Myeloid Sarcoma

Extramedullary Manifestation of Myeloid Disorders

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Abstract

Myeloid sarcoma (MS), also termed extramedullary acute myeloid leukemia, extramedullary myeloid tumor, and granulocytic sarcoma or chloroma, is a rare manifestation that is characterized by the occurrence of 1 or more tumor myeloid masses occurring at an extramedullary site.

The wide spectrum of this disorder and the conditions that it overlaps diagnostically were well reflected in the 25 cases submitted to the Society for Hematopathology/European Association for Hematopathology Workshop held in Indianapolis, IN, in November 2007. This review, on the one hand, focuses on the definition and most recent achievements on the pathobiology of MS, and on the other, also in the light of the revised World Health Organization classification, summarizes the main features of a representative series of this condition aiming to provide readers a useful document for daily practice.

Myeloid sarcoma (MS) is a rare neoplastic condition consisting of immature myeloid cells and occurring at an extramedullary site that most frequently corresponds to the bone, skin, or lymph node, although any part of the body may be affected. MS most commonly consists of myeloblasts, with or without features of promyelocytic or neutrophilic maturation, that partially or totally efface the tissue architecture. In a significant proportion of cases, it displays myelomonocytic or pure monoblastic morphologic features. Tumors with trilineage hematopoiesis or predominantly erythroid precursors or megakaryoblasts are rare and may occur in conjunction with transformation of a myeloproliferative neoplasm or, even less frequently, of other myeloid neoplasms.

MS may develop de novo or concurrently with acute myeloid leukemia (AML),2–5 myeloproliferative neoplasm (MPN),6,7 or myelodysplastic syndrome (MDS).8 MS may be the first manifestation of AML, precede it by months or years, or equally represent the initial manifestation of relapse in a previously treated AML in remission.9

Histologically, the morphologic subclassification proposed in the third edition of the 2001 World Health Organization classification showed no practical relevance in 2 recently published studies.1,10 In contrast, such studies, the results of which have been incorporated in the current fourth edition of the World Health Organization classification, demonstrated that the immunophenotype is of paramount importance for the lineage definition and differential diagnosis.

CD68-KP1 is the most commonly expressed marker followed by myeloperoxidase (MPO), CD117, CD99, CD68/PG-M1, lysozyme, CD34, terminal deoxynucleotidyl transferase (TdT), CD56, CD61/linker of activated T lymphocyte/
factor VIII–related antigen, CD30, glycoporphin A, and CD4. Foci of plasmacytoid dendritic cell (pDC) differentiation (CD123+) may be observed in cases carrying inv(16).11,12 In particular, the combination of the aforementioned markers enables the recognition of tumors with more immature myeloid phenotype and cases with myelomonocytic, monoblastic, erythroid, or megakaryocytic differentiation. Exceptionally, aberrant antigenic expression is observed (eg, cytokeratins, B- or T-cell markers). Moreover, immunohistochemical analysis allows the differentiation of MS from aggressive lymphomas (lymphoblastic lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma), blastic pDC neoplasm, and nonhematopoietic tumors, particularly in children (neuroblastoma, rhabdomyosarcoma, Ewing/primitive neuroectodermal tumor, and medulloblastoma).

Cytogenetically, MS has been found to occur in association with a variety of chromosomal abnormalities, including MLL rearrangement and t(8;21). The latter more often occurs in childhood and/or is seen in lesions occurring in the orbit.13-15 In the only study that has systematically applied fluorescence in situ hybridization (FISH) to the analysis of MS, several aberrations were detected, including monosomy 7, trisomy 8, MLL splitting, inv(16), trisomy 4, monosomy 16, 16q–, 5q–, 20q–, and trisomy 11.10 About 16% of cases carry NPM mutations, as shown by aberrant cytoplasmic nucleophosmin (NPM) expression.10 These cases usually correspond to MS with French-American-British M4 or M5 morphologic features and normal karyotype.

Finally, the clinical behavior and response to therapy seem not influenced by any of the following factors: age; sex; anatomic site; de novo presentation or clinical history related to AML, MDS, or MPN; histotype; phenotype; or cytogenetic findings.1 Notably, patients who undergo allogeneic or autologous bone marrow transplantation seem to have a higher probability of prolonged survival or cure.1

**Workshop Case Mix**

Following panel review, 25 cases submitted to the Society for Hematopathology/European Association for Haematopathology Workshop held in Indianapolis, IN, in November 2007, were included in session 6, devoted to MS. These covered the spectrum of conditions included within the diagnosis of MS and the main challenges in terms of differential diagnoses. In the following sections, they will be summarized according to the corresponding setting.

