Myeloid sarcoma: current approach and therapeutic options

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***Abstract*:** Myeloid sarcoma is a rare disease that can present as an isolated extramedullary leukemic tumor, concurrently with or at relapse of acute myeloid leukemia. Owing to the rarity of this disorder, most of the literature comprises small retrospective studies and case reports. The aim of this review is to summarize the current published data regarding the clinical presentation, morphological, cytogenetic and molecular features, prognosis and treatment of myeloid sarcoma.

***Keywords*:** acute myeloid leukemia, myeloid sarcoma, prognosis, therapy

Introduction

Myeloid sarcoma (MS), also known as chloroma (owing to its green color attributed to the enzyme myeloperoxidase), is a pathologic diagnosis for an extramedullary proliferation of blasts of one or more of the myeloid lineages that disrupt the normal architecture of the tissue in which it is found. It has also been addressed as granulocytic sarcoma, myeloblastoma and extramedullary myeloid cell tumor [Roth *et al.* 1995]. MS is included as one of the major subgroups of myeloid neoplasms and acute leukemia in the WHO classification and is most often found either concurrently or following a previously recognized AML. It may also occur as an isolated leukemic tumor or precede the appearance of blood or bone marrow (BM) disease [Vardiman *et al.* 2009]. Less often, MS may occur in association with a myeloproliferative neoplasm (MPN) or myelodysplastic disorder (MDS). In published series, MS is often included with extramedullary disease (EMD); however, these two phenomena may not share the same outcome and may need to be treated differently. In this review we focus mainly on isolated MS and MS occurring in the setting of AML with the aim of updating the current knowledge regarding the clinical approach to MS diagnosis and treatment. Owing to the rarity of this disorder, large series are seldom reported [Pileri *et al.* 2007], and the literature is mainly composed of case reports. The data reviewed here were extracted from case series reports including only MS cases, where possible, or from series on EMD that included MS cases where isolated data was not available, in which case it will be stated in the text.

Pathogenesis of extramedullary disease

The presence of EMD including MS suggests there might be an aberrant homing signal for the leukemic blasts precluding the more common BM localization. This may represent a subclone of an original AML clone in cases of concurrent presentation or in the relapse situation. Faaij and colleagues compared the expression of chemokine receptors on AML blasts from the blood, BM and skin in pediatric AML patients with skin involvement to the expression on blasts from patients without EMD [Faaij *et al.* 2010]. AML blasts isolated from the skin displayed a unique set of chemokine receptors including CCR5, CXCR4, CXCR7 and CX3CR1 compared with BM and blood blasts. The authors suggested that different chemokine/chemokine receptor interactions underlie the homing and retention of AML blasts in the skin. Stefanidakis and colleagues suggested that EMD represents an ability of leukemic blasts to invade the surrounding tissues and showed that specific interaction between the matrix metalloproteinase (MMP)-9 and the leukocyte surface beta (2) integrin is required for the migration of AML-derived cells [Stefanidakis *et al.* 2009]. Similarly, Wang and colleagues found a higher expression of MMP-2, membrane type 1 metalloproteinase and tissue inhibitor of metalloproteinase-2 in the highly invasive AML cell line SHI-1, coupled with a higher capacity for an *in vitro*

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invasion compared with other, noninvasive leukemic cell lines, supporting the role for MMPs in extramedullary blast penetration [Wang *et al.* 2010].

MS prevalence and clinical presentation

MS is reported in 2–8% of patients with AML either as a single or as a multifocal tumor. It can predate AML by months or years in approximately a quarter of cases, appear concomitantly with AML in 15–35% of cases, or occur after the diagnosis of AML in up to 50% of cases. It can also appear as an initial manifestation of relapse in a previously treated AML patient in remission [Tsimberidou *et al.* 2008; Pileri *et al.* 2007; Jaffe *et al.* 2001; Roth *et al.* 1995; Neiman *et al.* 1981]. In recent years, there is an increase in reports of MS presentation after allogeneic stem cell transplantation (allo-SCT) manifesting as an isolated disease or accompanying BM relapse [Cunningham, 2006]. It has been suggested that extramedullary relapse after allo-SCT may represent a reduced graft-*versus*-leukemia effect at extramedullary sites [Singhal *et al.* 1999]. Nevertheless, post-allo-SCT MS is not a common occurrence; a European bone marrow transplantation (EBMT) retrospective analysis reported MS in less than 1% of transplanted patients occurring 4–56 months after SCT [Szomor *et al.* 1997; Bekassy *et al.* 1996].

