Myeloid sarcoma (MS) is an extramedullary solid tumor composed of leukemic myeloid cells. MS is an uncommon tumor complicating acute myeloid leukemia (AML), or less commonly myelodysplastic syndrome (MDS) and myeloproliferative disorders. Rarely, MS may precede the systemic onset of AML, which usually follows within months. We report a 36-year-old lady who presented with a cervical-uterine mass, which proved to be MS. Initially, she had no systemic AML and was treated with hysterectomy and systemic chemotherapy. She developed bilateral-flank pain and renal impairment after 9 months. Imaging revealed a soft-tissue mass in the para-aortic and perisacral region with bilateral hydronephrosis. Biopsy from the mass confirmed recurrence of MS. Bone marrow (BM) biopsy revealed 20% blasts consistent with AML. She was treated with aggressive chemotherapy and local radiotherapy. Despite these measures, she died of progressive disease. MS should be considered and treated as systemic AML, rather than an isolated mass; and we discuss management issues in such patients.

Key Words: Acute myeloid leukemia. Myeloid sarcoma. Uterus.

INTRODUCTION

Myeloid sarcoma (MS) is an extramedullary manifestation of acute myeloid leukemia (AML), and less commonly myelodysplastic syndrome (MDS) or myeloproliferative disorders (MPD). MS is a solid collection of leukemic cells outside of bone marrow (BM). MS may develop concomitantly, follow or rarely precede the onset of systemic BM leukemia. There are limited case reports of isolated MS, in the setting of no history of leukemia and a negative BM biopsy. In the past, many of these patients were misdiagnosed as lymphoma, typically non-Hodgkin’s lymphoma. In almost all reported cases of isolated MS, acute leukemia developed shortly afterwards (median time 7 months); therefore, isolated MS should be considered an initial manifestation of AML, rather than a localized process, and should be treated as such.

We report here a female patient who presented with a uterine MS and discuss the management of such cases.

CASE REPORT

A 36-year-old lady, not known to have any medical illness in the past, presented to our institution complaining of vaginal bleeding for 6 months. The bleeding was irregular, of small to moderate amount, associated with clots and post-coital bleeding. She denied any bleeding from other sites and the rest of the systemic review was unremarkable. Her menstruation was regular and of average amount, previously. She gave history of an injectable contraception drug one year prior to her presentation. Physical examination revealed a 4 x 5 cm mass in the vagina, protruding from the cervix, which was fragile and bled easily. The rest of the examination was normal.

Blood counts were normal with a white cell count of 9.5x10^9/l, Hemoglobin (Hb) 12.4 g/dl, platelet 239x10^9/l and normal white cell differential; while liver and kidney function, lactic dehydrogenase (LDH) and electrolytes were also normal. An MRI of the pelvis showed an infiltrative mass involving the cervix and distal part of the uterine body (Figure 1). As the tumor was highly suspicious of carcinoma and because of the bleeding, she underwent total hysterectomy and the histopathology sections from the sample revealed infiltrating neoplastic lesion composed of sheets of undifferentiated mononuclear cells with eosinophils and precursor cells. Tumour cells were positive for myeloperoxidase (MPO), CD45, CD34, and focally positive for CD68, CD15 and CD117, and negative for CD99, CD20, CD3, Alk-1, CK, EMA and chromogranin, consistent with a diagnosis of MS (Figure 2). At this stage, patient's peripheral blood and bone marrow biopsy did not show any evidence of AML. Cytogenetic analysis of the bone marrow was normal.

The patient was started on an attenuated form of 7+3 AML chemotherapy regimen (5+2; cytarabine+ daunorubicin) on her request. She received a total of 3
cycles which she tolerated well and was kept under observation at regular intervals. Radiotherapy to the pelvis was considered, but not given as it was considered unnecessary after removal of the whole tumor along with the uterus.

She presented again 9 months later with bilateral flank pain radiating to the groin. Her physical examination was normal and laboratory results showed raised urea and creatinine with normal complete blood count (CBC), liver function and electrolytes. A CT scan of abdomen and pelvis revealed an extensive soft tissue density mass in the para-aortic region, with bilateral hydronephrosis, more on the right side (Figure 3-A). An MRI of pelvis showed a large upper peri-sacral enhancing mass, encasing the right distal ureter (Figure 3-B).

In view of the obstructive nephropathy, she was managed with bilateral nephrostomies and her renal function improved quickly. Biopsy from the pelvic mass showed similar picture as the earlier biopsy and briefly, tumor cells were positive for MPO, CD45 and CD34, focally positive for CD117, and negative for CK and CD68, consistent with a local recurrence of MS.

BM biopsy revealed 20% blast cells consistent with the diagnosis of AML and cytogenetic analysis of the bone marrow showed trisomy 8.

The patient was started on high dose cytarabine based chemotherapy regimen with shrinkage of the pelvic lesion. She received a further course of the same regimen. A search for a donor with a view to allogeneic hematopoietic stem-cell-transplant (HSCT) was initiated but no related or unrelated matched donor could be identified. Her disease did not show a significant response as she received palliative radiotherapy (RT) to the pelvis. She died of progressive disease after a short period.

