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Myeloid Sarcoma in a Patient with Marfan Syndrome: A Case Report and Review of Literature

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Abstract

Myeloid sarcoma is a rare Extramedullary (EM) manifestation of Acute Myeloid Leukemia (AML) and can precede the involvement of bone marrow. Clinical presentations can be diverse based on the size and location of the disease and can often be misdiagnosed. While imaging can aid in diagnosis and response to treatment, tissue diagnosis with further cytogenetic and molecular information aid in selecting treatment and predicting prognosis. Here, we present a case of 38-year-old male with Marfan syndrome who presented with small bowel obstruction in the initial imaging. Pathologic examination of the resected bowel specimen showed an extensive involvement of myeloid sarcoma. Next-Generation Sequencing (NGS) performed on the resected colonic tissue identified a CBFβ/MYH11 gene fusion, as well as mutations in WT1 (Variant Allele Frequency, VAF 48.8%) and CBL (VAF 20%). The patient was treated with myeloid sarcoma-directed induction therapy with a combination of cytarabine and daunorubicin followed by 3 cycles of consolidative therapy with High-Dose Cytarabine (HiDAC). Subsequent imaging demonstrated sustained Complete Remission (CR) and a post treatment bone marrow biopsy done after completion of consolidation therapy suggested no morphologic or cytogenetic evidence of acute leukemia. Patient continues to follow up in the ambulatory oncology clinic and is currently 13 months post completion of his consolidation therapy with sustained clinical remission.

Introduction

Myeloid Sarcoma (MS) is a rare Extramedullary (EM) manifestation of Acute Myeloid Leukemia (AML) that occurs synchronously or metachronously- rarely preceding the onset of systemic bone marrow involvement [1]. The first case of MS was reported in the early 19th century; however, the relationship between MS and acute leukemia was not identified until about a century later [2,3]. Historically, MS had also been named as chloroma or granulocytic sarcoma but the use of these identifiers has declined over the years [4,5]. The incidence of MS in AML patients is not clearly established and varies from 2.5% to 30%, with a higher incidence associated with certain AML cytogenetic abnormalities, such as t(8,21) [3,5-8]. MS can also occur in isolation, without a history of leukemia, Myelodysplastic Syndrome (MDS), or myeloproliferative neoplasm, although isolated cases have only been described in limited case reports [9]. Of note, while the diagnostic criteria for AML as specified by the World Health Organization specifies the presence of myeloblasts equal to or exceeding 20% in the peripheral blood or bone marrow or the presence of cytogenetic abnormalities definitive for AML in myeloblasts regardless of the blast percentage, the occurrence of isolated MS should also be considered as a basis for the diagnosis of AML [10]. Misdiagnosis of MS as lymphoma is common, particularly in extramedullary isolated cases [11,12]. When it does not present as a *de novo* disease, MS can also present as a relapse with or without bone marrow involvement. MS may present after allogeneic Hematopoietic Cell Transplantation (HCT) with incidence ranging from 0.2% to 1.3% and portending a poor overall survival [13,14].

Case Presentation

A 38-year-old male presented to the emergency department with 3 days of abdominal discomfort and a recent history of small bowel obstruction that was managed non-operatively. He was diagnosed in the past with Marfan Syndrome with type A aortic dissection repaired *via* aortic grafting and mechanical aortic valve replacement, later complicated by a thoracoabdominal aneurysm that was subsequently repaired. A Computed Tomography of the Abdomen and Pelvis (CTAP) revealed evidence of Small Bowel Obstruction (SBO) characterized by a soft tissue density adjacent to the

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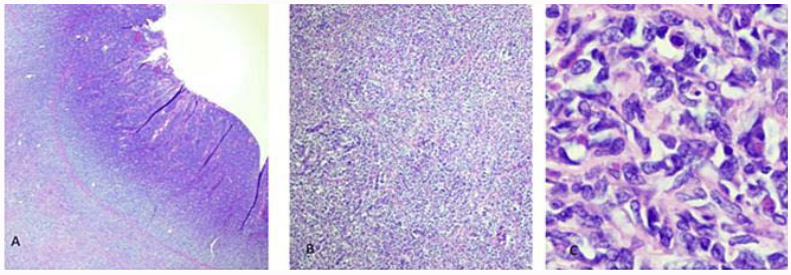

Figure 1: H&E staining of small intestine showing diffuse infiltration with sheets of immature cells (A: 100X, B: 200X, C: 400X).