The age of patients at MS presentation is highly variable, with cases being reported in patients 1–81 years old. Biopsy-proven EMD is most commonly reported in the skin, bone and lymph nodes. It can however involve many other body sites with reported cases in the central nervous system (CNS), oral and nasal mucosa, breast, genitourinary tract, chest wall, pleura, retroperitoneum, gastrointestinal tract and testis [Lan *et al.* 2009; Tsimberidou *et al.* 2008; Pileri *et al.* 2007; Cunningham, 2006; Yamauchi and Yasuda, 2002; Suh and Shin, 2000; Roth *et al.* 1995; Neiman *et al.* 1981]. In children with newly diagnosed AML, extramedullary involvement was most common in the skin (in 54%) with orbital involvement being the second most common site [Dusenbery *et al.* 2003]. MS size at diagnosis is highly variable ranging from 2 to 20 cm. Depending on size and localization, the most common signs and symptoms associated with the myeloid tumor are compression signs accompanied by severe pain and abnormal bleeding. Computerized tomography (CT) and magnetic resonance imaging (MRI) are often used for tumor localization and are helpful in distinguishing MS from other entities, i.e. hemorrhage or abscess [Pui *et al.* 1994].[18] FDG-PET CT imaging was recently shown by Stölzel and colleagues to be useful in studying and following extramedullary AML [Stölzel *et al.* 2010].

Morphological diagnosis

MS is often initially misdiagnosed, the most common alternative diagnoses being lymphoma, undifferentiated cancer, malignant melanoma, extramedullary hematopoiesis and inflammation [Pileri *et al.* 2007; Paydas *et al.* 2006; Suh and Shin, 2000]. The characteristic microscopic growth pattern of myeloid cells is either a diffuse or an Indian file pattern and the KI-67/MIBI is usually high, ranging from 50% to 95%. MS is subclassified according to the most abundant cell type into granulocytic, monoblastic or myelomonocytic [Lan *et al.* 2009; Pileri *et al.* 2007] and according to cell maturation into immature, mature and blastic types. MS blastic type is composed primarily of myeloblasts with little evidence of maturation. The immature type is an intermediate grade and consists of myeloblasts, promyelocytes and eosinophilic myelocytes. The differentiated or mature type is composed of promyelocytes and more mature cells with abundance of eosinophils [Lan *et al.* 2009; Pileri *et al.* 2007].

Immunohistochemistry and immunophenotying are crucial for the accurate diagnosis of MS. According to the WHO 2008 classification, cytochemical stains should include chloroacetate esterase, myeloperoxidase and nonspecific esterase. Immunophenotyping can be done either in paraffin section or via fluorescence-activated cell sorting (FACS) analysis on cell suspension derived from the tumor. The most common positive markers in paraffin sections include CD68/KP1, MPO, CD 117, CD 99, CD 68/PG-M1, lysozyme, CD34, TdT, CD56, CD61, CD30, glycophorin and CD4. CD13, CD33, CD117 and MPO are the most common markers in flow cytometric analysis in tumors with myeloid differentiation and CD14, CD163 and CD11c in tumors with monoblastic differentiation. B- and T-lineage markers, in particular CD20, CD 45RO, CD79a and CD3, should be added to the panel in order to exclude other differential diagnoses. Aberrant cytoplasmic NPM1 expression can be detected in paraffin-embedded MS samples and can be diagnostically and potentially prognostically helpful [Lan *et al.* 2009; Swerdlow

et al. 2008; Falini *et al.* 2007; Pileri *et al.* 2007; Suh and Shin, 2000; Menasce *et al.* 1999].

Cytogenetic and molecular characteristics

Cytogenetic analysis in patients with MS is usually performed on BM or peripheral blood blasts with reported cytogenetic abnormalities found in approximately 50% of cases [Swerdlow *et al.* 2008; Pileri *et al.* 2007; Jaffe *et al.* 2001]. Pileri and colleagues reported the results of fluorescent *in situ* hybridization (FISH) analysis done on cells derived from the sarcoma tissues in comparison with conventional BM cytogenetic analysis [Pileri *et al.* 2007]. A full concordance between the FISH and conventional cytogenetic results was found in only 71% of patients with available results. This suggests that conventional cytogenetic studies where BM or peripheral blood blasts are present and FISH analysis on sarcoma cells are complementary and should be both pursued in the clinical setting. In isolated MS, FISH or conventional cytogenetic analysis of freshly collected cell samples could be performed; alternatively, in the absence of a fresh sample, NPM1 staining in paraffin-embedded tissue could have prognostic implications in the setting of a clinical trial. Deeb and colleagues studied seven cases of MS with array comparative genomic hybridization and found that all cases exhibited genomic changes, the most common being chromosome 8 abnormalities, suggesting that genomic changes in MS are probably more common than conventionally characterized [Deeb *et al.* 2005]. The role of whole-genome array studies in this setting is as yet to be determined.