**De Novo MS**

Seven cases had de novo occurrence without evidence of pathologic involvement of the bone marrow (BM) and peripheral blood (PB). Affected sites were as follows: ileum, colon, soft tissue, lymph node, submandibular gland and breast, central nervous system, and brachial plexus with cerebrospinal fluid involvement.

The MS occurring in the ileum (case 173) and produced a stenotic, obstructive, and painful mass, partially eroding the mucosa. Neither lymphadenopathy nor other tumor masses or hepatosplenomegaly were detected by whole-body computed tomography (CT) scan.

The colonic MS (case 207) manifested with abdominal pain and a preoperative diagnosis of adenocarcinoma. The tumor formed a nodular mass in the transverse colon, massively involving the “gastrocolonic ligament” and invading the surrounding fat and soft tissue. In former reports, the prevalence of intestinal involvement varied extensively, the ileum being regarded as the most frequently affected segment of gastrointestinal tract. A recent study1 confirmed that the intestine is commonly involved by MS, representing its third most frequent localization, occasionally in association with nonhematopoietic lesions such as colonic adenoma.16

The tumor that developed in soft tissue (case 151) occurred at the site of a previous right inguinal hernioplasty and rapidly extended to the abdominal wall and lesser pelvis with compression of the bladder and colon and femoral vein thrombosis.1 Image 1A.

The nodal MS (case 71) affected the left side of the neck. Imaging revealed a lung nodule, pericardial lymphadenopathy, and multiple nodular lesions of the spleen. A splenic core biopsy revealed caseating granulomas without evidence of malignancy.

Another patient (case 24) had a history of Chernobyl radiation exposure; a firm lesion of the left breast and an enlarging mass of the right submandibular gland developed accompanied by sore throat and weight loss.

The 2 remaining cases showed central nervous system involvement. One of them (case 101) manifested with a 2-day history of “refusing to talk” and a 1-day history of decreased movement. In the recent past, the patient had otitis media. Magnetic resonance imaging (MRI) revealed a large contrast-enhancing mass in the left middle cranial fossa with extension into the subtemporal fossa and parapharyngeal space. In the other patient (case 179) with a history of multiple sclerosis, progressive left arm pain and weakness developed due to a hypermetabolic mass (MRI- and positron emission tomography–positive) in the left brachial plexus. A lumbar puncture revealed involvement of the spinal fluid.

Histologically, in all cases, the tumors were composed of medium-sized to large pleomorphic cells with irregular nuclear outline, finely dispersed chromatin, prominent nucleoli, and abundant variably eosinophilic cytoplasm. Case 151 showed megakaryoblastic differentiation with some admixed multinucleated giant cells. In the nodal case, morphologic features along with immunohistochemical findings suggested...
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possible histiocytic differentiation. In both of the latter cases, foci of necrosis were also observed. The lesions of the salivary gland and breast contained numerous mature eosinophils and eosinophil precursors, together with blasts. The pattern of growth was always diffuse, with features of sinusoidal spread in the lymph node.

Immunohistochemical analysis confirmed the hematopoietic nature of the neoplastic process, with myeloid differentiation in 3 cases (leukocyte common antigen+, CD117+/–, and MPO+), monoblastic in 2 (MPO–, CD68+/PGM1+, and lysozyme+), myelomonocytic in 1 (CD3–/+ , MPO+/–, and CD68+/PGM1+), and megakaryoblastic in 1 (CD61+, linker of activated T lymphocyte–positive) Image 1D. NPM studies were performed in 5 cases and were positive only in case 179, which showed a normal karyotype, as expected.17 It is interesting that this case revealed a myeloid phenotype and CD34 positivity that were observed in only 5% to 6% of the NPM+ cases described by Falini et al.17 Notably, case 101 weakly expressed PAX-5 and CD79a; it carried the t(8;21) ETO/AML1 fusion, as previously reported by Tiacci et al.18 In case 24, foci of pDCs were detected (CD123+, focally HECA+, platelet-derived growth factor receptor α–negative); these have recently been described in MS carrying inv(16) and presenting the same chromosomal aberration in blastic and pDC components.1 Finally, in the megakaryoblastic MS, monosomy 5 was demonstrated by FISH in routine sections;

Image 1 A, Myeloid sarcoma (MS) involving the ileum (H&E, ×200). B, MS with megakaryoblastic differentiation. The neoplasm is composed of large cells and multinucleated giant elements with abundant eosinophilic cytoplasm (H&E, ×400). C, MS of the ileum: positivity for CD68-KP1 (immunoperoxidase, ×200). D, Diffuse expression of the linker of activated T lymphocyte molecule in megakaryoblastic MS (immunoalkaline phosphatase, ×400).
according to Pileri et al,1 this is one of the most frequent chromosomal aberrations in MS.

