Myeloid Sarcoma: The Other Side of Acute Leukemia

Bhaskar Kahali

Abstract

Myeloid sarcomas are extramedullary myeloid masses with associated tissue damage. Myeloid sarcomas usually arise before, during or after diagnosis of acute leukemia, most often AML. Majority of the patients with myeloid sarcoma respond to upfront systemic chemotherapy and sometimes bone marrow transplant, but it is unclear which patients will benefit from which treatments. This is primarily due to the paucity of knowledge on myeloid sarcoma. At present, there are no prognostic biomarkers for myeloid sarcoma, which can help in risk stratification in patients with myeloid sarcoma. Several studies have suggested that myeloid sarcoma is more likely to occur with certain translocations such as CBF and MLL rearrangements. In addition, sequencing analysis has identified several mutations in genes such as FLT3, NPM1, EZH2, and KIT. Nevertheless, there is still lack of knowledge to understand why particular leukemia migrates to the skin and soft tissues and becomes refractory to systemic therapy.

Keywords: extramedullary infiltration, myeloid sarcoma, acute leukemia

1. Introduction

Myeloid Sarcoma (MS) constitutes a rare pathological condition of extramedullary manifestation of leukemic cells of primarily myeloid origins that destroy the normal tissue architecture at the site of origin. Presence of the enzyme myeloperoxidase (MPO), gives the tumors its characteristic green hue, leading to the term, ‘chloroma’ (Greek, Chloros, meaning green) coined by a British physician, A. Burns in 1811 [1, 2]. Alternatively, MS is also referred as, Granulocytic sarcoma or Myeloblastoma. In the majority of the cases, MS is associated with acute myeloid leukemia (AML), however, it may also manifest in non-leukemic individuals. In addition, MS has also been reported in cases of myeloproliferative neoplasms (MPN), or
myelodysplastic disorders (MPD) [3, 4]. At present, MS represents a major subgroup of myeloid neoplasms and acute leukemia in WHO classification [5].

2. Epidemiology

MS can manifest under different clinical scenarios including, (1) MS with concurrent AML, (2) as an isolated tumor and may precede the blood and bone marrow involvement or without any history of myeloid neoplasia and, (3) extramedullary relapse of AML [1, 3, 6–9]. However, with a limited number of prospective studies, the exact frequency and the extent of MS are not well described. Based on the retrospective and the autopsy studies, the occurrence of MS in AML patients is reported to be ~10% across genders and all age groups [3, 10, 11]. In depth analysis however revealed that MS primarily affects pediatric patients (>50% of all MS patients) with slight male biasness [7, 12, 13]. In 15–35% of cases, MS can appear concomitantly with AML, whereas, in 50% of cases MS appears following the diagnosis of AML. In rare instances (<1%), MS has also been diagnosed after allogenic stem cell transplantation (allo-SCT), which manifests as an isolated tumor with or without accompanying blood and bone marrow relapse [14, 15].

3. Mechanisms

The precise mechanism underlying the development of MS is unclear. However, extramedullary infiltration by acute leukemia strongly implicates the presence of an alternative homing signal that enables the blast cells to re-localize to these secondary sites. In this context, strong evidence was provided by the studies demonstrating the presence of different chemokine receptors on blast cells in MS and concurrent AML involving blood and bone marrow [16]. Taken together, these observations led to the proposal that unusual manifestations of adhesion molecules dictate the migration of AML subclones to surrounding tissues. Stefanidakis et al. provided further insights into the migratory capacity of blast cells. In their study, the authors reported that a major factor for the migration of AML cells into non-myeloid regions is the interactions between matrix metalloproteinase (MMP) – 9 and leukocyte β2 integrin along with some unidentified proteins [2]. Stefanidakis et al. termed the complex, ‘invadosome’ [2]. The observations that highly invasive AML cell lines express high level of MMP-2 and tissue inhibitor of metalloproteinase 2 (TIMP2) further support the conclusion of Stefanidakis and colleagues [17]. In a recent study, Zhu et al. has reported a correlation between high expression of enhancer of Zeste 2 (EZH2), the catalytic subunit of polycomb repressor complex 2 (PRC2), and extramedullary infiltration of AML [18]. The authors have indicated that increased expression of EZH2 attenuates the expression of TIMPs, which result in the upregulation of MMPs. The uninhibited MMPs ultimately degrades the extracellular matrix (ECM) and thus aid in the escape of the blast cells in the extramedullary space [18].
4. Sites of involvement and symptoms

