

Myeloid Sarcoma

Extramedullary Manifestation of Myeloid Disorders

Cristina Campidelli, MD, Claudio Agostinelli, MD, Richard Stitson, FRCPath, and Stefano A. Pileri, MD

Key Words: Myeloid sarcoma; Phenotype; Fluorescence in situ hybridization; FISH; Cytogenetics; Molecular biology

DOI: 10.1309/AJCP1ZA7HYZKAZHS

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 Haematopathology 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.¹ 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, glycophorin 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 11.¹ 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) **Image 1A** and **Image 1C** 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 nonulcerating 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 **Image 1B**.

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

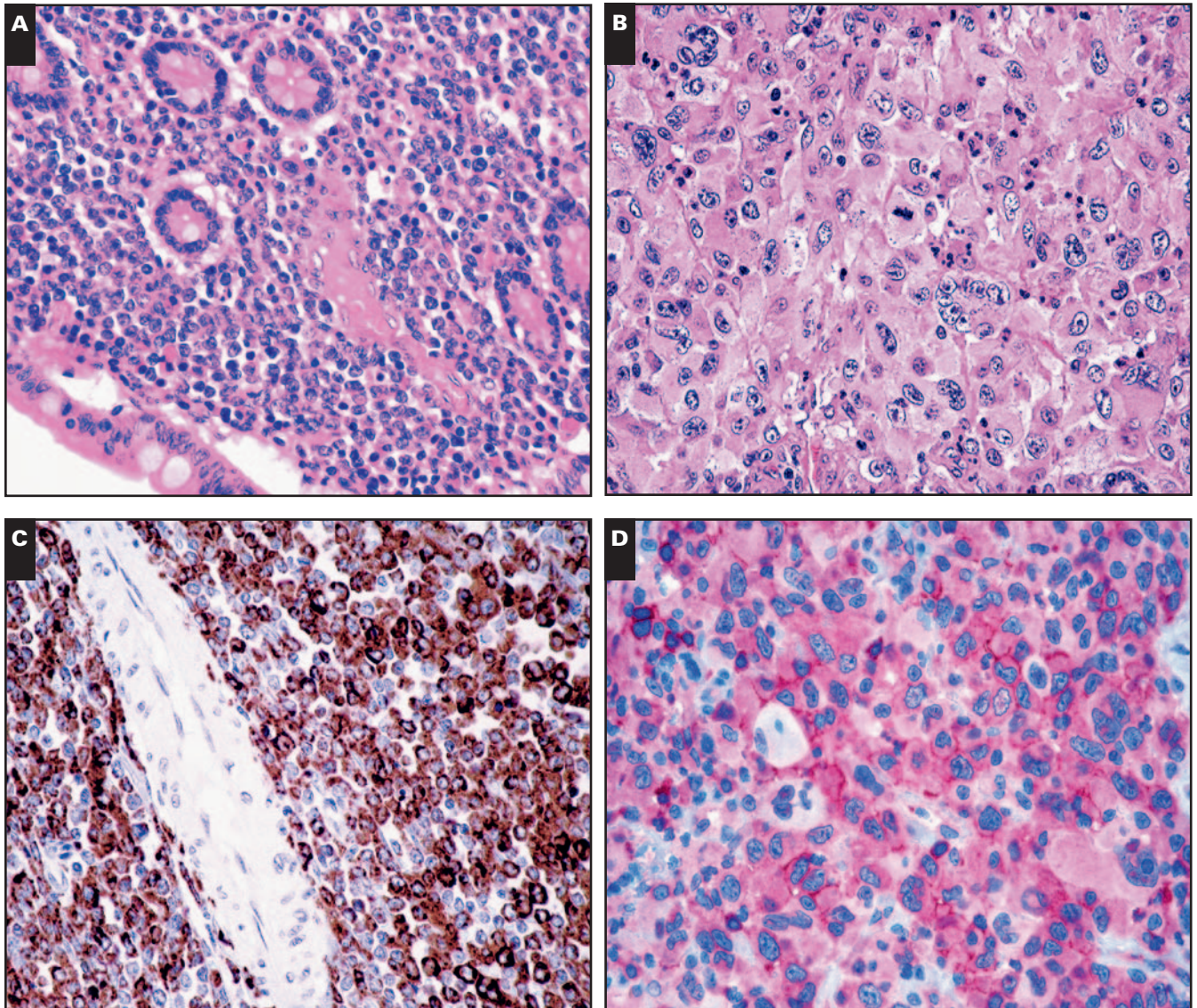
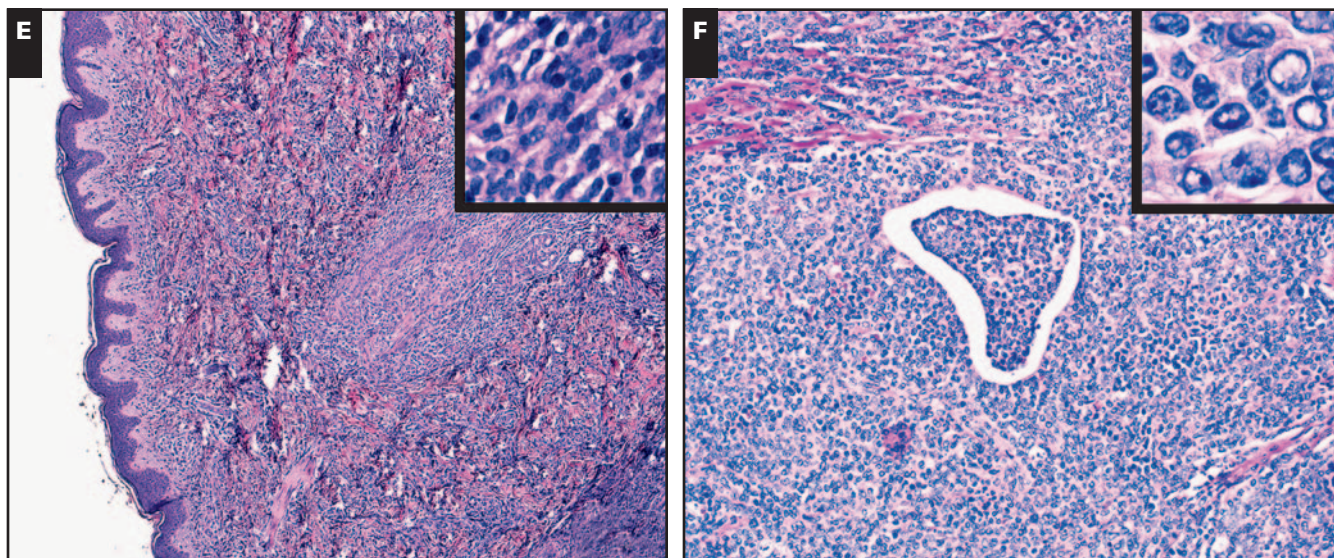