**AML-Related MS**

Four cases were associated with a preexisting, concomitant, or subsequent AML involving the BM.

In case 42, the patient, an 11-month-old girl, had multiple recurring red-brown asymptomatic papules on the face, trunk, and extremities. A skin biopsy revealed a mononuclear infiltrate of the superficial and deep dermis with periadnexal distribution and epidermal sparing [Image 1E]. Neoplastic cells had monocytic features with pale cytoplasm and folded nuclei; were positive for CD117, CD34, MPO, CD68, and lysozyme; and showed a high Ki-67 labeling index. These features were consistent with MS displaying monocytic differentiation; an **MLL** rearrangement was detected by FISH. Simultaneously, myeloid blasts (CD33+, CD34+, CD117+/–, CD14–, and MPO–) were found in the BM representing from 6% to 13% of total cellularity. They were regarded as suggestive of early involvement by AML. However, unlike the skin lesion in which **MLL** rearrangement was detected, BM biopsies failed to demonstrate any cytogenetic abnormality, thus raising the question of whether the blastic marrow component was reactive or leukemic.

In case 135, the patient complained of severe back pain. An MRI of the lumbar spine showed multiple focal bony lesions suggestive of metastatic carcinoma or lymphoma. An L3 bone biopsy was performed, yielding a diagnosis of an atypical myeloid infiltrate (MPO+ and CD15+). Although “suspicious,” a concurrent BM biopsy was regarded as not conclusive for acute leukemia. Six months later, a repeated BM biopsy showed clear-cut evidence of acute promyelocytic leukemia (APL) with detectable t(15;17). Vertebral bone and surrounding soft tissue were entirely infiltrated by large cells with finely dispersed chromatin, irregular nuclear contours, and clear to eosinophilic cytoplasm. The BM aspirate contained 40% blasts, including promyelocytes. The picture fulfilled the criteria for the diagnosis of the microgranular variant of APL, with deeply invaginated or dumbbell-shaped nuclear contours, prominent nucleoli, numerous small azurophilic granules, and occasional Auer rods. Initial occurrence of APL at an extramedullary site is extremely rare, with only 2 cases reported in the literature; in most cases, APL gives rise to an extramedullary tumor at relapse. The submitted case demonstrates the challenge of making a diagnosis of extramedullary APL in a decalcified bone trephine biopsy specimen that may be suboptimal in terms of cytologic details and for application of molecular techniques, including FISH.

Case 129 involved a 25-year-old man who entered the hospital for an acute abdomen preceded by progressively increasing epigastric pain. Emergency surgery revealed ascites associated with a large mediastinal mass [Image 1F], massive pericardial effusion, and cardiac tamponade. Mass debulking was performed and showed diffuse infiltration by a population of medium-sized cells, some showing monocytic differentiation by immunohistochemical analysis (leukocyte common antigen+, CD33+, CD163+, lysozyme+, and NPM–) [Image 2A]. In the BM, there were numerous blasts and promonocytes that led to a diagnosis of AML, characterized by a complex karyotype. Leukemic blasts were also noted in
**Image 21**

A. Myeloid sarcoma (MS) of the mediastinum. The tumor expresses CD33 (left) and CD163 (right) (immunoperoxidase, ×200) and is negative for CD123 (inset, ×100). B. Nucleophosmin staining in an MS of the gallbladder. Note the cytoplasmic expression of the protein (immunoalkaline phosphatase, ×400). C. Nodal MS in a patient affected by chronic myelogenous leukemia. The neoplastic population is arranged in sheets of blasts admixed with megakaryocytes (H&E, ×200). D. Nodal MS with myelomonocytic features (H&E, ×200). In the same case, positivity for myeloperoxidase (E) and CD34 (F) (E and F, immunoperoxidase, ×200).
the pericardial fluid. An AML occurring in a young patient with a mediastinal mass, pericardial effusion, and cardiac tamponade is indeed rare. In fact, such a manifestation is more typically observed in precursor T-lymphoblastic leukemia/lymphoma or classical Hodgkin lymphoma.