**DISCUSSION**

MS is also known as granulocytic sarcoma (GS) or chloroma. It is associated with AML in 2.5 - 9.1% of patients and may occur concomitantly, follow or rarely precede the onset of systemic BM origin of AML.1,2 MS can also develop at relapse of AML with or without marrow involvement. Isolated MS, without any evidence of AML, MDS or MPD, has been described only in few case reports.2

The exact mechanisms for the development of MS are not fully understood. The homing to specific tissues is controlled by a complex expression of different chemokine receptors and adhesion molecules. CD56 (Blast neural cell adhesion molecule) has long been implicated in the pathogenesis of extramedullary disease.3 Neural cell adhesion molecule is also highly expressed in breast, testicular, ovarian, and gut tissues, which can account for extramedullary homing of leukemia cells to these tissues. In further support of this, neural cell adhesion molecule blast expression has been associated with a high incidence of MS and is common in patients with chromosomal abnormality t(8;21),3,4 although in one of the largest series of MS, monosomy 7 (10.8%) and trisomy 8 (10.4%) were much more...
common than t(8;21), which was found in only 2.2% cases.\(^5\)

There are conflicting reports about the prognostic significance of MS; and the presence of MS has been associated with poor prognosis and shorter survival in most reports.\(^5\) In a recent population-based analysis of MS using the SEER database, 345 patients aged 15 or older, diagnosed with isolated MS between 1973 and 2010, 3-year survival of MS patients was better compared to non-MS AML, although survival varied according to the site of MS.\(^6\)

MS can appear at different sites in the body including bone, soft tissues, lymph nodes, breast, and skin; but occurrence in the female genital tract (FGT) is rare.\(^7,8\) Vaginal bleeding is the most common presenting feature of genital tract MS; but post-coital bleeding, abdominal pain or a combination of these may occur.\(^7,8\)

The diagnosis of MS can be challenging, particularly when the neoplastic cells are immature or tumor mass presents without evidence of systemic AML. MS can be mistaken for a variety of malignant tumors including lymphoma, undifferentiated carcinoma, sarcoma and melanoma. In the FGT, MS could be misdiagnosed for non-Hodgkin’s lymphoma (NHL), undifferentiated carcinoma, and epitheloid sarcoma.\(^9\) The identification of MS needs a tissue biopsy with immunohistochemical and flow cytometric analysis along with fluorescence-in-situ-hybridization and molecular analysis.\(^8,9\)

According to the WHO 2008 classification, cytochemical stains to diagnose MS should include chloroacetate esterase (CE), MPO, and non-specific esterase. The most common positive markers in paraffin sections include CD68/ KP1, MPO, CD 117, CD 99, CD 68/PG-M1, CD34, TdT, CD56, and CD61. Common markers in flow cytometric analysis in tumors with myeloid differentiation are CD13, CD33, CD117 and MPO; and CD14, CD163 and CD11c in tumors with monoblastic differentiation. B- and T-lineage markers like CD20, CD45RO, CD79a and CD3 should be added to the panel in order to exclude B- and T-cell lymphomas.\(^5,9\)

There are limitations in the interpretation of immunohistochemical and immunophenotypic markers in confirming the diagnosis of MS. The CE stain is helpful for the diagnosis of MS with some granulocytic maturation, but purely monocyctic and poorly differentiated neoplasms can be negative for CE and MPO. T-cell markers CD3, CD43 and CD45 are frequently expressed in MS cells and B-cell markers CD79a, CD20 and CD15 may be expressed in MS and not very useful to differentiate from NHL and Hodgkin’s lymphoma. CD43 is a non-specific marker and its expression should be interpreted with caution.

Many chromosomal and molecular abnormalities associated with MS have been described and the most common of these include t(8;21),\(^3,4\) monosomy-7, trisomy-8, and NPM1 mutation.\(^5,9\) Trisomy 8 is frequently found in AML and MS but its prognostic value in MS is not clear.

There are only few reports of NPM1 and FLT3 mutations in MS patients.\(^9\) In a series of 181 MS patients, 15% had NPM1 mutations and NPM1-positive MS cases showed similar features to de novo NPM1-positive AML patients. FLT3 mutations are detected in 20 - 30% of adult AML, and MS cases concurrently presenting with AML. The significance of NPM1 and FLT3 mutations on the prognosis of MS patients currently remains unknown.\(^9\)

In the majority of isolated MS, systemic AML will be evident within few months.\(^9\) In our case, the AML manifested 9 months after the diagnosis of MS; hence, MS should be looked as part of a broader systemic disease, rather than isolated process and should be treated aggressively.

Optimal initial therapy for isolated MS remains to be defined but most authors agree on use of intensive chemotherapy, similar to induction chemotherapy for AML.\(^5,9\)

Radiotherapy appears to be a useful adjunct to systemic therapy,\(^9\) and may prevent local relapse but unlikely to change the course of systemic disease. HSCT, soon after achieving remission, appears to be the optimal strategy as most of the long-term survivors in a recent series were those who received allogeneic-HSCT.\(^5\) In the largest reported series of 99 MS patients who received allogeneic-HSCT, the authors concluded that allogeneic-HSCT is an effective treatment for patients with MS. While prospective evaluations are needed, allogeneic-HSCT could be considered the optimal therapy for both isolated and leukemic MS.\(^9\)

REFERENCES