Image 1 **A**, Myeloid sarcoma (MS) involving the ileum (H&E, ×200). **B**, MS with megakaryoblastic differentiation. The neoplasm is composed of large cells and multinucleated giant elements with abundant eosinophilic cytoplasm (H&E, ×400). **C**, MS of the ileum: positivity for CD68-KP1 (immunoperoxidase,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

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;



E, Myelomonocytic MS of the skin. The tumor involves the dermis with perivascular and periadnexal distribution (H&E, $\times 40$). Inset, Cytologic details (H&E, $\times 400$). **F**, Mediastinal MS with infiltration of the lymphatic vessels (H&E, $\times 100$). Inset, The cells are medium-sized with dispersed chromatin and prominent nucleoli (H&E, $\times 600$).

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

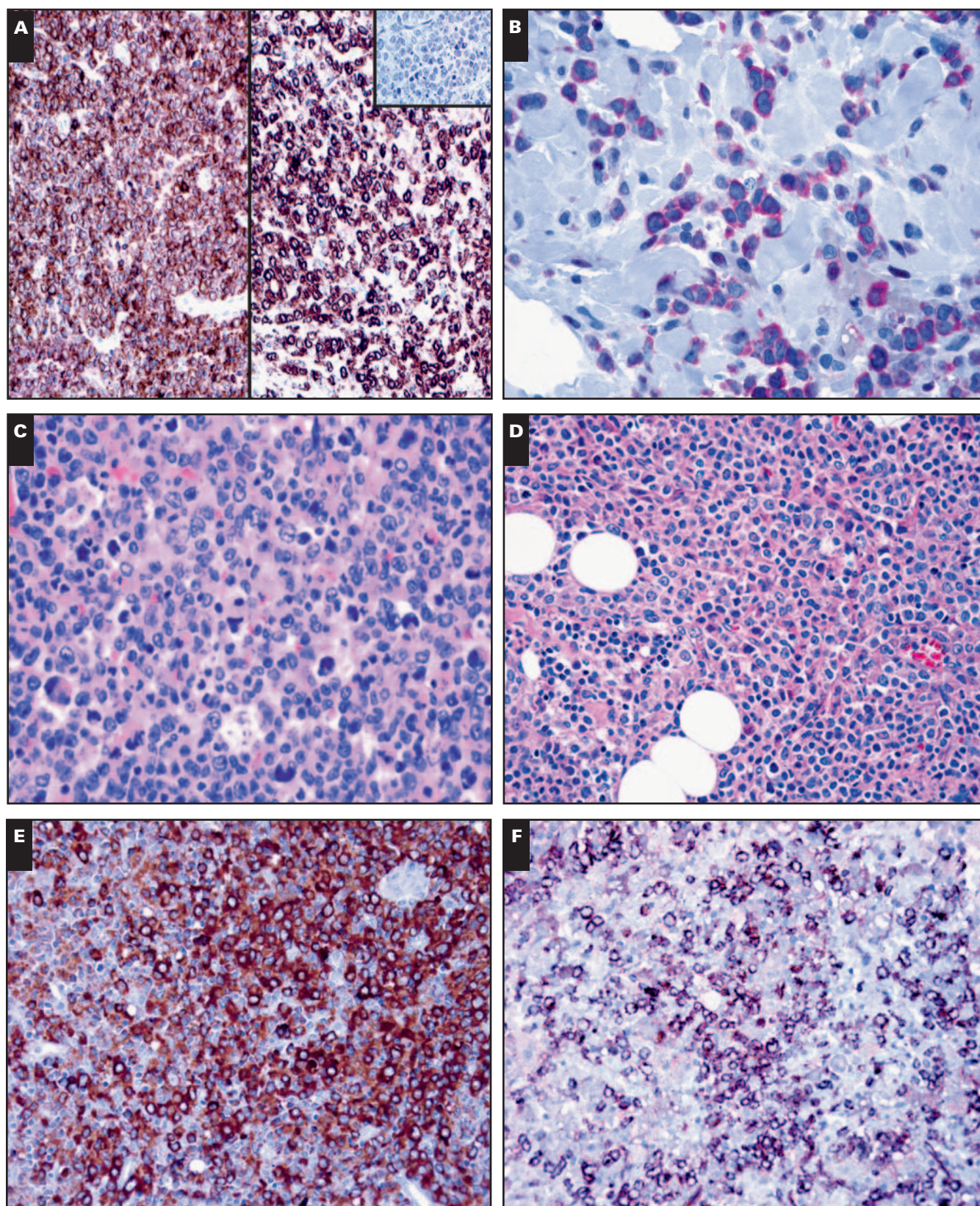


Image 2 **A**, Myeloid sarcoma (MS) of the mediastinum. The tumor expresses CD33 (left) and CD163 (right) (immunoperoxidase, $\times 200$) and is negative for CD123 (inset, $\times 100$). **B**, Nucleophosmin staining in an MS of the gallbladder. Note the cytoplasmic expression of the protein (immunoalkaline phosphatase, $\times 400$). **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, $\times 200$). **D**, Nodal MS with myelomonocytic features (H&E, $\times 200$). In the same case, positivity for myeloperoxidase (**E**) and CD34 (**F**) (**E** and **F**, immunoperoxidase, $\times 200$).