Extramedullary involvement in AML is often reported in association with core binding factor (CBF) leukemias. However, the reported rates of specific cytogenetic abnormalities are quite variable. The prevalence of MS in patients with translocation t(8;21) in different studies ranges between 9% and 35% [Byrd *et al.* 1997; Tallman *et al.* 1993; Abe *et al.* 1986; Swirsky *et al.* 1984]. On the other hand, the reported rate of t(8;21) in MS patients ranges from 3.3% (1/30 patients) [Pileri *et al.* 2007] to 43% (17/39 patients) [Dusenbery *et al.* 2003]. Interestingly, Dusenbery and colleagues reported that skin EMD in this subgroup of patients is less common than non-skin EMD [Dusenbery *et al.* 2003]. The true prevalence of inversion of chromosome 16 (Inv 16) in patients with MS is not known and only rare cases were reported in adult case series. In children, the Children's cancer group reported on chromosome 16 abnormalities occurring in 13% of MS patients with available cytogenetics [Dusenbery *et al.* 2003]. A unique feature that seems to be associated with Inv 16 cases in some reports is an intestinal presentation with a microscopic appearance of plasmacytoid monocyte clusters [Tsimberidou *et al.* 2008; Pileri *et al.* 2007].

In a retrospective analysis of 263 patients with acute promyelocytic leukemia (APL), the prevalence of EMD including MS was 3%, with CNS being the most commonly involved site [Vega-Ruiz *et al.* 2009]. EMD is usually associated with relapse of APL with only anecdotal cases of MS presentation at APL diagnosis [Worch *et al.* 2008]. The occurrence of EMD has been attributed to the use of all-trans retinoic acid (ATRA) by some authors, but others have shown a similar incidence of EMD in the standard chemotherapy only era [Specchia *et al.* 2001]. Reports on other chromosomal aberrations including MLL rearrangements, monosomy 7 or 5 and trisomy 8 are scarce, and variable rates are reported [Tsimberidou *et al.* 2008; Pileri *et al.* 2007; Dusenbery *et al.* 2003].

Data on molecular abnormalities have only recently been reported. Nucleophosmin (NPM) 1 mutations with the consequent aberrant cytoplasmic expression of NPM represent the most common genetic abnormality in AML. Falini and colleagues identified NPM1 mutations in 15% of 181 MS patients [Falini *et al.* 2007]. NPM1-positive MS cases showed similar features to *de novo* NPM1-positive AML patients including a frequent association with M4 and M5 FAB categories, a lack of CD34 expression and an association with a normal karyotype. FLT3 mutations are detected in 20–30% of adult AML cases with an increased incidence in patients with normal cytogenetics. Ansari-Lari and colleagues reported that three out of nine patients presenting with MS concurrently with AML had a FLT3-ITD mutation, with no FLT3 kinase domain mutations detected [Ansari-Lari *et al.* 2004]. The significance of NPM1 and FLT3 mutation on the prognosis of MS patients is currently unknown.

Prognosis of MS patients

Owing to the rarity of MS there are no large studies analyzing prognostic factors in these patients. Furthermore, MS cases are often grouped with EMD cases and even when reported as an

isolated group, few reports compare the prognosis of isolated MS with patients with either MS with concomitant AML or AML presenting without MS, making the contributing effect of MS on prognosis difficult to assess. Overall, however, it appears that there is a difference in prognosis between patients presenting with isolated MS compared with MS patients with either concomitant AML or at AML relapse. The presence of MS at diagnosis in a leukemic patient was traditionally considered to represent a marker for poor clinical outcome and shorter survival [Lan *et al.* 2009]. This is however not well established. In fact, in a retrospective analysis of 1832 children, including 199 with EMD, treated within the Children's Cancer Group's chemotherapy trials, the presence of non-skin EMD was actually associated with a better outcome compared with AML patients without EMD [Dusenbery *et al.* 2003]. In subgroup analysis, children with an isolated EMD had a significantly better event-free survival (EFS) compared with children with EMD concurrent with AML and children with AML and no EMD.

