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Case Series

Myeloid sarcoma cases with varied presentations leading to diagnostic delay: A case series

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ABSTRACT

Myeloid sarcoma (MS) is an extramedullary tumor, which may be isolated or associated with acute myeloid leukemia (AML). In isolated MS, diagnosis may be challenging. Although it may develop at any site, isolated MS of the spine and parotid region are very rare. We found such rare presentations in our patients, so we wanted to highlight the importance of early suspicion and proper evaluation of such cases. To find out cases of MS, we searched clinical records of our patients of AML/MS, who were treated in the past 1 year in our department at All India Institute of Medical Sciences Raipur. We found 20 such cases of AML/MS who were treated with standard 3 + 7 induction chemotherapy and out of them 3 had isolated or associated MS. We selected these three patients for this case series. In this report, we have described the presentations and treatment of these three cases. One of the patients had isolated MS of the spine, who presented initially with paraparesis. Due to atypical presentation, there was a diagnostic delay, but after treatment, he recovered fully. In another case of isolated parotid swelling, initially suspected to be lymphoma, later diagnosed as MS and also found to have bone marrow involvement with detection of t (8;21) consistent with AML. In another typical presentation, the patient had AML associated with orbital MS. With all these three cases, we want to bring to notice the rare presentations of this entity and which may help clinicians to suspect and diagnose it early and which can improve the overall outcome of such patients.

Keywords: Myeloid sarcoma, Acute myeloid leukemia, Parotid, Paraspinal, Positron emission tomography, Computed tomography

INTRODUCTION

Myeloid sarcoma (MS) or granulocytic sarcoma, first described in the 19th century, was earlier named as chloroma due to its greenish color with myeloperoxidase (MPO) staining.[1] It is an extramedullary deposit consisting of myeloid blasts and is defined as a subtype of acute myeloid leukemia (AML).[2,3] When it precedes the involvement of bone marrow, it is defined as isolated MS.[4] Isolated MS also known as primary or non-leukemic MS is a rare entity. As per the literature, it is seen in 2 out of 1 million adults and constitutes only 0.7% of all AML patients.[4,5] Its incidence in the childhood age group is 0.7 out of 1 million children. Although it can develop at any site, soft tissue is involved most commonly (31.3%) and roughly 4.9–6.6% of cases originate from the bone.[4,6] Isolated spine involvement by MS is extremely rare and so is unilateral parotid involvement. Here, we report three cases, where MSs were seen in different locations: One isolated MS in the spine, the second MS in the paroid gland, and the third one was periorbital in the case of AML during a period of the past 1 year.

CASE SERIES

To find out cases of MS, we searched clinical records of our patients of AML/MS, who were treated in the past 1 year in the Department of Clinical Hematology and Department of Medical Oncology at All India Institute of Medical Sciences Raipur. We found 20 such cases of AML/MS who were treated with standard 3 + 7 induction chemotherapy. We went through the clinical records of these patients and out of them three had isolated or associated MS. We selected these three patients for our case series. We found three cases of MS (isolated and/or associated with AML) as described below.

CASE 1

A 16-year-old male, without any comorbidities, presented with complaints of backache radiating to both lower limbs and difficulty in walking in August 2021. These problems, later on, progressed to paraparesis. There was not any history of fever or bleeding manifestations. On evaluation, power was 3/5 of all muscle groups and rest of the examination was normal. Blood reports including complete blood count, renal function test, and liver function test were normal.

Initially, the patient was evaluated at another center in Aug 2021, where magnetic resonance imaging (MRI) lumbosacral spine showed altered marrow signal intensity in L2 vertebral body with involvement of bilateral posterior elements with heterogeneous post-contrast enhancement and associated epidural and bilateral foraminal soft-tissue causing compression of cauda equina nerve roots and secondary canal narrowing. Similar altered intensity signal changes in L3 and L5 vertebrae. He underwent L1 and L3 pedicle screw with rod fixation with L2 laminectomy and decompression of cord on 12/08/21 there. He was started on empirical ATT and after that patient lost to follow-up. On worsening of symptoms, he presented to our institute in November 2021 where a repeat MRI showed a fairly large area of altered signal intensity virtually totally replacing the entire L2 vertebral body and associated large lobulated pre and paravertebral anterior epidural soft-tissue suggestive of underlying neoplastic etiology. Computed tomography (CT)-guided needle biopsy from the paravertebral mass was suggestive of a round cell tumor and immunohistochemistry (IHC) showed positivity for CD34, CD45, CD117, MPO and negativity for CD3, CD20, and NKX2.2 suggestive of MS. Positron emission tomography/PET/CT revealed mildly fluorodeoxyglucose (FDG) avid large, ill-defined minimally enhancing soft-tissue density mass at a pre-paravertebral region opposite to L1–L3 vertebrae, FDG avid lytic sclerotic skeletal lesions D12, L3, sacrum, and left acetabulum suspicious of skeletal metastatic lesions.