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 ($222.0 \times 10^9/\text{L}$) 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 lwoffii* bacteremia. Unexpectedly, the gallbladder wall was diffusely infiltrated by large atypical cells with abundant cytoplasm, round to folded nuclei, fine chromatin, and occasional small nucleoli, 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 **Image 2B** 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 al¹⁰ 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 [$371 \times 10^9/\text{L}$]), 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 **Image 2C** 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 nucleoli. Immunohistochemical analysis demonstrated a phenotypic profile consistent with cortical thymocytes (CD34+, TdT-/+, CD1a+, CD3e+, 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 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 **Image 2D** that was positive for MPO, CD68, and CD43 **Image 2E**. CD34 and CD45 were partially expressed, whereas the stains for CD117 and NPM were negative **Image 2F**. A diagnosis of MS with myelomonocytic features was made. The BM biopsy was characterized by hypercellularity and erythroid hyperplasia with dysplasia. The picture was regarded as consistent with refractory anemia. Subsequent BM biopsies showed progressive worsening of the MDS that evolved first to refractory anemia with excess blasts-2 and later progressed to overt AML. AML cells were CD34+, CD117+, HLA-DR+, CD13+, and CD33+; had a normal karyotype; and were negative by molecular testing for *JAK2* and *KIT* mutations.

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 was hypercellular and rich in myelomonocytic cells; a trilinear dysplasia was identified with micromegakaryocytes, megaloblastic erythroid precursors, hypergranular and hypogranular myeloid precursors, and 14% blasts. CD68 immunostaining confirmed the increased number of monocytes and allowed a diagnosis of chronic myelomonocytic leukemia (CMML) with excess of blasts. Cytogenetics performed on the BM showed trisomy 8 without evidence of *BCR-ABL1* rearrangement. The peculiarity of this case lies in the fact that MS developed in the soft tissue and represented the first clinical manifestation of the underlying CMML.

Finally, case 210 involved a 55-year-old woman who, 3 months after the diagnosis of CMML, developed subcutaneous skin nodules, particularly evident on the chest wall. A biopsy

from the skin of her right breast was taken, and histologic examination revealed diffuse to focally nodular infiltrates of a blastic population with some tendency to monocytic and granulocytic maturation **Image 3A**. The tumor was positive for lysozyme, CD68, and MPO. It is interesting that the blasts located around epithelial breast ducts revealed a more immature phenotype with expression of CD34 and CD117. Such a finding might represent an example of tumor-environment interaction. In fact, the local environment surrounding the ducts might have induced the proliferation of a more immature population or attracted it, via a homing phenomenon.

Putative MS With Accessory Cell Differentiation

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/ μ L [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 **Image 3B**. 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.²⁰ The present case might represent an example of divergent differentiation of a common aberrant ancestor into MDS/MPN, MS, and LCH at different sites.

The second case (case 130) **Image 3C** and **Image 3D** 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.²¹ 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