MS can manifest in different anatomical sites. However, there is a lack of study to establish a correlation between AML and predilection for sites by MS. The most commonly involved sites of MS are skin, bone and lymph nodes [3, 10, 11]. In addition, other sites associated with MS include central nervous system (CNS), oral and nasal mucosa, breasts, genitourinary tract, chest wall, testis etc. Skin is the primary sites for the development of MS in pediatric patients (~54%), followed by ocular region [3, 10, 11].

In majority of instances, MS is asymptomatic. Even so, depending on the size and location of the tumor, the most common signs and symptoms associated with MS are compression accompanied by pains, bleeding, fever and fatigues [1].

5. Diagnosis and disease pathology

At present, there is no specific diagnosis for MS. Given the fact that MS in majority of cases is asymptomatic and does not elicit any specific symptoms, it often poses serious diagnostic challenge for a clinician. Consequently, MS is often misdiagnosed as large cell lymphoma, malignant melanoma, extramedullary hematopoiesis or inflammation. However, diagnosis of MS in association with existing leukemia is comparatively easier than isolated MS. Detection and identification of MS requires the coordinated intervention of different medical procedure. Computed tomography (CT) and magnetic resonance imagery (MRI) are generally used for the detection of the tumors [19]. Following the detection of tumors biopsies are conducted to confirm the malignancy of the mass.

However, accurate diagnosis of MS requires histological examination and immunophenotypic analysis. Histological analysis of MS generally elicits myeloid cells at different stages of maturation. The infiltrating leukemic cells generally elicit irregular large nuclei and large cytoplasm-to-nuclear ratio. Depending on the predominant cell types in the tumors, MS are classified into granulocytic, monoblastic and myelomonocytic. In addition, depending on the maturity of the cells, MS are further subdivided into immature, mature and blastic types [11]. In addition to morphology, cytochemical stainings on imprints may allow for confirming the myeloid affiliation and differentiating granulocytic-lineage and monoblastic forms. According to the WHO 2016 classification, cytochemical stains may include myeloperoxidase and naphthol AS-D chloroacetate esterase (positive in granulocytic MS), as well as non-specific esterase (positive in monoblastic MS) [5]. The diagnosis is further validated by immunophenotyping. Flow cytometric analysis on cell suspensions can be performed; however, immunohistochemistry on paraffin-embedded tissue sections is more commonly used for the detection of lineage affiliation and evaluation of maturation. MS are usually positive for myeloid and monocytic markers, i.e. CD33, CD68, lysozyme, the more immature markers such as CD117 and CD34, CD61, glycophorin, CD4, etc. CD99 and TdT may also be positive. CD56 can be detected in
around 20% of MS cases [1, 12]. NPM1 cytoplasmic and nuclear staining indicates NPM1 gene mutations. To exclude the possibility of lymphoma the tumors should be interrogated for different T and B lineage markers such as, CD3, CD20, and CD79a. Aberrant expression of B/T-cell markers is possible, however, if criteria for a mixed-lineage leukemia are fulfilled the case is not classified as MS according to WHO 2016. Particular antigenic constellations may more precisely define subtypes shown in Table 1.

MS is also associated with several cytogenetic and chromosomal abnormalities (please see next section for detailed report). Consequently, fluorescence in situ hybridization (FISH) should be employed as a part diagnostic work up for patient stratification [20].

6. Cytogenetics and molecular genetics of myeloid sarcoma

Cytogenetic analysis conducted with bone marrow and peripheral blood blasts in MS patients has demonstrated cytogenetic abnormalities in more than 50% of instances [21]. Nonetheless, the rates of specific cytogenetic abnormalities associated with MS are rather diverse. Studies have elicited the frequent association of between MS and core binding factor (CBF) leukemia and AML with MLL rearrangements [22]. The most common chromosomal abnormality, t(8;21), is associated with pediatric MS or in patients with ocular involvement [21, 23, 24]. The second predominant chromosomal aberration associated with pediatric MS is inv16 [3, 25]. However, studies by Pileri et al. showed the relative rarity of t(8,21) in adult MS patients [21]. Instead, trisomy 8, monosomy 7 and MLL rearrangements constitute the majority of the cases [21]. The prevalence of inv16 was also not well documented in adult patients. In addition, other chromosomal aberrations including monosomy 5, 7 or 8 were reported in isolated cases. Nucleophosmin (NPM)-1 mutations have been reported to be in 15% of MS patients. This particular variant of MS elicits clinical attributes similar to NPM-1 positive AML and manifest primarily in M4 and M5 French American British (FAB) subclasses of AML [26].