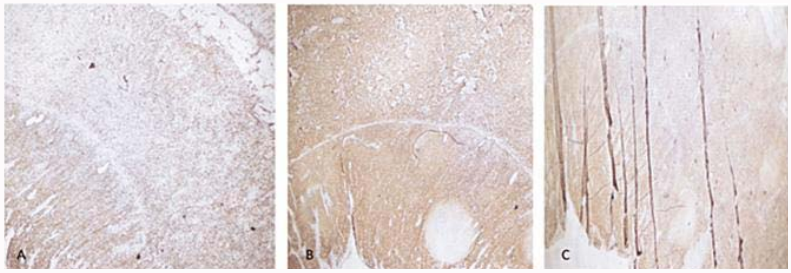

Figure 2: Immunohistochemistry shows staining of the tumor cells for CD45 (A), CD34 (B), Myeloperoxidase (MPO) (C).

descending aorta. Initially, the SBO was managed non-operatively, but it worsened over time, and based on clinical examination with follow-up CT imaging, an exploratory laparotomy was performed with bowel resection and lysis of adhesions. Pathological examination of the resected tissue confirmed extensive involvement of myeloid sarcoma, supported by diffuse strong expression of CD43, CD45, CD117, CD34, CD68, CD163, Myeloperoxidase (MPO), and Terminal deoxynucleotidyl Transferase (TdT) in a subset of cells (Figure 1, 2).

A bone marrow biopsy showed a normocellular marrow for the patient's age (60-70%) with maturing trilineage hematopoiesis and no morphological dysplasia or increased blasts (0.2% by aspirate). Flow cytometric analysis did not reveal a monoclonal population indicative of a myeloid neoplasm, and cytogenetic analysis demonstrated a normal male karyotype in only 7 metaphases (46, XY). Whole-body Positron Emission Tomography-Computed Tomography (PET-CT) confirmed scattered hypermetabolic lymph nodes in areas of the head and neck (maximum standardized uptake value [SUV] 1.1), chest (SUV range 2.2-4.0), and abdomen/pelvis (including periportal/portocaval region, general SUV range 4.1-8.0), along with an enlarged spleen measuring 20 cm (Figure 3A).

Next-Generation Sequencing (NGS) performed on the resected colonic tissue identified a CBFβ/MYH11 gene fusion, as well as mutations in WT1 (Variant Allele Frequency [VAF] 48.8%) and CBL (VAF 20%). Myeloid sarcoma-directed therapy was initiated with a combination of cytarabine and daunorubicin (7+3 regimen). Treatment was complicated by sepsis managed with intravenous antibiotics.

Prior to discharge, a peripheral blood differential revealed an elevated blast percentage of 10%. A repeat bone marrow biopsy was performed, which showed hypocellular marrow for the patient's age (30%) with trilineage hematopoiesis, although left-shifted maturation and slightly increased megakaryocytes were observed. Aspirate smear indicated the presence of 4% blasts. Flow cytometric analysis identified a myeloid population constituting 5% of cells expressing CD13, CD33, CD34, CD38, CD117, and HLA-DR. Cytogenetic analysis showed a normal male karyotype in 20 metaphases (46, XY).