Bone marrow aspiration/biopsy was cellular marrow with trilineage hematopoiesis and flowcytometry did not show any involvement by leukemia.

Reflex polymerase chain reaction (PCR) panel on bone marrow aspirate did not reveal any AML defining mutations. Cerebrospinal fluid (CSF) examination revealed no evidence of involvement by malignant cells. Hence, final diagnosis of MS without bone marrow involvement was made and he was treated with cytarabine 100 mg/m^2 continuous infusion for 7 days and daunorubicin 60 mg/m^2 for 3 days followed by one cycle of high-dose cytarabine consolidation (3 g/m^2 twice daily for 3 days). Response PET/CT was done after two cycles of chemotherapy (3 + 7 induction and first HiDAC) and showed a complete metabolic response [Figure 1]. He improved symptomatically and his paraparesis also recovered completely. After this, the patient received 2 more cycles of high-dose cytarabine consolidation. At present, he is on regular follow-up and doing well.

CASE 2

An 11-year-old male, without any known comorbidities, initially developed right parotid region swelling without any constitutional symptoms and got evaluated in the

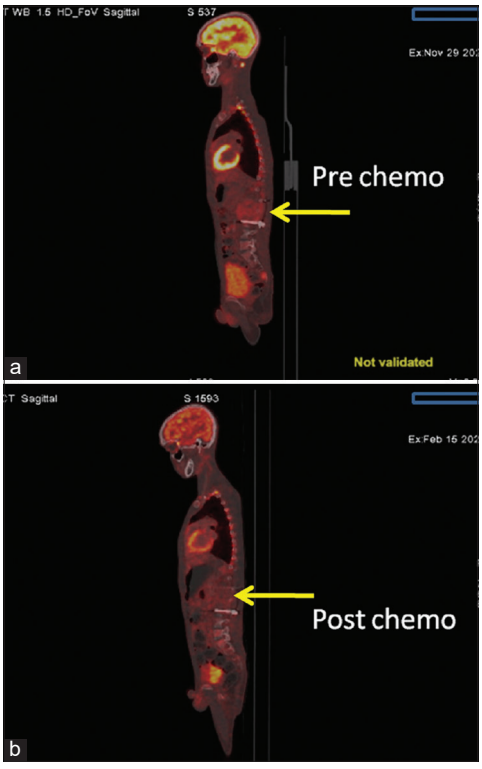

Figure 1: A 16-year-old male presented with paraparesis, (a) Positron emission tomography, computed tomography (PET-CT) image, shows increased fluorodeoxyglucose avidity in the paraspinal region (arrow on the right) at baseline. (b) PET-CT image shows complete metabolic response in the same region, post two cycles of chemotherapy (shown by arrow on the right).

Department of ENT and Head Neck surgery. MRI Neck and face revealed an 8 × 6 × 5.6 cm mass in the right parotid region, right preauricular region, infratemporal fossa region, masticator, and pterygoid spaces with infiltration of the right masseter muscle, along with bony erosion involving ramus of right mandible and effacement of right parapharyngeal fat space and enlarged rt level II cervical lymph node (LN) (2.3 × 1.6 cm). Fine-needle aspiration cytology (FNAC) from the parotid region mass was suspicious of non-Hodgkin lymphoma (NHL) or lymphoepithelial sialadenitis. PET-CT showed FDG avid large lobulated soft-tissue density mass 7.8 × 8.4 × 9.2 cm involving both superficial and deep lobes of the right parotid gland. Biopsy showed infiltration by abnormal cells which on IHC showed positivity for CD34+, CD117+, and MPO+ and was negative for CD5, CD10, CD20, and CD3 s/o MS. Bone marrow aspirate showed 8–9% blasts in a cellular marrow with trilineage hematopoiesis. Reflex PCR panel revealed AML1-ETO mutation, so consistent with a diagnosis of AML with MS. He was treated with 3 + 7 induction and developed culture-negative febrile neutropenia which was managed with iv antibiotics and supportive measures. Post 3 + 7 induction bone marrow was not in remission and PET-CT showed significant metabolic resolution with a mild reduction in size of the right parotid region mass. Since bone marrow and PET were not in complete remission, so second induction with high-dose cytarabine and daunomycin (HAD protocol) was given. Triple intrathecal given was given and CSF cytology was negative for malignant cells. Post HAD re-induction bone marrow was cellular with adequate trilineage hematopoiesis with no excess blast. PET-CT showed non-FDG avid soft-tissue density mass 4.2 × 4.6 × 4.2 cm right parotid gland suggestive of complete metabolic response [Figure 2]. Clinical exome testing for inherited predisposition hematological syndromes was also done and found normal. He was treated further with 3 cycles of high-dose cytarabine consolidation, and currently, he is asymptomatic and disease free.