Finally, in case 73, MS represented the extramedullary recurrence of AML-M5. The patient, a 58-year-old woman, originally manifested with abdominal pain, fever, nose bleeding, headache, double vision, gingival hypertrophy, and diffuse lymphadenopathy. The WBC count was 222,000/μL (222.0 × 10⁹/L) with 85% blasts. A diagnosis of AML with monocytic differentiation had been made, for which the patient received chemotherapy. After recovery of her peripheral blood cell counts, abdominal pain and low-grade fever developed. A cholecystectomy was performed because the gallbladder was thought to be inflamed and the source of an *Acinetobacter lwoffi* bacteremia. Unexpectedly, the gallbladder wall was diffusely infiltrated by large atypical cells with abundant cytoplasm, round to folded nuclei, fine chromatin, and occasional small nuclei, consistent with monoblasts and promonocytes. A BM biopsy confirmed the relapse of leukemia. Neoplastic cells expressed CD4, CD43, CD68, and CD163 but not CD34 and MPO, supporting the diagnosis of AML-M5. Further immunohistochemical studies revealed NPM cytoplasmic expression as observed in cases carrying mutated NPM.¹⁷ Cytogenetically, trisomy 8 and 13 and an FLT3 internal tandem duplication were found. Although an FLT3 internal tandem duplication is detected in a significant proportion of *NPM* mutated cases and confers a negative prognostic impact, the occurrence of a complex karyotype, as observed in this case, is exceedingly rare (about 5%) in AML/MS with cytoplasmic NPM expression. It is interesting that this was 1 of 2 cases found to carry *NPM* mutations based on immunostaining out of 16 tested; the corresponding incidence (12.5%) is similar to that recently reported by Falini et al.¹⁰ in a large series of MS.

**MS Associated With MPN**

Two cases were associated with chronic myelogenous leukemia (CML) that was present in the peripheral blood and bone marrow. One case (case 136) occurred in a young patient without significant medical history who had leukocytosis (WBC count, 371,000/μL [371 × 10⁹/L]), splenomegaly, and lymphadenopathy. The WBC count was 222,000/μL (222.0 × 10⁹/L) with 85% blasts. A diagnosis of AML with monocytic differentiation had been made, for which the patient received chemotherapy. After recovery of her peripheral blood cell counts, abdominal pain and low-grade fever developed. A cholecystectomy was performed because the gallbladder was thought to be inflamed and the source of an *Acinetobacter lwoffi* bacteremia. Unexpectedly, the gallbladder wall was diffusely infiltrated by large atypical cells with abundant cytoplasm, round to folded nuclei, fine chromatin, and occasional small nuclei, consistent with monoblasts and promonocytes. A BM biopsy confirmed the relapse of leukemia. Neoplastic cells expressed CD4, CD43, CD68, and CD163 but not CD34 and MPO, supporting the diagnosis of AML-M5. Further immunohistochemical studies revealed NPM cytoplasmic expression as observed in cases carrying mutated NPM.¹⁷ Cytogenetically, trisomy 8 and 13 and an FLT3 internal tandem duplication were found. Although an FLT3 internal tandem duplication is detected in a significant proportion of *NPM* mutated cases and confers a negative prognostic impact, the occurrence of a complex karyotype, as observed in this case, is exceedingly rare (about 5%) in AML/MS with cytoplasmic NPM expression. It is interesting that this was 1 of 2 cases found to carry *NPM* mutations based on immunostaining out of 16 tested; the corresponding incidence (12.5%) is similar to that recently reported by Falini et al.¹⁰ in a large series of MS.

**MS Associated With MDS or MDS/MPN**

Four cases were included in this group. Case 212 was characterized by the sudden onset of right axillary and inguinal lymphadenopathy in a patient with a history of hepatitis C virus infection and leukocytosis. A BM biopsy performed 10 years earlier had been regarded as normal. In 2005, an axillary lymph node was taken in the suspicion of an infection, and the BM biopsy was repeated. The former showed diffuse effacement of the normal structure with a blastic population arranged in sheets consisting of myeloid blasts (CD34+, MPO+, NPM–, and CD68–/PGM1–) and megakaryocytes. Accordingly, the lymph node biopsy was diagnosed as MS occurring in a patient with typical CML in the BM.

The other case (case 12) involved a 72-year-old man with CML in chronic phase who had been treated with imatinib and achieved complete hematologic remission. Three months after discontinuation of therapy, left supraclavicular lymphadenopathy developed. An excisional biopsy was performed that showed T-cell lymphoblastic lymphoma. A BM biopsy did not reveal obvious BM involvement by the lymphoblastic component. Neoplastic cells were medium-sized to large, with scant cytoplasm, vesicular chromatin, and inconspicuous nuclei. Immunohistochemical analysis demonstrated a phenotypic profile consistent with cortical thymocytes (CD34+, TdT–/+, CD1a+, CD3ε+, CD5+, CD7+, and MPO–). BM cytogenetics demonstrated a complex karyotype. Molecular studies displayed the presence of the *BCR-ABL1* fusion transcript in the lymph node and BM. A monoclonal T-cell receptor γ rearrangement was shown at the nodal level that unexpectedly also occurred in the PB and BM despite the absence of morphologic evidence of precursor T-lymphoblastic leukemia/lymphoma. This case, of which there are 12 similar previous records in the literature,¹⁹ has several interesting features: (1) the sudden onset of a blast crisis following complete hematologic remission and recent cessation of imatinib, (2) its T-lymphoblastic nature as opposed to the more common B-lymphoblastic and myeloid ones, and (3) the apparently exclusive extramedullary presentation of the process. Most important, the observed picture does not belong to the morphologic and pathobiologic spectrum of MS and should not be diagnosed as such.