The patient underwent a repeat PET-CT scan, which revealed decreased lymph nodal Fluorodeoxyglucose (FDG) avidity in the neck, chest, abdomen, and pelvis, along with a mild decrease in spleen size (also exhibiting decreased FDG avidity) to 18.4 cm, indicating a Complete Response (CR, Figure 3B). The patient subsequently underwent consolidative therapy with High-Dose Cytarabine (HiDAC) for 3 cycles. A repeat PET-CT scan demonstrated sustained CR with some inflammatory changes in the mediastinum but no definite additional sites of FDG nodal disease within the neck, chest, abdomen, or pelvis and a decrease in spleen size to 17.5 cm (Figure 3C). Furthermore, a bone marrow biopsy done after completion of consolidation therapy suggested no morphologic or cytogenetic evidence of acute leukemia (Fluorescence *in situ* Hybridization [FISH] studies were negative for CBFβ gene rearrangement). Due to the favorable risk of the patient's leukemia, allogeneic stem cell transplantation was deferred after consultation with stem cell transplant service. Patient continues to follow up in the ambulatory oncology clinic and is currently 13 months post completion of his consolidation therapy with sustained clinical remission.

Discussion

The clinical presentation of MS is heterogeneous due to its diverse locations, resulting in varied signs and symptoms dictated by its size and specific location. Soft tissue, bone, periosteum, and lymph nodes are the most frequent locations for MS while central nervous system involvement is rare, yet numerous other sites including small bowel have also been documented [12,15-18]. The diagnosis of Myeloid Sarcoma (MS) can be challenging in the absence of a clinical history of leukemia, and it is crucial to obtain a tissue diagnosis to avoid misdiagnosis, especially as Non-Hodgkin Lymphoma (NHL). Misdiagnosis can occur in as many as 46% of patients with MS, as poorly differentiated MS contains a diffuse infiltrate of medium-to-large cells, which may stain weakly for markers such

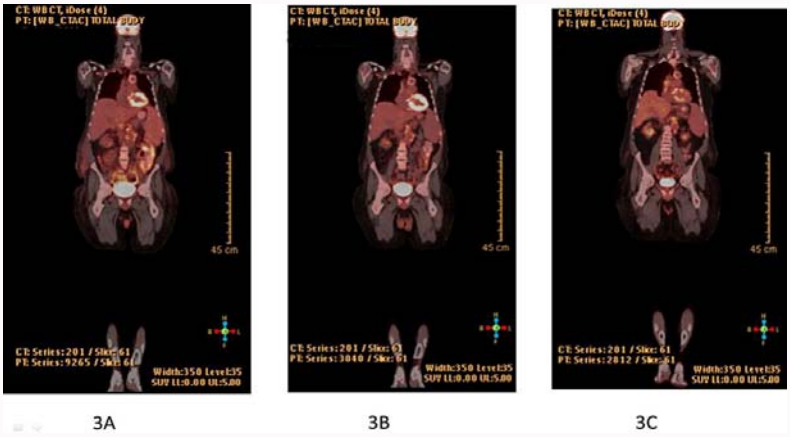

Figure 3: A) Showing scattered areas of hypermetabolic lymph nodes in the head, neck, chest, abdomen and pelvis (including periportal/portocaval region) along with an enlarged spleen measuring 20 cm; B) showing decreased lymph nodal FDG avidity in the neck, chest, abdomen, and pelvis, along with a mild decrease in spleen size to 18.4 cm; C) showing some inflammatory changes in the mediastinum and no definite additional sites of FDG nodal disease within the neck, chest, abdomen, or pelvis with a decrease in spleen size to 17.5 cm.

as myeloperoxidase, while sharing some leukocyte antigens such as CD45 and CD43 with NHL [7,12,19]. Furthermore, in addition to non-Hodgkin lymphoma, the differential diagnosis of MS should include other hematologic malignancies such as a lymphoblastic leukemia or blastic plasmacytoid dendritic cell neoplasm; soft tissue tumors such as Ewing sarcoma; melanoma; granulosa cell tumors; and extramedullary hematopoiesis [20]. To confirm the diagnosis of MS, biopsy samples should be sent for immunohistochemical analysis for CD3, CD 20, CD43, CD68, CD117 and myeloperoxidase; flow cytometry for similar antigens can be performed on cells in suspension. Fluorescence in situ hybridization should be performed to identify any chromosomal anomalies, and molecular analysis is recommended to identify gene mutations associated with differential prognosis [7]. Similar diagnostic tests should be performed on a bone marrow biopsy.

