Extramedullary manifestations of neoplastic myeloid disorders

Stefano A. Pileri and Claudio Agostinelli
Chair of Pathology and Unit of Haematopathology
Institute of Haematology and Clinical Oncology “L. and A. Seràgnoli”
Bologna University School of Medicine
EXTRAMEDULLARY MANIFESTATION OF NEOPLASTIC MYELOID DISORDERS

25 CASES WERE SUBMITTED:

• 19 MYELOID SARCOMAS (MS)
• 2 EXTRAMEDULLARY LOCALIZATION OF MDS
• 1 LYMPHOID BLAST CRISIS IN CML
• 2 PLASMACYTOID DENDRITIC CELL PRECURSOR TUMORS
• 1 CASE OF EXTRAMEDULLARY HEMOPOIESIS WITH MARKED PRONORMOBLAST PROLIFERATION
Myeloid sarcoma definition

A tumour mass consisting of myeloid blasts with or without maturation occurring at an anatomic site other than the bone marrow.

Infiltrates at any site of the body by myeloid blasts in leukaemic patients are not classified as myeloid sarcoma unless they present with tumour masses in which the tissue architecture is effaced.
## CASES SELECTED FOR ORAL PRESENTATION

<table>
<thead>
<tr>
<th>Case number</th>
<th>Presenter</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>750012</td>
<td>Kim AS</td>
<td>Chronic myelogenous leukemia in blast crisis with exclusively extramedullary presentation of T-LBL</td>
</tr>
<tr>
<td>750179</td>
<td>Feldman AL</td>
<td>Extramedullary myeloid tumor involving brachial plexus and cerebrospinal fluid</td>
</tr>
<tr>
<td>750017</td>
<td>Dunphy CH</td>
<td>Presentation of erythroblastic sarcoma in lymph node, in patient with previous history of MDS</td>
</tr>
<tr>
<td>750024</td>
<td>Rahemtullah A</td>
<td>MS with inv(16) of the sub-mandibular gland and breast without bone marrow involvement</td>
</tr>
<tr>
<td>750073</td>
<td>Zhao XF</td>
<td>Extramedullary recurrence of AML presenting as acute cholecystitis</td>
</tr>
<tr>
<td>750101</td>
<td>Grier D</td>
<td>Intracranial myeloid sarcoma</td>
</tr>
<tr>
<td>750035</td>
<td>Elkhalifa MY</td>
<td>Plasmacytoid dendritic cell precursor tumor of the skin</td>
</tr>
</tbody>
</table>
Case 750012

SUBMITTERS
Annette S. Kim, Steven Goldstein, Adam Bagg
Allied Hospital Pathologists

PROPOSED DIAGNOSIS
Chronic myelogenous leukemia in sudden blast crisis with an exclusively extramedullary presentation of precursor T-lymphoblastic lymphoma
Case 750012

ADDITIONAL IMMUNOSTAINS:
- CD1a +, CD3 +cyt, CD117 -, TdT +10%, MPO -, lysozyme -, CD163 -.

PANEL DIAGNOSIS:
- Agreed with the proposed diagnosis.

Case 750017

SUBMITTER
Cherie H. Dunphy
University of North Carolina

PROPOSED DIAGNOSIS
Erythroblastic Sarcoma
Case 750017

ADDITIONAL IMMUNOSTAINS:

Glycophorin C +, NPM - (+ in nuclei), MPO not evaluable, CD117 -, lysozyme -.

PANEL DIAGNOSIS:

Agreed with the proposed diagnosis.

COMMENTS:

There was no bone marrow exam concurrent to myeloid sarcoma (21% large unstained cells in the peripheral blood).
Case 750024

SUBMITTERS
Aliyah Rahemtullah, Martin K. Selig, Paola Dal Cin, Robert P. Hasserjian
Massachusetts General Hospital

PROPOSED DIAGNOSIS
AML with inv(16)(FAB AML-M4Eo) presenting as myeloid sarcoma of the sub-mandibular gland and breast without bone marrow involvement
Case 750024

ADDITIONAL IMMUNOSTAINS:
  - foci of plasmacytoid dendritic cells CD123 +, CLA focally +,
    PDGFRa -; leukemic cells were CD2 -, NPMc - (+ in nuclei).