| Immunophenotypic profiles | Most common markers |
|---------------------------|---------------------|
| Myeloid                   | Myeloperoxidase (MPO), CD33, CD68 (detected by KP1 monoclonal antibody but not by PG-M1), CD34, CD117 |
| Promyelocytic             | Myeloperoxidase (MPO), CD15, CD117, lacking CD34 and TdT |
| Myelomonocytic            | Homogeneous expression of CD68 (KP1), while CD68 (PG-M1) and MPO in distinct subpopulations |
| Monoblastic               | CD68 (PG-M1), CD14, lacking MPO, CD163, CD11c |
| Megakaryoblastic          | CD61, von Willebrand factor |
| Erythroid                 | CD71, glycophorin A, glycophorin C |

Table 1. Common immunophenotypes.
mutant positive MS is also associated with the loss of CD34 expression and normal karyotype. Studies conducted by Ansari-Lari et al. have reported the presence of \textit{FLT3-ITD} mutation in \~33\% (three of nine) of MS patients with concurrent AML [27]. However, the implications of \textit{NPM-1} and \textit{FLT3-ITD} mutations on prognosis of MS are still not clear and data are too scarce for definite conclusions. In their retrospective study, Vega-Ruiz et al. showed that 3\% of patients with acute promyelocytic leukemia (APL) manifest MS, predominantly in CNS [28]. Studies conducted by several groups have also attributed the development of MS to the use of all-trans retinoic acid (ATRA) or with conventional chemotherapy [29].

7. Imaging as a diagnostic tool

Timely identification of MS has a significant impact on the treatment outcomes and achieving remission in case of AML. As often, these extramedullary tumors serve as sanctuary sites for future relapse. However, detection and simultaneous identification of MS is challenging. The standard AML diagnosis does not include MS, nor there are any specific diagnostic regimens for MS. Consequently, in majority of cases diagnosis of MS is either significantly delayed or remain undetected. In this context, multimodal imaging procedure can be beneficial for early detection of tumors [30]. This generally involves employment of traditional imaging techniques such as, positron emission tomography (PET), CT and MRI [25]. Particularly, in the last decades, PET/CT is becoming an essential tool for disease detection [25]. In this context, 18F-fluorodeoxyglucose (18F-FDG)PET/CT has been recognized as a very potent instrument for the identification of not only leukemia but also extramedullary invasion of blast cells [8, 31, 32]. In a prospective study, Stölzel et al. have successfully employed whole-body 18F-FDG PET/CT in 94 AML patients, consisting of both newly diagnosed and relapsed cases of AML for detection of MS [33]. In a different study, Aschoff et al. have demonstrated the sensitivity of 18F-FDG PET/CT by reducing the number of false-positive associated with traditional PET imaging [34]. In addition, 18F-FDG PET/CT has also been able identify new sites of MS, which is not identified by traditional imaging techniques [8].

Although, encouraging, 18F-FDG PET/CT does have some restrictions. Several reports have shown that 18F-FDG PET/CT is not sensitive enough to pick up extramedullary infiltration in the soft tissues such as skin meninges and mucus membranes. In addition, 18F-FDG is not a tumor specific marker but rather depends on the glucose uptake by the cells [8]. As such, there is an increase chance of false-positive signals associated with 18F-FDG PET/CT specifically, in brain and kidney that have high basal glucose metabolism [9]. As an alternative, various groups have used 18F-fluorodeoxythymidine (FLT), a thymidine analogue and proliferating marker, as a tracer for PET/CT in place of 18F-FDG [8]. Unlike 18F-FDG, 18F-FLT has generally low uptake in different organs, such as brain and kidney and therefore elicits comparatively less background [35]. Although, as of now there has been no prospective/retrospective study with 18F-FLT PET/CT for MS detection, but the sensitivity and accuracy of 18F-FLT PET/CT has been demonstrated in different cancers including, non-small cell lung cancer (NSCLC) and NPM-ALK-Positive lymphoma [8, 36].
8. Treatment