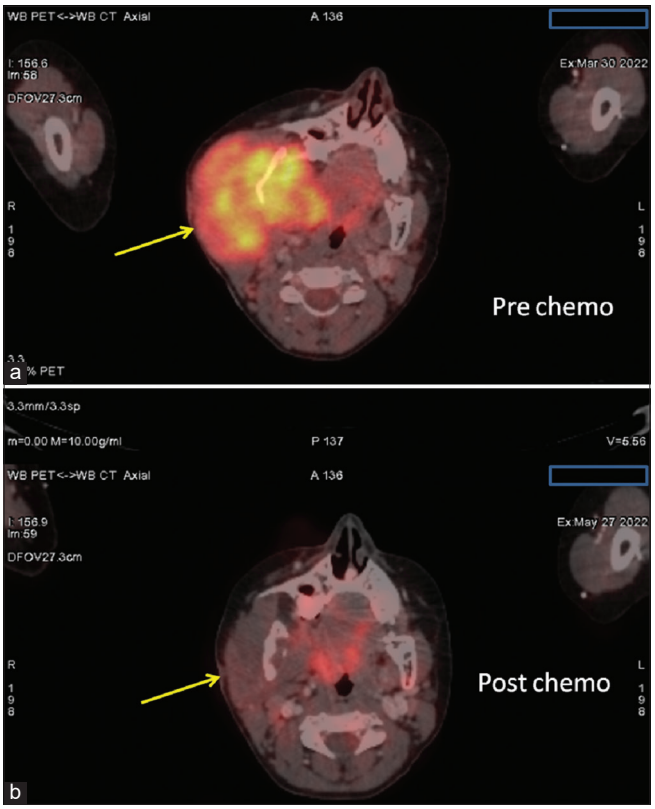

Figure 2: A 11-year-old male presented with the right-sided parotid swelling, (a) positron emission tomography-computed tomography (PET-CT) image shows increased fluorodeoxyglucose avidity in the right parotid region infiltrating masseter muscle (arrow on the left) at baseline. (b) PET-CT image shows the complete metabolic response in the same region, post two cycles of chemotherapy (shown by arrow on the left).

CASE 3

A 3-year-old kid initially presented with right peri-orbital swelling with proptosis of the right eye and bilateral earache. She later on developed intermittent fever and severe bone pains at multiple sites, but no bleeding manifestations. On examination, there wasn't any petechiae or purpura, gum hypertrophy, palpable lymphadenopathy or hepatosplenomegaly. MRI Brain + Orbit showed ill-defined soft-tissue opacification of the right maxillary sinus with extension into right orbit and posteriorly lesion involved right pterygoid fossa with collection along right medial pterygoid muscle with no obvious intra-cranial extension. Baseline blood investigations showed bicytopenia (Total leukocyte count – 8100/mm^3, Hemoglobin – 8.0, and Platelet – 30000/mm^3). Peripheral smear showed normocytic normochromic anemia with marked shift to left in myeloid series and thrombocytopenia. Over time she developed left temporal region swelling also and FNAC from left temporal region swelling was suggestive of MS/chloroma. Bone marrow aspirate morphology showed 40% MPO positive blasts and biopsy showed an increase in immature precursors – suggestive of acute leukemia. On flow cytometry, blasts showed CD45 dim expression, bright CD34, moderate CD13, CD33, HLA-DR, CD38, CD56, dim CD117 and negative CD64, CD11c, CD36, CD71, Cy CD41a, and Cy CD61 consistent with AML. Cytogenetics/molecular (reflex PCR panel) – Not done in view of financial constraints. She was treated with 3 + 7 induction and post-induction marrow was not in remission, so the patient was given second induction (3 + 7) chemotherapy and triple intrathecal was also given as per protocol. She developed febrile neutropenia, perianal infection, oral mucositis, and non-aspirable pelvic abscess (peri-vesical region) so treated with empirical antibiotics and supportive measures. Bone marrow aspiration post second induction showed hypercellular marrow with severe

suppression of erythropoiesis with the presence of 4% blasts. The patient was planned for three more cycles of HiDAC (18 g/m^2) as consolidation, but, unfortunately, we lost the patient during the second consolidation chemotherapy due to severe sepsis and pneumonia.