PANEL DIAGNOSIS:
  Agreed with the proposed diagnosis.

COMMENTS:
  Presence of foci of plasmacytoid dendritic cells recently
described in MS carrying inv(16) and presenting the same
chromosomal aberration in both blastic and plasmacytoid
dendritic cell components (Pileri et al Leuk 2007).
ORIGINAL ARTICLE

Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients


1Institute of Hematology and Clinical Oncology ‘L. and A. Seràgnoli’, University of Bologna, Bologna, Italy; 2Institute of Pathologic Anatomy, University of Perugia in Terni, Terni, Italy; 3Chair of Hematology, ‘La Sapienza’ University of Rome, Rome, Italy; 4Division of Pathologic Anatomy, S. Maria Nuova Hospital, Reggio Emilia, Italy; 5Institute of Pathology, University of Turin, Turin, Italy; 6Division of Pathologic Anatomy, Casa Sollievo della Sofferenza Hospital, S Giovanni Rotondo, Italy; 7Institute of Pathologic Anatomy, Vita-Salute S. Raffaele University, Milan, Italy; 8Institute of Pathologic Anatomy, University of Bari, Bari, Italy; 9Division of Pathologic Anatomy, Infermi Hospital, Rimini, Italy; 10Institute of Pathologic Anatomy, University of Palermo, Palermo, Italy; 11Division of Hematology, Bianchi-Melacrino-Morelli Hospital, Reggio Calabria, Italy; 12Institute of Dermatology, University of Bologna, Bologna, Italy; 13Department of Pathology, San Camillo-Forlanini Hospital, Rome, Italy and 14Institute of Haematology, University of Perugia, Perugia, Italy
Case 750035

SUBMITTER
Mohamed Y. Elkhalifa
King Faisal Specialist Hospital

PROPOSED DIAGNOSIS
Plasmacytoid Dendritic Cell Tumor/Leukemia
(also referred to as CD4+/CD56+ hematodermic neoplasm)
Case 750035

ADDITIONAL IMMUNOSTAINS:
  CD56 strongly +, CD123 +, NPM - (+ in nuclei).

PANEL DIAGNOSIS:
  Agreed with the proposed diagnosis.

COMMENTS:
  CD15 positivity unusual. In the forthcoming WHO Classification, precursor plasmacytoid dendritic cell tumor (to be distinguished from MS and HDCTs).
CD4-negative or CD56-negative cases of pPDC exist, and represent a diagnostic problem. The term CD4+/CD56+ hematodermic neoplasm may be misleading, and should probably be revised in the light of all data published in the literature.

‘Agranular CD4+ CD56+ Hematodermic Neoplasm’ (Blastic NK-Cell Lymphoma) Originates From a Population of CD56+ Precursor Cells Related to Plasmacytoid Monocytes

About 17% following FLT3 activation
Case 750073

SUBMITTERS
Xianfeng F. Zhao, Wenle Wang, William Rodgers, Sanford A. Stass
UCI Medical Center

PROPOSED DIAGNOSIS
Extramedullary acute myeloid/monoblastic sarcoma of the gallbladder
Case 750073

ADDITIONAL IMMUNOSTAINS:

NPMc +.

PANEL DIAGNOSIS:

Agreed with the proposed diagnosis.

COMMENTS:

This case showed NPMc +, M5 phenotype and association with trisomy 8 and 13 and FLT3 internal tandem duplication mutation (5-6% of cases carrying NPM mutations. (Falini et al NEJM 2005).
Case 750073

ADDITIONAL IMMUNOSTAINS:

NPMc +.

PANEL DIAGNOSIS:

Agreed with the proposed diagnosis.