Given the scarcity of positively diagnosed MS and randomized prospective trials, there is at present no consensus MS specific therapeutic regimen. The current routine includes conventional AML-type chemotherapy and radiotherapy for both isolated and MS or MS with concomitant AML. Studies led by different groups have shown that standard AML therapy exhibits better overall survival in case of isolated MS incidents [10]. Nevertheless, there is a lack of data addressing a particular chemotherapeutic regimen for MS. Existing data indicates cytarabine to be an essential drug in this regard [37].

The use of radiotherapy is also not well studied as a prospective means of treatment of MS. Although, in some instances, radiation is used in combination with chemotherapy to treat MS. However, no added advantage was observed in those cases [11, 38]. In addition, hematopoietic stem cell transplantation is also used, albeit retrospectively, in MS patients [1]. Reported data does suggest an advantage of auto- or allo-HSCT in MS patients with or without concomitant AML irrespective of age, gender, anatomic location, clinical presentation or cytogenic status [1, 3, 11]. In addition, retrospective chemotherapy trials conducted by the Children’s Cancer Group demonstrated a better event-free survival for children with isolated MS than patients with concurrent AML [38].

Taken together, however, no studies ever compared the different prognostic factors in MS patients with or without AML and consequently, their effects on the treatment regimens. The published data, nevertheless, do suggest a difference in prognosis between patients with isolated MS and with concurrent or relapsed AML. Traditionally, the simultaneous expression of MS at diagnosis of AML is considered as poor prognosis. However, there is evidence contrary to this observation.

As stated above, till now there is no specific treatment for MS. Consequently, to a large extent the treatment of MS depends on the site, volume as well as the timing of diagnosis of the extramedullary tumor. Based on these factors, the clinicians determine the treatment plan by employing singly chemotherapy, radiation therapy or bone marrow transplantation or in combination. A detailed discussion of these different therapeutic regimens is discussed below.

9. Chemotherapy

Systemic chemotherapy is the primary choice of treatment for both isolated MS and MS with simultaneous bone marrow involvement. This is largely due to the fact that even if there is no primary bone marrow involvement, isolated or primary MS ultimately gives rise to AML in majority of the cases [3, 39]. Consequently, the chemotherapy regimens for MS generally follow the same protocol as AML. All these regimens mainly include cytarabine with fludarabine, idarubicin, or both. In some instances, granulocyte colony-stimulating factor (G-CSF), daunorubicin and cyclophosphamide are also used [32, 37, 40]. In particular, combination therapy with cytarabine and daunorubicin has been demonstrated to achieve complete
remission in ~65% of MS patients. In addition, chemotherapy has also shown to be effective in attenuating AML development in isolated MS cases (~71%) in both adult and pediatric population [37, 41]. However, at present there is not enough data to identify a specific chemotherapy plan that is beneficial for MS.

10. Radiotherapy

In some instance, radiation is also used as a part of the treatment plan for MS. However, existing data does suggest that radiation alone may not be sufficient enough to completely eradicate MS. Study conducted by Bakst et al. has demonstrated that patients with isolated MS generally respond better to systemic chemotherapy compared to radiotherapy [39]. In addition, there is also no conclusive data demonstrating that radiotherapy in MS alone can prevent the development of systemic leukemia involving bone marrow (~40%). Consequently, in most cases radiation is used in combination with chemotherapy in treating MS [42].

11. Bone marrow transplantation

Allo-SCT has also been demonstrated to be beneficial in treating isolated MS. Consequently, many investigators/clinicians considered allo-SCT as a primary line treatment following remission in MS patients [21, 43]. However, in a retrospective study, Chevallier et al. have showed that there is no difference in 5-year survival rate in patients with isolated or MS with leukemia when treated with allo-SCT [43]. In both the cases, the average survival was ~48% for 5-year survival. In a different study, Pileri et al. showed that MS patients receiving transplantation demonstrated a better overall survival rate (~70%), than patients who did not receive transplantation (0%) as a part of the treatment plan [21]. In subgroup analysis, transplantation did not display any biasness depending on age, tumor site, timing of diagnosis etc. [21].