Role of imaging

Imaging plays a crucial role in the diagnosis and monitoring of treatment response in MS due to its varied presentation across different anatomical sites. Computed Tomography (CT) is particularly useful in visualizing soft-tissue masses, which are common in MS and is often the initial imaging modality used [21]. Positron Emission Tomography (PET) can be used alone or in combination with CT for Radiation Treatment (RT) planning and monitoring of treatment response [22]. In cases where MS develops in the CNS, Magnetic Resonance Imaging (MRI) provides superior visualization and is recommended [23].

Cytogenetic and molecular abnormalities

AML with Extramedullary (EM) involvement has been associated with a range of chromosomal abnormalities. Recent studies have suggested an association between cytogenetic abnormalities and the site of EM involvement; however, further research is needed to confirm these findings [24,25]. The t(8;21) translocation resulting in AML1/ETO fusion gene product defines a subset of AML patients with EM involvement, is found in 10% to 20% of younger patients, and is often associated with childhood orbital MS [24,26-29]. Similarly, the more rarely occurring inv(16) inversion resulting in the CBFβ/MYH11 fusion gene product is a cytogenetic abnormality that has been associated with isolated MS of the intestinal tract [7,25,30]. Prior studies have reported other cytogenetic abnormalities like 11q23, t(9;11), t(8;17), t(8;16), t(1,11), del(16q), del(5q), del(20q) and t(1;11) [7,31-35]. Of these, t(8;21) and inv(16) have been reported to carry favorable prognosis [7,36]. The identification of these cytogenetic abnormalities in patients with MS can aid in the prognosis and management of the disease.

In a study by Pileri et al, systematic FISH analysis identified chromosomal aberrations in MS samples, most commonly monosomy 7, trisomy 8 or mixed-lineage abnormalities, and more rarely trisomy 4 or trisomy 11 [37]. Their report suggested a high overall prevalence of chromosomal aberrations, which were detected in 54% of 92 adult MS patients. Interestingly, they did not always find concordance in abnormalities identified by FISH in tissue samples and karyotyping in the marrow or peripheral blood. In a subset of 14 of Peleri's patients, discordance between marrow and tissue sample abnormalities was found in 4 patients, with full concordance in ten [37].

In recent years, molecular mutations and genetic aberrations have emerged as important prognostic tools for acute leukemia. In cytogenetically-normal AML patients, Nucleophosmin gene (NPM1) mutations are observed in approximately half of the cases, and have been associated with a higher rate of complete remission after treatment [38]. One study of 181 MS samples reported NPM1 mutations in approximately 14% of MS cases [35,39]. FMS-related tyrosine kinase 3 gene (FLT3) mutations, which are associated with an unfavorable prognosis, are found in approximately one-third of AML patients with a normal karyotype [40]. In a series of 20 patients with myeloid sarcoma, FLT3 Internal Tandem Duplications (ITD) were identified in 15% (3/20) of MS cases; however, two cases showed discordance in the mutations identified between the MS and bone marrow specimens in this series [41]. Discordance in mutations between paired bone marrow and leukemic tissue samples has been reported to occur in up to 46% of patients, and the authors speculate that the clonal heterogeneity responsible for this phenomenon may eventually become a focus of targeted therapies [42]. As in the studies by Pileri described above, the significance of this discordance warrants further investigation, as interpretation of this finding is currently limited by the small number of patients and the speculative etiologies.

