "chloroma."

Several antigens are commonly expressed in myeloid sarcoma, including CD43, CD68, lysozyme, myeloperoxidase, and CD117. Additional frequently observed markers encompass CD11c, CD13, and CD33 [5].

Classification

The European Society for Haematology recognizes several extramedullary manifestations of myeloid neoplasms [6] which encompass:

1. Myeloid Sarcoma (MS) concurrent with Acute Myeloid Leukemia (AML)
2. Extramedullary relapse of AML, including occurrences post bone marrow transplantation
3. Blast phase or transformation of a Myeloproliferative Neoplasm (MPN) or Chronic Myelomonocytic Leukemia (CMML)
4. Isolated Myeloid Sarcoma, observed in conjunction with a normal bone marrow biopsy and blood film, and lacking any history of myeloid neoplasia.

General Management

The absence of randomized controlled trials presents limitations in devising treatment strategies for myeloid sarcoma (MS). The management approach for MS is influenced by several variables, including the location and size of the tumor, its relationship to local structures, the patient's age, and their performance status. The timing of the diagnosis is also significant, particularly in relation to any prior AML treatment. The management strategy is further shaped by the patient's response to systemic chemotherapy and whether the MS develops during the initial diagnosis or at the stage of relapse.

In the contemporary era of targeted therapies, relying solely on a basic pathological diagnosis of MS is inadequate for effective treatment planning. It's essential to strive for a characterization of the genetic abnormalities present, as this information guides treatment decisions and helps stratify prognosis.

Chemotherapy

Systemic therapy remains the fundamental approach to treatment, even in cases of isolated myeloid sarcoma (MS). This is due to the fact that a significant majority (ranging from 71% to 100%) of patients treated solely with localized methods such as surgery and/or radiotherapy eventually progress to acute leukemia. As a result, the initiation of chemotherapy is recommended for all cases, including those that have undergone local therapy for isolated MS. Various chemotherapy regimens, akin to those used for AML remission induction, have been applied in the treatment of myeloid sarcoma [7].

Radiation Therapy

INDICATION

Radiotherapy (RT) yields remarkable, rapid, and enduring local control at the targeted site. When chloroma is simultaneously accompanied by marrow involvement at the time of initial diagnosis, it warrants systemic treatment aimed at addressing the underlying disease. An incomplete response following chemotherapy is indicative of a noteworthy risk for early medullary relapse post-therapy. In such cases, the inclusion of radiation therapy is advised, especially when a complete response hasn't been attained with chemotherapy.

Isolated chloromas emerging at the time of relapse are infrequent and frequently foreshadow systemic relapses. The median duration until marrow relapse in this context has been reported as approximately 7 months. Treatment strategies hinge on whether the patient relapsed after chemotherapy alone or subsequent to transplantation. Management approaches in such scenarios have encompassed donor lymphocyte infusion, which has exhibited clinical promise in select cases. Additionally, the consideration of radiation therapy is pertinent for all cases of isolated chloroma at relapse, particularly those that arise after allogeneic transplantation [7].

To recap, radiotherapy should be contemplated for patients dealing with isolated chloroma who haven't demonstrated a satisfactory response to chemotherapy. It should also be considered for instances of isolated recurrence following hematopoietic stem cell transplantation (HCT). Furthermore, radiotherapy can play a pivotal role in situations requiring rapid relief from symptoms due to compression of vital structures.

Technique of RT

The initial step in radiotherapy (RT) planning involves determining the patient's optimal positioning to ensure both comfort and reproducibility during the setup. Comfort is key for achieving consistent positioning.

Based on the international guideline on Use of Radiation in Extramedullary Leukemia/ Chloroma Guidelines from the International Lymphoma Radiation Oncology Group [8], the target volumes encompass the gross tumor volume (GTV), which is defined as the visibly evident tumor outlined by the post-gadolinium MRI T1. It's strongly recommended to fuse the diagnostic MRI or TEP FDG scan with the planning CT for the most precise target delineation. The clinical target volume (CTV) encompasses a margin of 0.5 to 1 cm around the GTV, including any osseous involvement or changes observed on the bone window setting of the CT scan. Elective regional irradiation isn't typically required. The choice of immobilization technique and the need for image guidance depend on the treated anatomical site. While three-dimensional conformal RT techniques are applicable in most cases, intensity-modulated RT might be advantageous for leukemia affecting the head and neck to minimize toxicity. For superficial lesions, electron beam radiation is recommended.