COMMENTS:

This case showed NPMc +, M5 phenotype and association with trisomy 8 and 13 and FLT3 internal tandem duplication mutation (5-6% of cases carrying NPM mutations. (Falini et al NEJM 2005).
Case 750101

SUBMITTERS
David Grier, Samer Al-Quran, Ying Li, Brain Gray, Raul Braylan
University of Florida

PROPOSED DIAGNOSIS
Intracranial myeloid sarcoma
Case 750101

ADDITIONAL IMMUNOSTAINS:

PAX5 +, CD79a weakly+, MPO +,
NPMc - (+ in nuclei) (mistake in the book).

PANEL DIAGNOSIS:

Agreed with the proposed diagnosis.

COMMENTS:

PAX5 and CD79a expression described in AML with t(8;21) (Tiacci E et al Cancer Res 2004).
Case 750179

SUBMITTERS
Andrew L. Feldman, Rebecca F. McClure, Curtis A. Hanson
Mayo Clinic

PROPOSED DIAGNOSIS
Extramedullary myeloid tumor involving brachial plexus and cerebrospinal fluid
Case 750179

ADDITIONAL IMMUNOSTAINS:
NPMc⁺ (2/18), CD34⁺.

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis.

COMMENTS:
This case showed NPMc⁺ and normal karyotype, but myeloid phenotype and CD34 positivity (about 2% of cases; Falini et al NEJM 2005).
SUMMARY OF THE REMAINING CASES
# De novo Myeloid Sarcoma

<table>
<thead>
<tr>
<th>ICD-11 Code</th>
<th>Authors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>750173</td>
<td>Hosone M et al.</td>
<td>MS of the ileum</td>
</tr>
<tr>
<td>750207</td>
<td>Mosse CA</td>
<td>MS of the colon presenting with abdominal pain and preoperative diagnosis of adenocarcinoma</td>
</tr>
<tr>
<td>750151</td>
<td>Pileri SA et al.</td>
<td>MS with megakaryoblastic differentiation (soft tissue)</td>
</tr>
<tr>
<td>750071</td>
<td>Ranheim EA et al.</td>
<td>MS with histiocytic differentiation (lymph node)</td>
</tr>
</tbody>
</table>
Association with non haematopoietic tumors

In six cases, a previous history of non-hematopoietic tumor was recorded: embryonal carcinoma of the testis (N=1), prostate carcinoma (N=1), endometrial carcinoma (N=1), breast carcinoma (N=1), intestinal carcinoma with liver metastases (N=1) and association of prostate and larynx carcinoma (N=1).

Finally, a de novo MS was associated with a colonic adenoma.

Phenotypic characteristics

<table>
<thead>
<tr>
<th>Histotype/marker</th>
<th>CD34</th>
<th>TdT</th>
<th>CD99</th>
<th>MPO</th>
<th>CD117</th>
<th>CD68</th>
<th>KP1</th>
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<tbody>
<tr>
<td>1 (N=3)</td>
<td>2+</td>
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<td>3+</td>
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<tr>
<td>2 (N=46)</td>
<td>31+</td>
<td>22+</td>
<td>28+</td>
<td>46+</td>
<td>45+</td>
<td>46+</td>
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<tr>
<td>3 (N=1)</td>
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<td>1+</td>
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<tr>
<td>4 (N=1)</td>
<td>-</td>
<td>1+</td>
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</tr>
<tr>
<td>5 (N=1)</td>
<td>1+</td>
<td>-</td>
<td>1+</td>
<td>-</td>
<td>1+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6 (N=20)</td>
<td>2+</td>
<td>2+</td>
<td>9+</td>
<td>3+</td>
<td>7+</td>
<td>20+</td>
<td></td>
</tr>
</tbody>
</table>
| 7 (N=20)         | 4+   | 2+  | 10+  | 20+ | 17+   | 20+  |    *

CD68 PG-M1  ^CD61/LAT /FVIIIIRAg Gly A+C  CLA  CD56  CD4

Patho-biology of myeloid sarcoma
SA Pileri et al

Leukemia (2007) 21, 340-350
Case 750173
Submitters: M. Hosone, Y. Sugisaki, S. Maeda, Z. Naito
Clinical History: A 36-year-old Japanese male with lower abdominal pain due to intestinal obstruction. Partial resection of the ileum. Whole body CT: no lymph node swelling, no other tumor masses nor hepatosplenomegaly. The CBC on admission was normal. Bone marrow aspirates showed normocellular marrow.