**MS Associated With MPN**

Two cases were associated with chronic myelogenous leukemia (CML) that was present in the peripheral blood and bone marrow. One case (case 136) occurred in a young patient without significant medical history who had leukocytosis (WBC count, 371,000/μL [371 × 10⁹/L]), splenomegaly, and lymphadenopathy. A BM aspirate showed marked left shift associated with 5% blasts. A BM biopsy revealed 100% cellularity with myeloid hyperplasia and marked fibrosis. Cytogenetic studies demonstrated the presence of t(9;22), thus confirming the clinical diagnosis of CML. A cervical lymph node revealed complete effacement of the normal structure due to a neoplastic population arranged in sheets consisting of myeloid blasts (CD34+, MPO+, NPM–, and CD68–/PGM1–) and megakaryocytes. Accordingly, the
This case, in which MS developed in the setting of refractory anemia followed by progression of MDS to frank AML, showed association with hepatitis C virus infection; to the best of our knowledge, this represents an unprecedented finding. Whether it had any role in the disease development remains unanswered, as does the significance of the leukocytosis that preceded the onset of MS and MDS. It is interesting that this case also shows phenotypic differences between the MS and supervening AML, being myelomonocytic and myeloid, respectively. This finding suggests that they stemmed from a common precursor that underwent divergent differentiation in the lymph node and BM.

Case 17 occurred in a 42-year-old man with a history of alcohol abuse, in whom retroperitoneal and superficial lymphadenopathy developed. Seven months earlier, the patient had received a diagnosis of an MDS, not further specified, with multiple cytogenetic abnormalities, including extra copies of chromosomes 5 and 8 and monosomies of chromosomes Y and 15. A biopsy from a left supraclavicular lymph node disclosed massive infiltration by a blastic population with condensed nuclear chromatin and dark blue, occasionally vacuolated cytoplasm. It stained positively for CD45 and glycophorin A and was negative for B-cell, T-cell, myelomonocytic markers, and cytoplasmic NPM. Cytogenetic studies performed on the lymph node biopsy specimen revealed ring chromosomes besides the previously recorded abnormalities. The final diagnosis was erythroblastic sarcoma in a patient with a history of MDS.

Case 204 involved a 64-year-old man who entered the emergency room with a left foot ulcer that had developed after a spider bite 4 months earlier. The lesion was firm and lobulated with no radiographic evidence of bony destruction. The blood cell count revealed pancytopenia; a BM biopsy and aspirate were performed. Histologic examination of debrided tissue from the foot ulcer demonstrated large, immature, mitotically active cells infiltrating the soft tissue. Positivity for CD45, CD68, and CD15 indicated a hematologic neoplasm with monocytic and granulocytic differentiation. The BM aspirate showed infiltration of the paracortex by medium-sized cells with kidney-shaped nuclei, condensed nuclear chromatin, and abundant pale eosinophilic cytoplasm, which were positive for CD45 and glycophorin A and was negative for B-cell, T-cell, myelomonocytic markers, and cytoplasmic NPM. Cytogenetic studies performed on the BM aspirate revealed hypercellular and rich in myelomonocytic cells; a trilinear differentiation of myeloid/erythroid ratio and scattered micromegakaryocytes. Based on morphologic features and BCR-ABL1 negativity, a diagnosis of MDS/MPN (atypical CML) was made. A lymph node biopsy was performed that showed effacement of the normal structure due to a blastic population, at times with intrasinusoidal distribution, that expressed MPO, CD68, and occasionally CD117 and CD34. Within this context, there were nodular aggregates of large cells with grooved nuclei and abundant pink cytoplasm, which were positive for CD1a and S-100. The pattern was regarded as an association between MS and LCH. Notably, FISH studies revealed the occurrence of trisomy 8 in MDS/MPN, MS, and LCH. Langerhans cell proliferations associated with malignant tumors (mainly Hodgkin and non-Hodgkin lymphomas) have repeatedly been reported in the literature, their nature being a matter of speculation. In fact, some authors regard them as reactive components not undergoing clinical progression, while others postulate trans-differentiation owing to the occurrence of common genetic abnormalities. The present case might represent an example of divergent differentiation of a common aberrant ancestor into MDS/MPN, MS, and LCH at different sites.