Taken together, these reports do suggest that transplantation should be considered as a part of the consolidation therapy following remission in both isolated and leukemic MS in adult and pediatric patients. However, one should be cautious as there are reports of manifestation of MS postallo-SCT, most likely due to reduced graft-versus-leukemia (GVL) state at extramedullary sites [25].

At present, there is not enough data in the field to make an informed choice for the best course of treatment for different variants of MS. Based on the existing data, it is reasonable to consider systemic chemotheraphy as the best course of action, in association with radiotherapy and allo-SCT depending on the bone marrow involvement. Given the fact that most of the reports are isolated, single center analysis with small patient pool, it is not possible to develop a consensus therapeutic regimen. To achieve such MS specific therapy, large multicenter collaboration and development of prospective clinical trials is imperative.
12. Targeted therapy: a possibility for the future?

Next-generation sequencing (NGS) and mutational analysis have uncovered significant insights into the pathogenicity of leukemia. Consequently, the chances to develop targeted therapies for leukemia have become a distinct possibility. However, due to misdiagnosis and paucity of clinical samples, such comprehensive analysis for MS is still lacking. Nonetheless, studies conducted with small cohorts of patients did report mutations in genes such as \textit{FLT3} and \textit{NPM1}. Li et al. performed an NGS analysis with six patients with a custom panel targeting 21 common genes associated with AML and myelodysplastic syndrome (MDS) [44]. In addition to \textit{FLT3} and \textit{NPM1}, the authors were also able to identify mutations in several genes such as \textit{KIT}, \textit{TET2}, \textit{EZH2}, \textit{SF3B1} and \textit{ASXL1} akin to AML [44]. This report does provide substantial evidence of an underlying similarity in the pathogenicity between MS and AML. The importance of targeted therapy is further accentuated by Piccaluga and colleagues [45]. In this study, the authors used an anti-CD33 monoclonal antibody to treat MS patients with concurrent CD33-positive AML. Two out five patients in the study elicited a complete remission of both MS and AML, while two patients showed reductions of extramedullary disease only [45]. In a different study, treatment of MS patients with BCR-ABL1, FLT3-ITD and FIP1L1-PDGFRA mutations by tyrosine kinase inhibitors (TKIs) also showed encouraging outcome [46].

Taken together these observations does suggest that akin to AML a similar sequencing (whole genome, whole exome, and RNA seq.) base analysis should be employed in case of MS. However, the success of such an endeavor depends on the obtainability of large cohorts of samples, which unfortunately is a rarity in case of MS. Large multicenter collaboration is essential to circumvent this problem.

13. Conclusion

Myeloid sarcoma is acknowledged as a separate disease entity for a significant period. It is an extremely rare hematological malignancy and is often associated with poor prognosis. Due to the scarcity of samples, there is no risk assessment study for MS. There are several unanswered questions for MS. Specifically, is there a bias for certain AML (such as CBF leukemia) to induce extramedullary infiltration. If yes, what is the primary mechanism(s) that drives the processes? Does MS represent alternate molecular landscapes, clonal evolution, from the original bone marrow disease? It can be argued that MS reflects a state of reduced immune surveillance in a patient at diagnosis or following hematopoietic stem cell transplantation. Consequently, this raises the possibility that MS may serve as a sanctuary site for leukemic relapse. The observation supports this implication that isolated MS ultimately gives rise to leukemia involving bone marrow.

MS is often challenging to identify and even more challenging to diagnose. Owing to its similarity with solid tumors, MS is often misdiagnosed, particularly as non-Hodgkin lymphoma. Accurate diagnosis of MS required an orchestrated approach involving whole body imaging (PET/CT, MRI), broad panels of immunohistochemical staining, and FISH assay for
cytogenetic and chromosomal abnormalities. Also, bone marrow biopsy should be that part of the diagnosis. In fact, all isolated MS cases should be prophylactically treated for AML even if there is no detectable leukemia. Caution should be exercised when analyzing immunohistochemistry for MS. For example, CD43 and CD68, although, a reliable indicator of AML, should be correlated with CD33, myeloperoxidase staining for accurate MS diagnosis. Treatment should involve systemic chemotherapy as the first line of treatment with radiotherapy and allo-HCT as part of the consolidation therapy. Surgery should be employed for tumor resection, if possible.