PHENOTYPE: MPO +, CD68-KP1 +, CD68PGM1 +/-, CD117 +/-, NPMc −, CD43 +, CD45 +, CD45RO −, CD3 −, CD20 −, CD79a −.
PROPOSED DIAGNOSIS:
Myeloid sarcoma/granulocytic sarcoma of ileum.
*Myeloid/granulocytic sarcoma of small intestine/ileum is a rare manifestation of extramedullary acute myeloid leukemia in previous reports.*

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
Case 750207
Submitter: C.A. Mosse

Clinical History: 79-yr-old male with abdominal pain of two weeks duration. CBC not available. At colonoscopy: non-ulcerating mass in the transverse colon. Endoscopic biopsies non-diagnostic. On CT, the mass was several cm in diameter and appeared to encroach the transverse colon invading the mucosa. Exploratory laparotomy was performed and identified numerous masses in the mesentery and adjacent to the transverse colon. Fragments of mass in transverse colon and gastro-colon ligament.

PHENOTYPE: Flow cytometry: CD45+, CD13+, CD64+, HLA-DR+, CD7+, CD117+, CD14 weak+, CD34-, MPO-, cytCD79a-, cytCD3-, CD1a-, CD8-, CD5-, CD2-.

Immunohistochemistry: Lysozyme+, CD43+, MPO-, CD3-.
**PROPOSED DIAGNOSIS:**
Extramedullary myeloid tumors.
The presentation in this case was unusual with abdominal pain as the presenting symptom and suspected adenocarcinoma of the colon as the pre-operative diagnosis.

**PANEL DIAGNOSIS:**
Agreed with the proposed diagnosis.
Case 750151

Submitters: S.A. Pileri, E. Sabattini, C. Campidelli, C. Agostinelli, F. Bacci

Clinical History: 67-yr-old male operated in January 2005 for a right inguinal hernia, which relapsed the following September needing a second surgical procedure. Soon after, a rapidly growing mass observed at the site of surgical wound: a biopsy was performed. Peripheral blood: Hb 7.2g/dL, WBC 32,000/mm3 with neutrophilia, platelets 335,000/mm3. After diagnosis, a BM aspirate and biopsy showed mild dyserythropoiesis with macrocytic features. At CAT, a 20 cm-across mass in the context of the abdominal wall, provided with extensive necrosis, which reached the small pelvis, compressed bladder and colon, with femoral thrombosis. CHT was initiated, in spite of initial regression, the inguinal mass rapidly regrew ulcerating the skin with massive bleeding. The patient underwent surgery for debulking and haemostasis, but deceased in February 2006.

Phenotype:
IHC performed: CD1a, CD2, CD3, CD7, CD20, CD21, CD34, CD45, CD56, CD61, CD68K, CD68P, CD117, MPO, LAT, FVIII related antigen, S100, lysozyme, HECA, KWS, HMB45. The neoplastic cells were only positive for CD61 and LAT, being negative for all the remaining markers.
FISH ANALYSIS:
Monosomy of chromosome 5 was detected in routine sections.