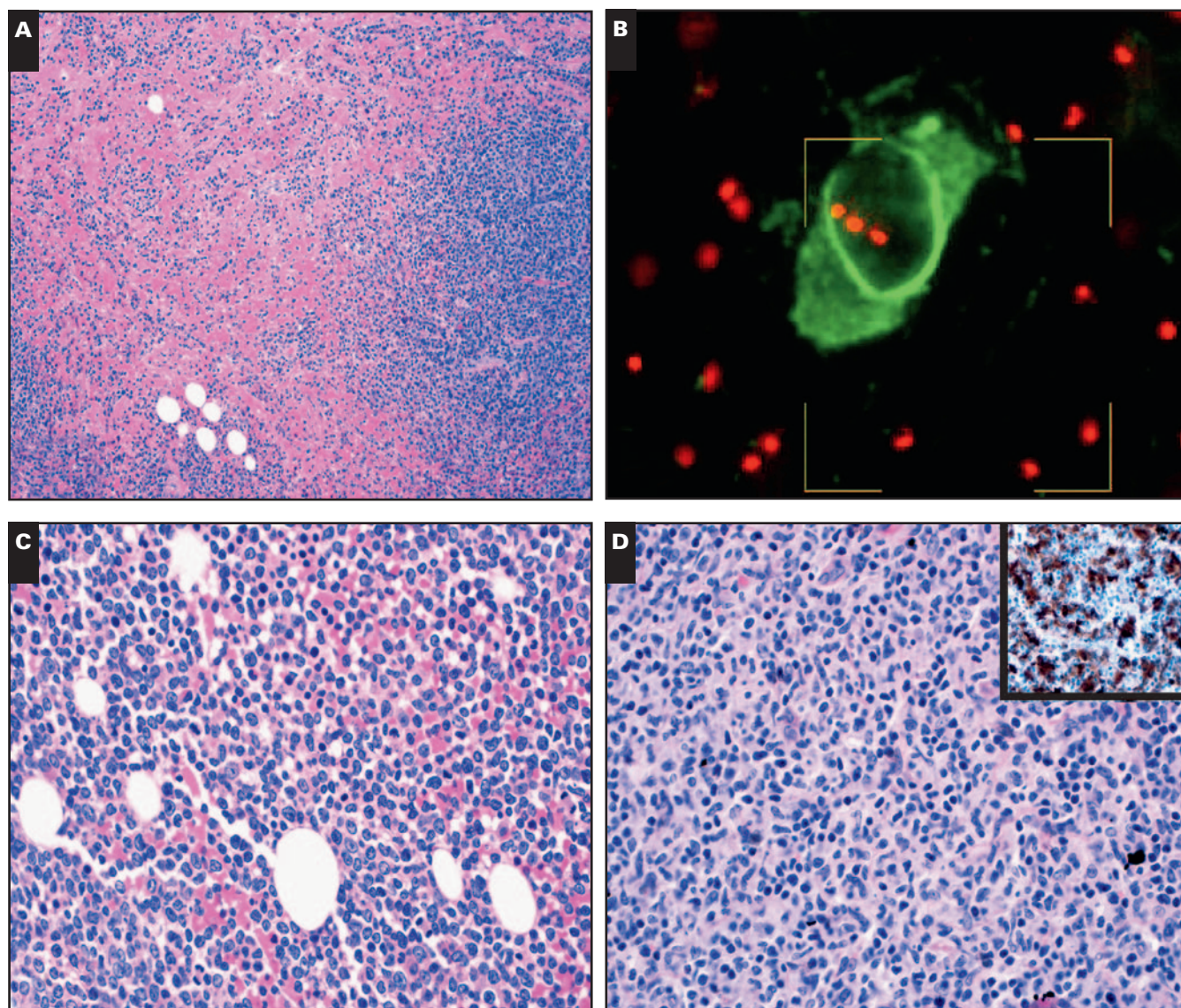


Image 3 **A**, Myeloid sarcoma (MS) of the breast skin in a woman affected by chronic myelomonocytic leukemia (H&E, ×100). **B**, Trisomy 8 detected by fluorescence in situ hybridization analysis in MS and concurrent Langerhans cell histiocytosis. **C**, Acute myeloid leukemia, M4, in the bone marrow. Blasts have round to folded nuclear contours, finely dispersed chromatin, and agranular cytoplasm (H&E, ×200). **D**, In the same case, the extramedullary manifestation shows differentiation to interdigitating dendritic cells (H&E, ×200) that is confirmed by S-100 protein expression (inset, ×100).

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.