We need more prospective studies with larger patient cohorts to understand the mechanism(s) of MS development. In addition, future studies should be directed to whole genome sequencing of MS samples to understand the different genetic abnormalities associated with MS and how they differ from the corresponding bone marrow disease. Genetic information will also help in better patient stratification. As evident from the whole-body PET/CT imaging, the incidence of MS is more prevalent than expected indicating that we most likely have underestimated the impact and implications of MS.

Author details

Bhaskar Kahali
Address all correspondence to: bhaskar.kahali@stjude.org
Bone Marrow Trans and Cell Therapy, St Jude Children’s Research Hospital, Memphis, United States

References

[1] Avni B, Koren-Michowitz M. Myeloid sarcoma: Current approach and therapeutic options. Therapeutic Advances in Hematology. 2011;2(5):309-316
[2] Stefanidakis M, Karjalainen K, Jaalouk DE, Gahmberg CG, O’Brien S, Pasqualini R, Arap W, Koivunen E. Role of leukemia cell invadosome in extramedullary infiltration. Blood. 2009;114(14):3008-3017
[3] Bakst RLTM, Douer D, Yahalom J. How I treat extramedullary acute myeloid leukemia. Blood. 2011;118:3785-3793
[4] Ravandi-Kashani F, Cortes J, Giles FJ. Myelodysplasia presenting as granulocytic sarcoma of mediastinum causing superior vena cava syndrome. Leukemia & Lymphoma. 2000;36(5–6):631-637
[5] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405
[6] Fleckenstein K, Geinitz H, Grosu A, Goetze K, Werner M, Molls M. Irradiation for conjunctival granulocytic sarcoma. Strahlentherapie und Onkologie. 2003;179(3):187-190

[7] Neiman RS, Barcos M, Berard C, Bonner H, Mann R, Rydell RE, Bennett JM. Granulocytic sarcoma: A clinicopathologic study of 61 biopsied cases. Cancer. 1981;48(6):1426-1437

[8] Stolzel F, Rollig C, Radke J, Mohr B, Platzbecker U, Bornhauser M, Paulus T, Ehninger G, Zophel K, Schaich M. (1)(8)F-FDG-PET/CT for detection of extramedullary acute myeloid leukemia. Haematologica. 2011;96(10):1552-1556

[9] van Veen S, Kluin PM, de Keizer RJ, Kluin-Nelemans HC. Granulocytic sarcoma (chloroma). Presentation of an unusual case. American Journal of Clinical Pathology. 1991;95(4):567-571

[10] Avni B, Rund D, Levin M, Grisariu S, Ben-Yehuda D, Bar-Cohen S, Paltiel O. Clinical implications of acute myeloid leukemia presenting as myeloid sarcoma. Hematological Oncology. 2012;30(1):34-40

[11] Lan TY, Lin DT, Tien HF, Yang RS, Chen CY, Wu K. Prognostic factors of treatment outcomes in patients with granulocytic sarcoma. Acta Haematologica. 2009;122(4):238-246

[12] Campidelli C, Agostinelli C, Stitson R, Pileri SA. Myeloid sarcoma: Extramedullary manifestation of myeloid disorders. American Journal of Clinical Pathology. 2009;132(3):426-437

[13] Kawamoto K, Miyoshi H, Yoshida N, Takizawa J, Sone H, Ohshima K. Clinicopathological, cytogenetic, and prognostic analysis of 131 myeloid sarcoma patients. The American Journal of Surgical Pathology. 2016;40(11):1473-1483

[14] Bain EE, Rothman I, Lin L. De novo myeloid sarcoma in a 4-month-old infant: A case report and review of the literature. Journal of Cutaneous Pathology. 2013;40(3):321-325

[15] Yoo SW, Chung EJ, Kim SY, Ko JH, Baek HS, Lee HJ, Oh SH, Jeon SC, Lee WS, Park CK, et al. Multiple extramedullary relapses without bone marrow involvement after second allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. Pediatric Transplantation. 2012;16(4):E125-E129

[16] Faaij CM, Willemze AJ, Revesz T, Balzarolo M, Tensen CP, Hoogeboom M, Vermeer MH, van Wering E, Zwaan CM, Kaspers GJ, et al. Chemokine/chemokine receptor interactions in extramedullary leukaemia of the skin in childhood AML: Differential roles for CCR2, CCR5, CXCR4 and CXCR7. Pediatric Blood & Cancer. 2010;55(2):344-348