Two cases were included in this category. The first (case 108) was recorded in an 80-year-old woman undergoing management of Langerhans cell histiocytosis (LCH) diagnosed 1 month previously who was found to have inguinal, axillary, and occipital lymphadenopathy associated with a diffuse maculopapular skin rash. The blood cell count revealed leukocytosis (WBC count, 29,300/μL [29.3 × 10^9/L]) with neutrophilia, anemia, and mild thrombocytopenia. Examination of the PB and BM aspirate smears revealed granulocytic dysplasia with increased precursors, hypogranulation, and abnormal nuclear lobation. The BM biopsy was hypercellular with an increased myeloid/erythroid ratio and scattered micromegakaryocytes. Based on morphologic features and BCR-ABL1 negativity, a diagnosis of MDS/MPN (atypical CML) was made. A lymph node biopsy was performed that showed effacement of the normal structure due to a blastic population, at times with intrasinusoidal distribution, that expressed MPO, CD68, and occasionally CD117 and CD34. Within this context, there were nodular aggregates of large cells with grooved nuclei and abundant pink cytoplasm, which were positive for CD1a and S-100. The pattern was regarded as an association between MS and LCH. Notably, FISH studies revealed the occurrence of trisomy 8 in MDS/MPN, MS, and LCH. The second case (case 130) manifested with diffuse lymphadenopathy and progressive pancytopenia. Lymph node and BM biopsies were performed. The former showed infiltration of the paracortex by medium-sized cells with kidney-shaped nuclei, condensed chromatin, and abundant pale eosinophilic cytoplasm. They
expressed S-100 protein, CD68, lysozyme, bcl-6, CD4, CD43, and CD45 but lacked CD1a, CD163, and myeloid and lymphoid markers (Image 3D). The BM biopsy specimen was markedly hypercellular with 60% blasts and promonocytes with round to folded nuclear contours, finely dispersed chromatin, and agranular cytoplasm (Image 3C). Scattered cells with abundant cytoplasm similar to those seen in the lymph node were admixed. By flow cytometry, BM blasts were positive for CD13, CD33, CD34, CD117, and HLA-DR. Immunohistochemical analysis on the trephine biopsy specimen revealed a subset of cells that were S-100+, bcl-6+, and CD1a−. These findings were regarded as consistent with myelomonocytic AML with extramedullary differentiation to interdigitating dendritic cell (IDC) sarcoma. The case shows some interesting features. First, the IDC component expressed bcl-6; this is not surprising because the molecule, besides germinal center B cells, is constitutively expressed by myeloid and plasmacytoid dendritic cells, being rapidly down-regulated following maturation triggered by selected stimuli. Second, the occurrence of a subset of elements with an IDC phenotype within the AML in the BM biopsy specimen might support the derivation of the 2 neoplastic populations from a
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common precursor, despite lack of cytogenetic or molecular proof. It remains controversial whether this situation can be included within the spectrum of MS; future studies based on more recent techniques can likely answer this question.

Extradmedullary Involvement by MDS/MPN

According to the preceding definition, 2 cases were not included within the MS spectrum, but rather were regarded as extramedullary manifestations of CMML.

Case 10 involved a 38-year-old man with leukocytosis (WBC count, 15,500/μL [15.5 × 10^9/L]), monocytosis (monocyte count, 17% [0.17]), and progressive cervical lymph node enlargement lasting several weeks in the absence of a history of malignancy. A BM aspirate exhibited myeloid and granulocytic hyperplasia, increased megakaryocytes, 10% blasts, and foci of typical pDCs, a picture deemed consistent with a diagnosis of CMML. A lymph node biopsy was performed that revealed partial effacement of the paracortex due to the occurrence of large clusters of mature pDCs, similar to those observed in the BM, and staining for CD4, CD68, HECA, CD123, and lysozyme Image 3E. Within this context, there were a few admixed myeloid precursors evident on staining for CD34, MPO, and CD99. Foci of pDCs have been described in MDS and AML,22,23 as well as in MS,1 and regarded as features of tumor differentiation based on the detection of the same chromosomal abnormalities. In addition, neoplasms derived from pDCs (formerly termed malignant lymphoma of plasmacytoid T cells) have been reported in association with CMML.24 The uniqueness of the present case lies in the fact that, in contrast with the latter condition, the lymph node was involved by clusters of mature pDCs displaying no cytologic atypia, thus suggesting that the MDS/MPN observed in the BM and PB had colonized it while undergoing striking pDC differentiation.