Prognostic significance

There is only limited data available to suggest the prognostic

significance of MS. The presence of EM disease may be associated with a worse prognosis and shorter survival, though 5-year survival rates for patients with MS range between 20% and 30%, similar to AML in general [7,15,43,44]. In MS, the prognostic significance of cytogenetic alterations remains unclear. While patients with translocation t(8;21) may achieve a remission rate of up to 90% following induction chemotherapy with anthracycline and cytarabine, conflicting reports exist regarding the prognosis of patients with this mutation in the presence of EM disease [45-47]. Analysis of 84 AML patients with t(8;21) reported by Byrd et al. suggested that the presence of EM disease, specifically spinal or meningeal involvement, contributed to significantly worse overall survival [7,47]. In another study, abnormalities in chromosome 8 appeared to suggest worse outcomes, however, this was limited by the small number of patients studied and was not statistically significant [4]. When treated with anti-AML chemotherapy, isolated MS may be associated with improved event-free survival and overall survival [48].

Treatment approaches

The optimal timing and treatment of isolated MS remain uncertain, but if left untreated or inadequately treated, progression to AML typically occurs within 5 to 12 months [11,44,49,50]. Recent studies of patients with isolated MS using RT-PCR have reported that genetic abnormalities associated with AML may be detectable in the bone marrow prior to the onset of clinical manifestation [51]. Therefore, remission-induction chemotherapy similar to that used for AML is the preferred treatment for isolated MS [15,44,50,52-54]. However, the role of post-remission chemotherapy, particularly hematopoietic cell transplantation, is unclear and must be assessed based on individual risk-factor analysis, taking into account the patient's age, gender, body mass index, comorbidities, karyotype, degree of dissemination, and the presence of molecular abnormalities such as mutations in FLT3 or NPM1 [7]. Low-dose radiation therapy can be recommended for patients with isolated MS and in some cases, upfront radiation or surgery may be necessary to provide rapid symptom relief or debulking of vital structures; however, studies have shown that the addition of radiotherapy to chemotherapy regimens does not increase overall survival [43].

Consolidation treatment

Following induction therapy, MS patients with bone marrow involvement but without cytogenic abnormalities are typically treated with repeated cycles of high-dose cytarabine with or without adjuncts such as idarubicin, to address concurrent AML [55,56]. However, there is no consensus on the optimal treatment approach for patients with isolated EM disease, and no randomized trials have been conducted to date possibly due to the rarity of isolated MS itself. Two retrospective studies by Chevallier et al. and Pileri et al. reported increased survival with the use of allogeneic or autologous HCT following CR [37,57]. Chevallier et al. reported a 5-year overall survival of 47% in 51 patients with MS who underwent allogeneic HCT, while Pileri et al. reported that long-term survival was only achieved in patients who had received HCT. However, factors such as cytomegalovirus reactivation following HCT, the use of reduced-intensity conditioning treatments or incomplete response to induction therapy have been associated with a decreased median overall survival, higher risk of recurrent/relapsing MS and early bone marrow relapse [58,59]. Therefore, consolidation treatment for MS patients generally follows similar guidelines as for conventional AML therapy, with the addition of radiotherapy or HCT as warranted, but individualized with patient-specific and cytogenetic factors [7,60,61].

MS as a relapsed disease

Isolated myeloid sarcoma relapse may indicate systemic relapse and is a rare occurrence. The median time to bone marrow relapse in such cases is approximately 7 months [62]. Relapsed isolated MS has been associated with a prior history of EM disease, abnormalities such as 5q and 7q deletions and FLT3 mutations, following HCT, and in children [63-66]. For patients who experience relapse after chemotherapy alone, radiotherapy or repeated induction therapy are usually considered, and HCT may be recommended. As there is no defined optimal treatment, consideration for enrolling patients in clinical trials that include relapsed MS should be made.

In the rare case of relapse of isolated MS after HCT, the prognosis is poor [67,68]. In such situation, it is advised to evaluate each patient individually, and consider a second allogenic HCT, donor lymphocyte infusion, reduction of immunosuppressive drugs if feasible, or investigational therapies such as nucleoside analogues, FLT3 inhibitors, farnesyl-transferase inhibitors, and histone deacetylase inhibitors [68-70]. The palliative use of RT may be appropriate, as further chemotherapy choices may be limited following HCT; however, a chemotherapy regimen that is appropriate for relapsed AML should be selected if possible [58]. An alternative strategy is the use of low-dose azacytidine, a DNA methyltransferase inhibitor that has been proposed for use after HCT in AML and myelodysplastic syndrome, but its efficacy in MS is inadequately studied [71].