[17] Wang C, Chen Z, Li Z. The essential roles of matrix metalloproteinase-2, membrane type 1 metalloproteinase and tissue inhibitor of metalloproteinase-2 in the invasive capacity of acute monocytic leukemia SHI-1 cells. Leukemia Research. 2010;34:1083-1090

[18] Zhu Q, Zhang L, Li X, Chen F, Jiang L, Yu G, Wang Z, Yin C, Jiang X, Zhong Q, et al. Higher EZH2 expression is associated with extramedullary infiltration in acute myeloid leukemia. Tumour Biology. 2016;37(8):11409-11420

[19] Pui MH, Fletcher BD, Langston JW. Granulocytic sarcoma in childhood leukemia: Imaging features. Radiology. 1994;190(3):698-702
[20] Wilson CS, Medeiros LJ. Extramedullary manifestations of myeloid neoplasms. American Journal of Clinical Pathology. 2015;144(2):219-239

[21] Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, Piccioli M, Piccaluga PP, Agostinelli C, Asioli S, Novero D, et al. Myeloid sarcoma: Clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia. 2007;21(2):340-350

[22] Park KU, Lee DS, Lee HS, Kim CJ, Cho HI. Granulocytic sarcoma in MLL-positive infant acute myelogenous leukemia: Fluorescence in situ hybridization study of childhood acute myelogenous leukemia for detecting MLL rearrangement. The American Journal of Pathology. 2001;159(6):2011-2016

[23] Klco JM, Welch JS, Nguyen TT, Hurley MY, Kreisel FH, Hassan A, Lind AC, Frater JL. State of the art in myeloid sarcoma. International Journal of Laboratory Hematology. 2011;33(6):555-565

[24] Schwyzer R, Sherman GG, Cohn RJ, Poole JE, Willem P. Granulocytic sarcoma in children with acute myeloblastic leukemia and t(8;21). Medical and Pediatric Oncology. 1998;31(3):144-149

[25] Ohanian MFS, Ravandi F, Pemmaraju N, Garcia-Manero G, Cortes J, Estrov Z. Is acute myeloid leukemia a liquid tumor. International Journal of Cancer. 2013;133:534-544

[26] Falini B, Mecucci C, Tiacci E, Alcalay M, Rosati R, Pasqualucci L, La Starza R, Diverio D, Colombo E, Santucci A, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. The New England Journal of Medicine. 2005;352(3):254-266

[27] Ansari-Lari MA, Yang CF, Tinawi-Aljundi R, Cooper L, Long P, Allan RH, Borowitz MJ, Berg KD, Murphy KM. FLT3 mutations in myeloid sarcoma. British Journal of Haematology. 2004;126(6):785-791

[28] Vega-Ruiz A, Faderl S, Estrov Z, Pierce S, Cortes J, Kantarjian H, Ravandi F. Incidence of extramedullary disease in patients with acute promyelocytic leukemia: A single-institution experience. International Journal of Hematology. 2009;89(4):489-496

[29] Specchia G, Lo Coco F, Vignetti M, Avvisati G, Fazi P, Albano F, Di Raimondo F, Martino B, Ferrara F, Selleri C, et al. Extramedullary involvement at relapse in acute promyelocytic leukemia patients treated or not with all-trans retinoic acid: A report by the Gruppo Italiano Malattie Ematologiche dell’Adulto. Journal of Clinical Oncology. 2001;19(20):4023-4028

[30] Cunningham I. A basis for updating our approach to resistant acute leukemia. American Journal of Hematology. 2012;87(3):251-257

[31] Kuenzle K, Taverna C, Steinert HC. Detection of extramedullary infiltrates in acute myelogenous leukemia with whole-body positron emission tomography and 2-deoxy-2-[18F]-fluoro-D-glucose. Molecular Imaging and Biology. 2002;4(2):179-183