The second case (case 142) occurred in an 86-year-old woman. It is interesting that her family history showed an identical twin sister died of a poorly defined leukemia 1 year earlier. The patient had dual-lineage cytopenia (hemoglobin, 9.3 g/dL [93 g/L]; platelets, 79 × 10^3/μL [79 × 10^9/L]) with monocytosis (WBC count, 7,800/μL [7.8 × 10^9/L] with 47% monocytes [0.47]) associated with bilateral moderate axillary and retrocrural lymphadenopathies. A BM trephine biopsy specimen was markedly hypercellular with myeloid and megakaryocytic hyperplasia and dysplasia together with 13% monocytes but no increase in blasts. A diagnosis of CMML was made. An axillary lymph node measuring 1.2 cm in diameter was excised and showed a histologic picture that was characterized by extramedullary hematopoiesis with foci of erythroid precursors and megakaryocytes admixed with myeloid elements in variable phases of maturation, numerous monocytes, and an absence of blasts. In particular, the myeloid and monocytic components were respectively MPO+ and CD68+/PGM1+, but CD34−. Within this context, there were a few admixed CD34+, MPO+, and CD99. Foci of pDCs have been described in MDS and AML,22,23 as well as in MS,1 and regarded as features of tumor differentiation based on the detection of the same chromosomal abnormalities. In addition, neoplasms derived from pDCs (formerly termed malignant lymphoma of plasmacytoid T cells) have been reported in association with CMML.24 The uniqueness of the present case lies in the fact that, in contrast with the latter condition, the lymph node was involved by clusters of mature pDCs displaying no cytologic atypia, thus suggesting that the MDS/MPN observed in the BM and PB had colonized it while undergoing striking pDC differentiation.

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Image 3 (cont) E, Partial effacement of the nodal paracortex by clusters of mature plasmacytoid dendritic cells highlighted by CD68-PGM1 staining (immunoperoxidase, ×100). F, Sheets of basophilic blasts located in the nodal paracortex (H&E, ×100). Inset, Their erythroid nature is demonstrated by glycophorin C immunostain (×400).
detected a monoclonal onstrated t(6;8) and del(13), and molecular biology studies for the first time CD56 positivity. Cytogenetic studies dem-
lar neoplastic population; notably, this population displayed and TdT was observed; CD56 staining was negative. A new bcl-2. In addition, partial staining for CD20, CD79a, CD10, ity of tumor cells for CD45, CD4, CD7, CD43, CD123, and were carried out on both biopsy specimens revealing positiv-
was almost identical. Accordingly, new phenotypic analyses was compared with that observed in the skin 1 year earlier and
immunoblast-like cells with no epidermotropism. The pattern that displayed a diffuse dermal infiltrate consisting of large newly developed skin lesions. A skin biopsy was performed persistent leukemic population, pancytopenia, and numerousFour months later, disease progression was noted with auous lineage, possibly therapy-related, was proposed. Therapy for AML was started, which produced only partial remission. Four months later, disease progression was noted with a persistent leukemic population, pancytopenia, and numerous newly developed skin lesions. A skin biopsy was performed that displayed a diffuse dermal infiltrate consisting of large immunoblast-like cells with no epidermotropism. The pattern was compared with that observed in the skin 1 year earlier and was almost identical. Accordingly, new phenotypic analyses were carried out on both biopsy specimens revealing positiv-
ity of tumor cells for CD45, CD4, CD7, CD43, CD123, and bcl-2. In addition, partial staining for CD20, CD79a, CD10, and TdT was observed; CD56 staining was negative. A new BM biopsy was performed and revealed infiltration by a similar neoplastic population; notably, this population displayed for the first time CD56 positivity. Cyto genetic studies demon-
strated t(6;8) and del(13), and molecular biology studies detected a monoclonal IgH rearrangement of the incomplete (DJ-H) type in the PB at the time of progression and in the initial skin specimen. Accordingly, a final diagnosis of BpDCN was made.

This case shows some interesting features. First, the initial lack of CD56 points to the fact that the term CD4+/CD56+ hematodermic neoplasm proposed by some authors may be misleading owing to the possible absence of one of these markers as recently reported by Ascani et al. Second, the occurrence of t(6;8) and del(13) and of IgH gene rearrangement expands the spectrum of previous knowledge on the pathobiology of the tumor that was found to be occasionally associated with aberrations of chromosomes 5, 12, 13, 15, and 21 and T-cell receptor γ and/ or δ gene rearrangements. In the present case, a rearranged IgH gene fits with the partial expression of B-cell markers and TdT and underlines the multipotentiality of the precursor cell from which BpDCN arises.