Extramedullary 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/ μ L [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, $79 \times 10^3/\mu$ L [79×10^9 /L]) with monocytosis (WBC count, 7,800/ μ L [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-, with a small subset expressing CD117. Immunohistochemical analysis for CD4, CD56, and CD123 was negative, thus excluding a pDC differentiation. The present case also shows quite unusual features, the lymph node being affected not by MS, as generally seen under these circumstances, but rather by extramedullary

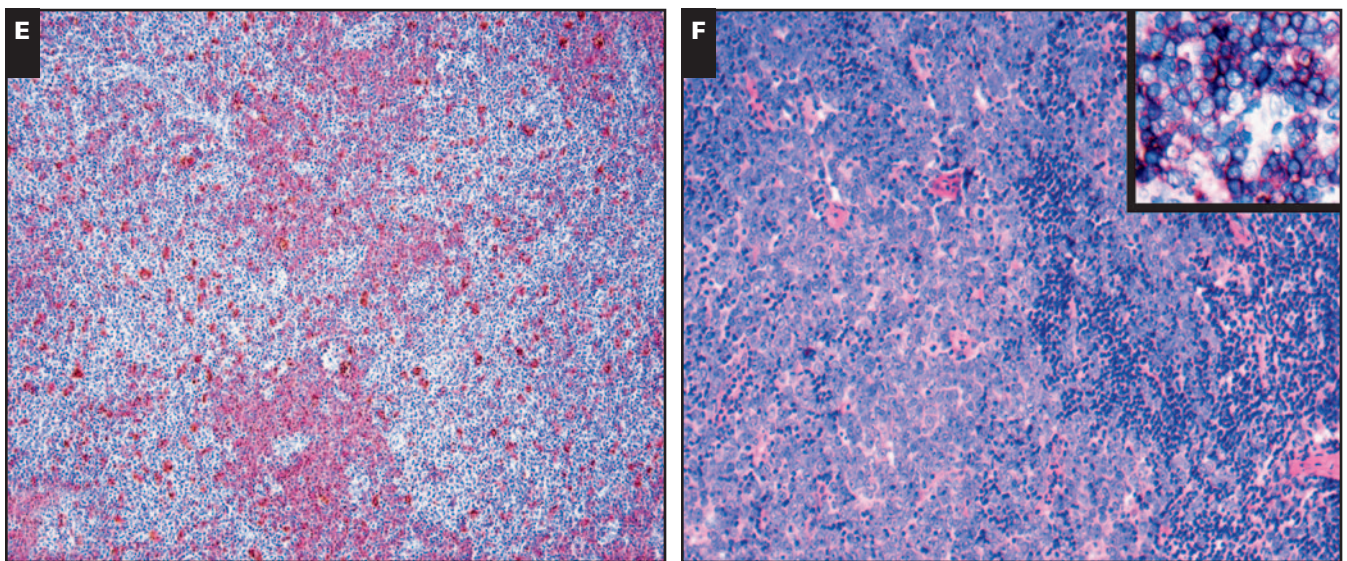


Image 3 (cont) **E**, Partial effacement of the nodal paracortex by clusters of mature plasmacytoid dendritic cells highlighted by CD68-PGM1 staining (immunoperoxidase, $\times 100$). **F**, Sheets of basophilic blasts located in the nodal paracortex (H&E, $\times 100$). Inset, Their erythroid nature is demonstrated by glycophorin C immunostain ($\times 400$).

hematopoiesis. The latter was regarded as a putative manifestation of extramedullary involvement by CMML.

Miscellaneous

This group included 4 cases, 2 of which corresponded to examples of blastic pDC neoplasm (BpDCN).

Case 172 involved a 70-year-old man with a skin lesion of the right flank diagnosed as diffuse large B-cell lymphoma (CD45+, bcl-2+, partially CD20+, and CD10+). A staging BM biopsy was negative. Six cycles of rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy produced a complete remission. One year later, the patient developed malignant circulating cells in the peripheral blood. A BM biopsy showed diffuse infiltration by a blastic population with oval nuclei, fine chromatin, one or more nucleoli, and abundant deeply basophilic cytoplasm without granulation. At fluorescent-activated cell sorting analysis, circulating PB and BM blasts were found to be CD13+, CD33+, CD4+, CD7+, CD45+, CD19–, and CD56– with partial expression of B-cell markers. A diagnosis of AML of ambiguous 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 positivity 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. Cytogenetic studies demonstrated 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^{25,26} may be misleading owing to the possible absence of one of these markers as recently reported by Ascani et al.²⁷ 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.²⁸ 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 “myeloproliferative 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 glycophorin 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 paracortex and surrounded by abundant maturing erythroid elements (at times entering the sinuses), some myelocytes, and rare megakaryocytes. **Image 3F1.** The BM biopsy was markedly hypercellular with large clusters of blasts resembling those observed in the lymph node and displaying the same phenotypic 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. Cytogenetics 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 $7,200/\mu\text{L}$ ($7.2 \times 10^9/\text{L}$) with 6% blasts (0.06), and a platelet count of $260 \times 10^3/\mu\text{L}$ ($260 \times 10^9/\text{L}$). 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 adivantibus*) 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.