[32] Rao S, Langston A, Galt JR, Halkar RK. Extramedullary acute myeloid leukemia and the use of FDG-PET/CT. Clinical Nuclear Medicine. 2009;34(6):365-366
[33] Friedrich Stölzel TL, Parmentier SB, Paulus T, Kuithan F, Kramer M, Alakel N, Sockel K, Taube F, Kotzerke J, Röllig C, Bornhäuser M, Ehninger G, Zoephel K, Schaich M. The prevalence of extramedullary AML detected by 18-FDG/PET-CT: Results from the prospective PET-AML trial. Blood. 2014;124(21):2270

[34] Aschoff P, Hantschel M, Oksuz M, Werner MK, Lichy M, Vogel W, Pfannenberg C. Integrated FDG-PET/CT for detection, therapy monitoring and follow-up of granulocytic sarcoma. Initial results. Nuklearmedizin. 2009;48(5):185-191

[35] Chandrasekaran S, Hollander A, Xu X, Benci JL, Davis JJ, Dorsey JF, Kao G. 18F-fluorothymidine-pet imaging of glioblastoma multiforme: Effects of radiation therapy on radiotracer uptake and molecular biomarker patterns. Scientific World Journal. 2013;2013:

[36] Li Z, Graf N, Herrmann K, Junger A, Aichler M, Feuchtinger A, Baumgart A, Walch A, Peschel C, Schwaiger M, et al. FLT-PET is superior to FDG-PET for very early response prediction in NPM-ALK-positive lymphoma treated with targeted therapy. Cancer Research. 2012;72(19):5014-5024

[37] Yamauchi K, Yasuda M. Comparison in treatments of nonleukemic granulocytic sarcoma: Report of two cases and a review of 72 cases in the literature. Cancer. 2002;94(6):1739-1746

[38] Dusenbery KE, Howells WB, Arthur DC, Alonzo T, Lee JW, Kobrinsky N, Barnard DR, Wells RJ, Buckley JD, Lange BJ, et al. Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia: A report from the Children’s cancer group. Journal of Pediatric Hematology/Oncology. 2003;25(10):760-768

[39] Bakst R, Wolden S, Yahalom J. Radiation therapy for chloroma (granulocytic sarcoma). International Journal of Radiation Oncology, Biology, Physics. 2012;82(5):1816-1822

[40] Bleul CC, Fuhlbrigge RC, Casasnovas JM, Aiuti A, Springer TA. A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). The Journal of Experimental Medicine. 1996;184(3):1101-1109

[41] Crazzolara R, Kreczy A, Mann G, Heitger A, Eibl G, Fink FM, Mohle R, Meister B. High expression of the chemokine receptor CXCR4 predicts extramedullary organ infiltration in childhood acute lymphoblastic leukaemia. British Journal of Haematology. 2001;115(3):545-553

[42] Aiuti A, Webb IJ, Bleul C, Springer T, Gutierrez-Ramos JC. The chemokine SDF-1 is a chemoattractant for human CD34+ hematopoietic progenitor cells and provides a new mechanism to explain the mobilization of CD34+ progenitors to peripheral blood. The Journal of Experimental Medicine. 1997;185(1):111-120

[43] Chevallier PMM, Lioure B, Michel G, Contentin N, Deconinck E, Bordigoni P, Vernant JP, Hunault M, Viguexou S, Blaise D, Tabrizi T, Buzyn A, Socie G, Michallet M, Volteau C, Harousseau JL. Allogeneic hematopoietic stem-cell transplantation for myeloid sarcoma: A retrospective study from the SFGM-TC. Journal of Clinical Oncology. 2008;26:4940-4943
[44] Li Z, Stolzel F, Onel K, Sukhanova M, Mirza MK, Yap KL, Borinets O, Larson RA, Stock W, Sasaki MM, et al. Next-generation sequencing reveals clinically actionable molecular markers in myeloid sarcoma. Leukemia. 2015;29(10):2113-2116

[45] Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, Isidori A, Bonini A, Gugliotta L, Luppi M, Morselli M, et al. Gemtuzumab ozogamicin for relapsed and refractory acute myeloid leukemia and myeloid sarcomas. Leukemia & Lymphoma. 2004;45(9):1791-1795

[46] Vedy D, Muehlematter D, Rausch T, Stalder M, Jotterand M, Spertini O. Acute myeloid leukemia with myeloid sarcoma and eosinophilia: Prolonged remission and molecular response to imatinib. Journal of Clinical Oncology. 2010;28(3):e33-e35