Tsimberidou and colleagues compared the outcome of 23 patients with isolated MS with that of 1720 consecutive AML patients diagnosed in the same time period [Tsimberidou *et al.* 2008]. EFS was longer in the 16 patients with isolated MS treated with cytarabine containing regimens ($p = 0.08$). However, in a multivariate analysis the diagnosis of MS *versus* AML was not an independent significant prognostic factor ($p = 0.11$). In the subgroup of patients presenting with MS concurrently with AML, we have recently shown comparable outcomes in AML patients either with or without MS [Avni *et al.* 2011]. On the other hand, Byrd and colleagues reported a lower complete remission (CR) rate in patients with t(8;21) presenting with MS (50%) compared with those without MS (92%), accompanied with a significantly shorter overall survival (OS) rate ($p = 0.002$) [Byrd *et al.* 1997]. Importantly, only one of the patients with MS who attained CR received high-dose cytarabine (HDAC), while HDAC seems to be an important component in the treatment and survival of patients with t(8;21). The poor prognosis observed in this group of patients may be due to inadequate treatment. It thus appears that the differences in prognosis between AML patients and MS patients presenting with and without AML reported by different groups, can be at least partially attributed to differences in treatment regimens and patients' characteristics [Bloomfield *et al.* 98].

Several small retrospective studies addressed specifically the question of prognostic factors in patients with MS. Pileri and colleagues analyzed 92 patients presenting with either isolated MS, MS with concurrent myeloid neoplasm (AML, MPN or MDS) or MS developing after a hematological disease [Pileri *et al.* 2007]. Disease course and response to therapy were not influenced by patients' age, gender, anatomic location, clinical presentation (isolated MS, MS concurrent or following AML), previous clinical history, morphological classification, immunophenotype and cytogenetic findings. In the study by Lan and colleagues [Lan *et al.* 2009] analyzing 24 patients with MS (with AML, CML or MDS in nine, six and two patients, respectively, and isolated in seven), patients with MS accompanying CML or MDS had a worse outcome compared with MS with AML. Treatment with systemic chemotherapy was associated with favorable survival outcomes.

Currently available treatment options

Since randomized prospective trials are lacking, there is no consensus on the treatment of MS. The current recommended treatment regimen in patients presenting with isolated MS or MS presenting concomitantly with AML is conventional AML-type chemotherapeutic protocols. A comprehensive overview of AML treatment is beyond the scope of this review and can be viewed in recently published review papers [Burnett *et al.* 2011; Ofran and Rowe, 2011]. This recommendation is based on the observation of a higher rate of progression to AML in isolated MS patients receiving localized treatment (88–100%) compared with patients given systemic chemotherapy (42%) [Lan *et al.* 2009; Tsimberidou *et al.* 2008; Yamauchi and Yasuda, 2002]. In isolated MS patients treated with AML-based induction regimens, CR rates are at least comparable with AML without MS with similar prognostic features, and prolonged disease-free survival (DFS), from 3.5 to 16 years, has been reported [Tsimberidou *et al.* 2008; Meis *et al.* 1986]. Imrie and colleagues analyzed the survival of 90 patients with isolated MS collected from the published literature and reported that OS was significantly longer in patients receiving systemic chemotherapy at diagnosis [Imrie *et al.* 1995]. Cunningham reported on a collection of 27 previously published patients

with isolated breast MS showing that 11 out of the 12 patients (92%) treated only with local therapy relapsed compared to 5 out of 12 (42%) given systemic therapy [Cunningham, 2006].

There is hardly any data addressing the type of chemotherapeutic regimen that should be used to treat MS patients. Some indirect evidence suggests that cytarabine may be an important agent in this regard. Yamauchi and Yasuda reported prolonged DFS in patients treated with cytarabine-containing regimens compared with patients who were initially misdiagnosed and treated with agents used to treat lymphoma, sarcoma or multiple myeloma [Yamauchi and Yasuda, 2002]. It is not clear whether postinduction therapy has any role in these patients.

Radiotherapy

The role of radiotherapy in addition to systemic chemotherapy is not established, although it is often given. Tsimberidou and colleagues suggested that radiotherapy may prolong failure-free survival but not OS in patients presenting with isolated MS [Tsimberidou *et al.* 2003]. In a group of 19 MS patients (17 patients with concurrent AML at presentation) we found that the median time to death was the same in patients receiving radiotherapy in addition to chemotherapy and those not receiving radiotherapy ($p = 0.79$) [Avni *et al.* 2011]. Similarly, Lan and colleagues found no effect on survival in MS patients (isolated or following the diagnosis of AML) treated with radiotherapy in addition to chemotherapy compared to chemotherapy alone ($p = 0.56$) [Lan *et al.* 2009]. The children's cancer group also reported no difference in EFS between children with EMD treated with or without radiation therapy [Dusenbery *et al.* 2003].