Chloromas exhibit significant radiosensitivity, yet the optimal radiation dose hasn't been definitively established. Limited studies have explored the role of RT in managing chloroma (Table 1). The selected dose depends on the clinical scenario. A common approach is a low-dose RT regimen of 24 Gy delivered in 12 fractions, yielding excellent disease control and minimal morbidity [8]. However, lower doses ranging from 6 to 20 Gy administered in 2-Gy fractions can offer symptomatic relief and reduce disease burden if a more extended radiation course isn't feasible [9].

A study by Chak *et al*., [10] involving 23 patients with MS found that doses between 20 to 30 Gy led to 85% to 89% local tumor control. Experience suggests a correlation between chloroma size and the necessary total irradiation dose for control.

In the case of orbital chloroma, radiation therapy may be urgently required to prevent visual loss. Bakst *et al*., [11] reported on 38 patients treated for chloromas, with 33 courses of RT administered to 22 patients, 39% involving the head and neck. The median RT dose was 20 Gy. The progression-free survival (PFS) and overall survival in the RT cohort were 39% and 43%, respectively, at 5 years. The authors recommend irradiating chloromas to at least 20 Gy, proposing a 24 Gy regimen in 12 fractions as appropriate.

Prognosis

Due to the rarity of myeloid sarcoma (MS), large prospective series reporting prognosis are lacking. The variation in tumor location, timing of presentation, tumor genetics, and treatment approaches further compounds the challenge of predicting outcomes. Nonetheless, the prognosis for MS is generally understood to be poor, and without treatment, the vast majority of patients experience a rapid decline and succumb to the disease within a relatively short timeframe. Isolated MS, when left untreated, typically transforms into acute myeloid leukemia (AML) over a period of 10-12 months, although there are rare instances where this transformation has not occurred even over a follow-up period exceeding 16 years [12].

A study by Movassaghian *et al*., [13], utilizing the Survival, Epidemiology, and End Results (SEER) database, evaluated outcomes for 345 adult MS patients diagnosed between 1973 and 2010. Their analysis based on a population-based approach indicated a better 3-year survival rate for MS patients compared to non-MS AML patients. Furthermore, the prognosis varied based on the site of involvement, with improved outcomes observed for isolated MS affecting the pelvis/genitourinary organs, eyes/gonads, and gastrointestinal mucosa, as opposed to primary soft tissue sites, lymphatic/hematopoietic tissues, or nervous system tissue.

Several series have attempted to identify poor prognostic factors in MS. One study by Pileri *et al*., [14] involving 92 MS patients, found that factors such as age, tumor location, presentation with or without concomitant AML, or morphological classification did not significantly influence disease course or response to therapy. Another series revealed that individuals under 47.5 years of age, receiving systemic chemotherapy, and possessing a favorable karyotype were associated with a lower risk of death according to multivariate analysis [15] Kawamoto *et al*., recently conducted a significant prognostic analysis of MS patients, where assessment of 131 patients indicated that the expression of the protein CXCR4 in the Golgi of tumor cells, as determined by immunohistochemistry (IHC), correlated with increased overall survival (OS) in de novo MS, MS with concomitant AML, and recurrent MS arising from AML [16].

The emergence of genetic analyses has the potential to shed light on underlying genetic abnormalities, facilitating better stratification of prognosis in the future.

CONCLUSION

Myeloide sarcoma is often associated with a worse prognosis, and current literature does not demonstrate a survival benefit from radiotherapy. In the majority of chloroma cases, patients are referred for radiotherapy when there's extramedullary progression, isolate relapse, or an urgent need for symptom relief. A commonly used low-dose regimen of 24 Gy delivered in 12 fractions using conventional treatment has shown excellent results in achieving local disease control and alleviating symptoms without causing significant toxicity.

To better understand the role of radiotherapy in chloroma, both in cases with or without marrow involvement and at the time of relapse, prospective randomized studies that investigate combined multimodality treatments are necessary. Such studies could provide valuable insights into the most effective treatment strategies for this condition.

Competing interests: We (authors) declare that we have no conflict of interest.

Authors' Contribution: Mouhcine Hommadi and Khalid hadadi contributed equally to the work and should be considered co-first authors, Maroua Benlemlih, Elamin Marnouch, Abdelhak Maghouss, Amine Bazzine, Noha zaghba, Issam Lalya, Khalid Andaloussi Saghir, Mohammed Elmarjany, and Hassan Sifat designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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