From the Unit of Haematopathology, Department of Haematology and Oncological Sciences "L. and A. Seragnoli," St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

Supported by BolognAIL, Cassa di Risparmio in Bologna Foundation, Banca del Monte e Ravenna Foundation, SPES Onlus, and ABSTE, Bologna.

Address reprint requests to Drs Pileri and Campidelli: Unit of Haematopathology, Institute of Haematology and Oncological Sciences "L. & A. Seragnoli," St. Orsola-Malpighi Hospital, University of Bologna, via Massarenti 9, 40138 Bologna, Italy.

References

1. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia*. 2007;21:340-350.
2. Kasahara S, Tsurumi H, Hara T, et al. Idiopathic myelofibrosis developing isolated granulocytic sarcoma with der(1;7)(q10;p10) after splenectomy and finally transforming to acute myelogenous leukemia. *Leuk Lymphoma*. 2000;39:427-433.
3. Cankaya H, Ugras S, Dilek I. Head and neck granulocytic sarcoma with acute myeloid leukemia: three rare cases. *Ear Nose Throat J*. 2001;80:224-226, 228-229.
4. Suzer T, Colakoglu N, Cirak B, et al. Intracerebellar granulocytic sarcoma complicating acute myelogenous leukemia: a case report and review of the literature. *J Clin Neurosci*. 2004;11:914-917.
5. Szomor A, Baranyai F, Tornoczky T, et al. Penile chloroma in a patient with secondary acute myeloid leukemia [letter]. *Eur J Haematol*. 2002;68:322.
6. Imamura T, Matsuo S, Yoshihara T, et al. Granulocytic sarcoma presenting with severe adenopathy (cervical lymph nodes, tonsils, and adenoids) in a child with juvenile myelomonocytic leukemia and successful treatment with allogeneic bone marrow transplantation. *Int J Hematol*. 2004;80:186-189.
7. Elenitoba-Johnson K, Hodges GF, King TC, et al. Extramedullary myeloid cell tumors arising in the setting of chronic myelomonocytic leukemia: a report of two cases. *Arch Pathol Lab Med*. 1996;120:62-67.
8. Hancock JC, Prchal JT, Bennett JM, et al. Trilineage extramedullary myeloid cell tumor in myelodysplastic syndrome. *Arch Pathol Lab Med*. 1997;121:520-523.
9. Maeng H, Cheong JW, Lee ST, et al. Isolated extramedullary relapse of acute myelogenous leukemia as a uterine granulocytic sarcoma in an allogeneic hematopoietic stem cell transplantation recipient. *Yonsei Med J*. 2004;45:330-333.
10. Falini B, Lenze D, Hasserjian R, et al. Cytoplasmic mutated nucleophosmin (NPM) defines the molecular status of a significant fraction of myeloid sarcomas. *Leukemia*. 2007;21:1566-1570.
11. Russell SJ, Giles FJ, Thompson DS, et al. Granulocytic sarcoma of the small intestine preceding acute myelomonocytic leukemia with abnormal eosinophils and inv(16). *Cancer Genet Cytogenet*. 1988;35:231-235.
12. Vermi W, Facchetti F, Rosati S, et al. Nodal and extranodal tumor-forming accumulation of plasmacytoid monocytes/interferon-producing cells associated with myeloid disorders. *Am J Surg Pathol*. 2004;28:585-595.
13. Schwyzer R, Sherman GG, Cohn RJ, et al. Granulocytic sarcoma in children with acute myeloblastic leukemia and t(8;21). *Med Pediatr Oncol*. 1998;31:144-149.
14. Böning H, Göbel U, Nürnberger W. Bilateral exophthalmus due to retro-orbital chloromas in a boy with t(8;21)-positive acute myeloblastic acute leukemia. *Pediatr Hematol Oncol*. 2002;19:597-600.
15. Rubnitz JE, Raimondi SC, Halbert AR, et al. Characteristics and outcome of t(8;21)-positive childhood acute myeloid leukemia: a single institution's experience. *Leukemia*. 2002;16:2072-2077.
16. Gorczyca W, Weisberger J, Seiter K. Colonic adenomas with extramedullary myeloid tumor (granulocytic sarcoma). *Leuk Lymphoma*. 1999;34:621-624.

17. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. *N Engl J Med*. 2005;352:254-266.
18. Tiacci E, Pileri S, Orleth A, et al. PAX5 expression in acute leukemias: higher B-lineage specificity than CD79a and selective association with t(8;21)-acute myelogenous leukemia. *Cancer Res*. 2004;64:7399-7404.
19. Raanani P, Trakhtenbrot L, Rechavi G, et al. Philadelphia-chromosome-positive T-lymphoblastic leukemia: acute leukemia or chronic myelogenous leukemia blastic crisis. *Acta Haematol*. 2005;113:181-189.
20. Christie LJ, Evans AT, Bray SE, et al. Lesions resembling Langerhans cell histiocytosis in association with other lymphoproliferative disorders: a reactive or neoplastic phenomenon? *Hum Pathol*. 2006;37:32-39.
21. Pantano S, Jarrossay D, Sacconi S, et al. Plastic downregulation of the transcriptional repressor BCL6 during maturation of human dendritic cells. *Exp Cell Res*. 2006;312:1312-1322.
22. Chen YC, Chou JM, Ketterling RP, et al. Histologic and immunohistochemical study of bone marrow monocytic nodules in 21 cases with myelodysplasia. *Am J Clin Pathol*. 2003;120:874-881.
23. Vermi W, Bonecchi R, Facchetti F, et al. Recruitment of immature plasmacytoid dendritic cells (plasmacytoid monocytes) and myeloid dendritic cells in primary cutaneous melanomas. *J Pathol*. 2003;200:255-268.
24. Muller-Hermelink HK, Stein H, Steinmann G, et al. Malignant lymphoma of plasmacytoid T-cells: morphologic and immunologic studies characterizing a special type of T-cell. *Am J Surg Pathol*. 1983;7:849-862.
25. Petrella T, Meijer CJ, Dalac S, et al. TCL1 and CLA expression in agranular CD4/CD56 hematodermic neoplasms (blastic NK-cell lymphomas) and leukemia cutis. *Am J Clin Pathol*. 2004;122:307-313.
26. Petrella T, Bagot M, Willemze R, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol*. 2005;123:662-675.
27. Ascani S, Massone C, Ferrara G, et al. CD4-negative variant of CD4+/CD56+ hematodermic neoplasm: description of three cases. *J Cutan Pathol*. 2008;35:911-915.
28. Herling M, Jones D. CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. *Am J Clin Pathol*. 2007;127:687-700.

First and Only FDA Cleared Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager



Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System



Click or Scan
to discover more

ADS-04159-001 Rev 001 © 2024 Hologic, Inc. All rights reserved. Hologic, Genius, and associated logos are trademarks and/or registered trademarks of Hologic, Inc. and/or its subsidiaries in the United States and/or other countries. This information is intended for medical professionals in the U.S. and other markets and is not intended as a product solicitation or promotion where such activities are prohibited. Because Hologic materials are distributed through websites, podcasts and tradeshows, it is not always possible to control where such materials appear. For specific information on what products are available for sale in a particular country, please contact your Hologic representative or write to diagnostic.solutions@hologic.com.

genius™
DIGITAL DIAGNOSTICS