DISCUSSION

MS can be subclassified into (a) MS with concurrent AML; (b) isolated MS; (c) blastic transformation of Myelodysplastic syndrome (MDS), Myeloproliferative neoplasm (MPN) or MDS/MPN; and (d) extramedullary relapse of AML.[7]

If we take all the subtypes of MS together, it occurs more frequently in the pediatric population compared to adults. Its incidence in children is up to 30% as compared to 2–5% in adult patients.[8] In adults, nearly one-third are diagnosed with "MS and concurrent myeloid disease" and one-third patients have a preceding history of a myeloid neoplasm.[9] Although most of these cases subsequently involve bone marrow within a year.[10] MS itself is diagnostic of AML, regardless of the bone marrow or blood blast count. It can also develop at relapse with or without marrow involvement. As per reports, after allogeneic hematopoietic cell transplantation, incidence of MS ranges between 0.2% and 1.3%. Cytogenetic and molecular testing should be attempted in similar fashion as in a case of AML.

Bone, periosteum, soft tissues, LNs, and skin are the most common sites of MS, but they can occur in the gastrointestinal tract, breast, genital tract, salivary glands, mediastinum, pleura, and peritoneum as well. Skin and orbit are the most frequently involved sites in children.[11]

Parotid gland involvement in adults at presentation has been reported in various hematolymphoid malignancies, but very few cases of parotid involvement as presenting manifestation in pediatric AML have been reported.[12] In a study from Denmark, only 0.4% of patients had CNS involvement.[13] Isolated MS can have various symptoms at presentation, based on the tumor size and primary tissue/organ, leading to misdiagnosis rates up to 47%. Movassaghian *et al*., in their analysis of 345 cases of isolated MS, found only four cases of isolated MS involving vertebral column (1.17%, 4/339) and two cases involving the spinal cord (0.59%, 2/339).[4] When MS involves the bone or nerve system, these patients have poorer overall survival compared to others.

In our cases also, one case of isolated MS was in the vertebral column which is reported in occasional cases only. Another one presented as unilateral parotid enlargement as the initial manifestation which is also not seen so frequently. The third one was a case of commonly seen orbital presentation of MS in the case of AML.

In any patient of AML presenting with a soft-tissue mass, MS should always be included in the differential diagnosis. However, in absence of leukemia, its diagnosis can be challenging. It can frequently be misdiagnosed, most commonly asNHL, in up to 46% of patients. The most frequent chromosomal abnormality found with extramedullary involvement of AML is t (8;21) translocation, either at presentation or at relapse.[14] The next commonly reported cytogenetic abnormality with higher rates of extramedullary involvement is inv (16). Both of these chromosomal abnormalities are found to have relatively favorable prognosis in AML, but whether these chromosomal abnormalities have any prognostic implications in patients with MS is not yet clear.[15] The imaging modality most commonly used for diagnosis and response evaluation is PET-CT. However, in patients with CNS involvement by MS, magnetic resonance is the preferred modality for imaging. Five-year survival rates for patients with MS range between 20% and 30%, which appear similar to patients with AML.[16]

Untreated or inadequately treated cases of isolated MS will most likely progress to AML within a year, so they should be treated as early as diagnosed, although the optimal treatment of isolated MS is not clear. Surgical excision, systemic chemotherapy, radiation therapy (RT), and hematopoietic stem cell transplantation (HSCT) are the available treatment modalities, which can be used alone or in combination for the treatment of patients with MS. However, there are no consensus guidelines for the treatment of MS due to its rarity. Preferred chemotherapy regimens include standard induction chemotherapy with daunorubicin and cytarabine, followed by high-dose Ara-C (Cytarabine). Radiotherapy can be considered in partial responders for consolidation. In MS associated with systemic disease, a standard induction chemotherapy regimen followed by consolidation with chemotherapy or allogenic HSCT is recommended, as per risk stratification, patient fitness, and response to induction chemotherapy. In an emergency situation, where there is compression of any vital structure and debulking is required for rapid symptom relief, RT or surgery may be used, before standard chemotherapy based treatment. Although, the superiority of this combined approach over standard chemotherapy alone is not proven by the currently available evidence.

Similarly, we also treated our isolated MS patient with systemic therapy (cytarabine/daunomycin followed by high-dose cytarabine) and our patient improved after the first cycle of therapy, and PET/CT post two cycles showed a complete metabolic response and he completed planned chemotherapy well and is doing well post 6 months of treatment completion. The other two cases of AML with MS were also treated similarly.

CONCLUSION

MS is a malignant neoplasm of myeloid lineage which can involve any body site; however, involvement of CNS and LNs

is relatively uncommon and prone to misdiagnosis if there is monocytic morphology. The most important thing for their diagnosis is high clinical suspicion, followed by thorough clinical history, examination, laboratory investigations, proper imaging, and biopsy/immunohistochemistry from involved sites. Further bone marrow examination and cytogenetic and molecular testing should be done in a diagnosed case of MS. Even in isolated MS, the patient should be treated with standard AML induction followed by consolidation chemotherapy. AlloSCT may be considered in patients fit enough to undergo transplants. With further knowledge of molecular pathways and the underlying pathogenesis of the disease, we may have novel treatment options in the future, which can change the course and outcome of this entity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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