Case 35 involved a 48-year-old man with a 3-month history of multiple, rapidly enlarging, subcutaneous nodules that were initially diagnosed as T-cell lymphoma on an excisional biopsy specimen. Staging investigations, including BM examination, were negative. The patient received cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy with no significant response and died after the sixth cycle. A second opinion on the skin biopsy specimen was requested. This showed subcutaneous tissue replaced by large mononuclear cells with folded to indented nuclei, fine chromatin, small nucleoli, and granular eosinophilic cytoplasm. These were strongly positive for CD4 and weakly positive for CD45 and CD43. Focal localized cytoplasmic positivity was also noted with anti-CD56, CD7, and CD15. B- and T-cell markers, CD30, anaplastic lymphoma kinase, epithelial membrane antigen, human herpesvirus-8, and NPM were negative. The final diagnosis was BpDCN. This case further underlines the difficulties encountered in the recognition of this tumor and the variability of its phenotypic profile.

Case 159 was recorded in a 31-year-old woman who had sudden enlargement of supraclavicular and cervical lymph nodes 1 week postpartum. Lymph node and BM biopsies were performed. Notably, when the patient was 12 years old, she had undergone splenectomy for massive splenomegaly and thrombocytopenia associated with infectious mononucleosis. The spleen was thought to be involved by a “myeloprolif-
erative process” with extramedullary hematopoiesis and a “CD45– blast-like infiltrate.” At that time, a BM biopsy was thought to be affected by the same myeloid proliferation. The original slides were not available for critical review. The patient received no treatment and remained clinically well for 19 years. The lymph node biopsy showed partial effacement of the normal structure due to sheets of blasts (CD43+, partially glycoporphin C+, weakly CD117+, MPO–, CD45–, CD2–, CD3–, CD20–, PAX5–, CD30–, IRF4–, CD79a–, CD21–, CD34–, CD68–, lysozyme–, CD56–, and S-100–, with a Ki-67 proliferation fraction of 100%) located in the paracor-
tex and surrounded by abundant maturing erythroid elements (at times entering the sinuses), some myelocytes, and rare megakaryocytes Image 3F. The BM biopsy was markedly hypercellular with large clusters of blasts resembling those observed in the lymph node and displaying the same pheno-
typic profile. On the marrow aspirate smears, erythroid and myeloid elements demonstrated maturation and blasts corresponded to less than 5% of the examined population. Pronormoblasts were increased, and some erythroid elements showed nuclear irregularities and megaloblastoid features. Cyto genetics and molecular biology (including BCR-ABL1 and JAK2 gene status) did not reveal abnormalities. The
blastic component described above mimicked large cell lymphoma or MS, but immunohistochemical analysis supported its erythroid origin, favoring a diagnosis of prominent pronormoblastic proliferation. According to the microscopic report issued 19 years earlier, the patient was thought to have the same process as in childhood and, therefore, received no therapy. At follow-up, she has remained well for more than 1 year. Based on clinical behavior, cell morphologic features, and lack of chromosomal/molecular abnormalities, this case has been considered reactive. In particular, the erythroid proliferation might have been evoked by a stressing condition (Epstein-Barr virus infection in childhood and pregnancy 19 years later) and related to an abnormal growth factor receptor expression or immunodeficiency.

Case 221 occurred in a 5-year-old boy who had pallor, fatigue, fever, and chest and joint pain in November 2006. CT scans showed multiple lytic bone lesions in the ribs, scapula, sternum, and skull. PB cell counts revealed moderate anemia, a WBC count of 7,200/μL (7.2 × 10⁹/L) with 6% blasts (0.06), and a platelet count of 260 × 10³/μL (260 × 10⁹/L). BM smears were hypercellular, mostly consisting of mononuclear blasts with a high nuclear/cytoplasmic ratio, fine chromatin, and cytoplasmic pseudopodia formation. At fluorescent-activated cell sorting analysis, the blasts were CD13+, CD33+, CD117+, and CD61+. The patient was treated for AML (with possible megakaryocytic differentiation). After the second cycle of chemotherapy, CT scans demonstrated resolution of all bone lesions. The latter were regarded as potentially (ex adiuvantibus) consistent with MS. However, in the absence of any histologic material, a firm diagnosis could not be made by the panel.

Conclusion

The workshop cases provided us with unique insight into the multifaceted manifestation and varied histopathologic characteristics of MS and highlighted the diagnostic challenges encountered in this setting. In particular, the various contexts in which MS may commonly arise and the diverse range of phenotypic and morphologic differentiation, much broader than formerly reported, have been well demonstrated.

References