Hematopoietic stem cell transplantation

The role of hematopoietic stem cell transplantation (HSCT) in patients with MS was not studied prospectively but the outcome of patients undergoing HSCT was shown in several retrospective reports. Pileri and colleagues reported the outcome of 67 patients with MS, retrieved from the Italian pathologic anatomy services files [Pileri *et al.* 2007]. At a median follow up of 150 months, only seven patients were alive, six of whom had MS concurrent with AML. Six patients from the cohort underwent allo-SCT and four had autologous SCT (auto-SCT). The OS rate at 48 months of patients who underwent auto- or allo-HSCT was 76% compared with 0% in those who did not ($p = 0.0000$). Response to therapy was not influenced by patients' age, gender, anatomic location, clinical presentation, previous clinical history, morphological classification, immunophenotype or cytogenetic findings. We showed [Avni *et al.* 2011] that SCT had a significant impact on OS in a cohort of 19 patients presenting with MS with or without concomitant AML. At the end of the follow up four patients in the MS group who underwent SCT were alive, compared with none in the group not undergoing HSCT with a significant prolongation of OS in patients undergoing HSCT ($p = 0.018$). In a multivariate analysis there was no statistically significant difference in the risk of death between subjects in the AML and the MS group, after controlling for age, karyotype and transplantation. Age less than 47.5 years and favorable and intermediate karyotype were associated with a lower risk of death. Subjects who did not undergo transplantation had an increased risk of death compared with subjects who underwent the procedure (HR = 1.88).

Chevallier and colleagues published, and recently updated in an abstract format, their retrospective data on 99 MS patients undergoing allo-SCT, including 30 cases of isolated MS. With a median follow up of 48 months, the 5-year OS was 48% with no significant differences in outcomes between isolated and leukemic MS [Chevallier *et al.* 2010]. Importantly, there was a trend toward improved OS in patients experiencing graft-*versus*-host disease, suggesting this may be important even in localized disease. In a multivariate analysis in that report, age ≥ 15 and remission at the time of allo-SCT were factors associated with a significantly improved OS. The role of auto-SCT in adults with MS is even less clear and there are no published case series. The results in case reports have variable outcomes, probably reflecting the difference in prognostic factors in each case [Finnegan *et al.* 2005].

Targeted therapy

As molecular data on abnormalities contributing to AML pathogenesis are accumulating, these aberrations are anecdotally being reported in MS cases. Vedy and colleagues reported successful therapy with imatinib mesylate in a patient presenting with AML, eosinophilia and paravertebral leukemic masses, and complex cytogenetic anomalies, FLT3-ITD and FIP1L1-PDGFRA

mutations [Vedy *et al.* 2010]. Piccaluga and colleagues treated 24 CD33-positive AML patients with Gemtuzumab ozogamicin (humanized anti-CD33 monoclonal antibody, conjugated to calicheamicin) [Pileri *et al.* 2007; Piccaluga *et al.* 2004]. Among the five patients with MS, two achieved a CR, one was resistant and two showed a complete clearance of the extramedullary tumor, in the absence of marrow CR.

The ability to identify specific patients who may benefit from molecularly targeted therapies holds great promise in this emerging era of personalized medicine. The recent discoveries of gene mutations in the different AML subtypes have provided additional opportunities for targeted therapeutics. New agents, including the nucleoside analogues, FLT3 inhibitors, farnesyl-transferase inhibitors, histone deacetylase inhibitors and DNA methyltransferase inhibitors, are currently being tested for AML treatment and may change treatment options and prognosis in the different subgroups of patients with MS as well. Clearly, the data on targeted therapy is scarce and should be further studied in larger groups before any recommendation regarding such therapy can be made.

Conclusions and future perspective

Although EMD and MS are recognized disease entities for more than a century, the reasons for their occurrence in a small proportion of AML patients and the difference in the timing of this complication during the course of AML remain as enigmas. MS is a relatively rare phenomenon, making it difficult to study its' impact in different AML subgroups. The literature suggests that patients with isolated MS may have a better prognosis compared with AML patients without MS. MS patients treated with AML-type chemotherapy regimens seem to have comparable outcomes to AML patients. Radiotherapy may not be needed as an adjunct to chemotherapy and allo-HCT in the setting of MS with concurrent AML may improve the outcome of these patients. The current treatment recommendation for isolated MS and MS occurring in AML patients is AML-type chemotherapy. There are not enough data currently available to support a risk-adjusted therapy in the setting of isolated MS. Owing to the rarity of this disorder and in order to include larger groups of patients, controlled prospective multicenter studies are necessary.

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The authors declare no conflicts of interest in preparing this article.

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