Salvage treatment options for concurrent bone marrow and extramedullary relapse

In many cases, relapsed extramedullary MS presents concurrently with bone marrow relapse. In such cases, reinduction chemotherapy is the standard of care. Radiotherapy may be considered for patients who fail to achieve a complete response with chemotherapy. When bone marrow and extramedullary relapse occur concurrently after HCT, the prognosis is very poor [14]. In such cases, consideration should be made for palliative measures or entry into a clinical trial depending on the individual patient's circumstances.

Role of radiotherapy

In the management of MS, the role of RT has been studied to a limited extent [22,72]. RT is usually considered in cases of isolated MS, after incomplete response to conventional chemotherapy, and in recurrence after HCT. It has also been used in the palliative setting for rapid symptom relief due to compression of vital structures [22]. RT has been shown to result in excellent and durable local control at the targeted site, but its addition to chemotherapy alone has not been demonstrated to result in superior overall outcomes.

Post treatment monitoring

There is a higher risk of EM relapse in patients with MS than other patients with AML. In order to manage this risk, patients with MS should be periodically monitored with regular physical examinations and routine peripheral blood tests. Any new or suspicious soft tissue abnormalities are always biopsied, and if recurrence is confirmed, the bone marrow should be reevaluated. Imaging studies may be repeated in patients with MS after completion of treatment, but if the initial post-treatment scans are negative, routine further imaging is not recommended.

Current understanding and future directions

Current understanding of EM pathogenesis remains incomplete. The specific mechanisms underlying homing to certain tissues are complex and involve the expression of chemokine receptors

and adhesion molecules. For example, CD56 which is expressed in patients with t(8;21) and is associated with high incidence of MS, has been also found to be frequently expressed in breast, ovarian, and gut tissues which could explain homing to such EM sites [12,62,73-76]. In other instances, degranulation of CBF transcription factors have been suggested in the pathogenesis of MS associated with inv(16) [30]. Relapses of MS may occur at sanctuary sites in EM, including reproductive organs and CNS structures, which possess inherent barriers, and are known to evade systemic therapy [77,78]. Taken together, the molecular pathway for EM pathogenesis is likely multifactorial and future studies are required to show a clear signal explaining homing to EM sites. Clinical correlations are necessary to confirm the relevance of these mechanisms, and blast chemokine or adhesion molecule receptor profiling could serve as a predictor of EM site involvement and be exploited therapeutically with targeted agents.

Association with Marfan syndrome

Overactivation of the Transforming Growth Factor-β (TGF-β) is typically associated with Marfan syndrome besides the well-known deficiency of the structural extracellular matrix component fibrillin-1. Among patients with Marfan syndrome, cardiovascular abnormalities are the major causes of morbidity and mortality [79]. However, there have been prior case reports and studies suggesting occurrence of malignancies, including both hematologic and solid malignancies, in patients with Marfan syndrome and thus contributing to the morbidity and mortality [80,81]. A population-based nested case-control study in the Asian population had previously shown association between malignancies and Marfan syndrome [81]. However, prior literatures only show correlation, and a direct causality has not been identified so far, and it would be interesting to explore if overexpression of (TGF-β) in Marfan syndrome is also implicated in pathogenesis of myeloid sarcoma and EM homing.

Conclusion

As our knowledge of AML continues to expand, our understanding of EM involvement should evolve accordingly. MS can occur synchronously or metachronously with bone marrow involvement. It can often precede bone marrow involvement and can rarely present as an isolated disease. Both molecular and cytogenetic studies have prognostic significance in the natural course of MS and need to be studied further to show concordance with the bone marrow. Novel pathways that confirm molecular pathogenesis of MS should be explored further to better utilize targeted treatments in this unique space. Furthermore, occurrence of MS in patients with Marfan syndrome should be studied further and a causal link should be established, if any.

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