MOLECULAR ANALYSIS:
N/A

PROPOSED DIAGNOSIS:
Myeloid sarcoma with megakaryoblastic differentiation

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis

Facchetti F et al. Linker for activation of T cells (LAT), a novel immunohistochemical marker for T cells, NK cells, mast cells, and megakaryocytes: evaluation in normal and pathological conditions. AJP 1999; 154:1037-46.
<table>
<thead>
<tr>
<th>Abnormality</th>
<th>FISH</th>
<th>Site(s) involved</th>
<th>De novo MS</th>
<th>MS aroused after</th>
<th>MS synchronous to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosomy 7 failure</td>
<td>10/56 (17.8%)</td>
<td>Skin+testis</td>
<td>RA</td>
<td>CML</td>
<td>AML-M1</td>
</tr>
<tr>
<td>Positivity</td>
<td>5/46 (10.8%)</td>
<td>Testis, Pericardium, Bone+soft tissues, Uterus+breast</td>
<td>RAEB-1</td>
<td></td>
<td>AML-M5</td>
</tr>
<tr>
<td>Trisomy 8 failure</td>
<td>8/56 (14.3%)</td>
<td>Testis, Breast++</td>
<td>AML-M2</td>
<td></td>
<td>AML-M5</td>
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<tr>
<td>Positivity</td>
<td>5/48 (10.4%)</td>
<td>Skin, Lymph node</td>
<td>AML-M4</td>
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<td>AML-M5</td>
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<tr>
<td>MLL splitting</td>
<td>9/56 (16%)</td>
<td>Lung</td>
<td>AML-M4</td>
<td></td>
<td>AML-M5</td>
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<tr>
<td>Failure</td>
<td>4/47 (8.5%)</td>
<td>Breast++</td>
<td>AML-M5++</td>
<td>IMF</td>
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<tr>
<td>Positivity</td>
<td>12/56 (21.4%)</td>
<td>Ileum+bone+brain</td>
<td>AML-M4</td>
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<td>Trisomy 4 Failure</td>
<td>2/44 (4.5%)</td>
<td>Kidney</td>
<td>CML</td>
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<td>Positivity</td>
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<td>Lymph node#</td>
<td>5q- syndrome#</td>
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<td>Monosomy 16 failure</td>
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<td>Testis</td>
<td>AML-M5</td>
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<td>Positivity</td>
<td>1/44 (2.3%)</td>
<td>Skin#</td>
<td>AML-M5$</td>
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<td>16q- Failure</td>
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<td>Lymph node#</td>
<td>5q- syndrome#</td>
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<tr>
<td>Failure</td>
<td>2/38 (6.2%)</td>
<td>Lymph node#</td>
<td>5q- syndrome#</td>
<td></td>
<td></td>
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<tr>
<td>20q- Failure</td>
<td>15/56 (26.8%)</td>
<td>Skin+brain</td>
<td>AML-M5</td>
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</tr>
<tr>
<td>Positivity</td>
<td>1/41 (2.4%)</td>
<td>Testis</td>
<td>AML-M5</td>
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<tr>
<td>AML1/ETO fusion failure</td>
<td>12/56 (21.4%)</td>
<td>Skin+brain</td>
<td>AML-M5</td>
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<tr>
<td>Positivity</td>
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<td>Trisomy 11</td>
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<tr>
<td>11q- Failure</td>
<td>10/56 (17.8%)</td>
<td>Testis</td>
<td>AML-M5</td>
<td></td>
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<tr>
<td>Positivity</td>
<td>1/46 (2.2%)</td>
<td></td>
<td>AML-M5</td>
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</tbody>
</table>
Case 750071
Submitters: E.A. Ranheim, C.P. Leith
Clinical History: 42-yr-old male with a history of sarcoidosis presented with a left neck mass. Excisional biopsy mostly consistent with myeloid sarcoma. BM bx was negative. Imaging revealed lung lesions, pericardial lymphadenopathy, and mass-like lesions in the spleen. Core biopsy of the spleen revealed extensive caseating granulomas. Urinary histoplasma Ag was positive. Splenectomy 6 months after presentation again showed caseating granulomas. Adenopathy persisted. Biopsy of a left cervical lymph showed MS with histiocytic differentiation. The patient was treated with ABMT and has done well.

Phenotype:
IHC of the initial neck mass revealed that the atypical cells expressed CD45, CD68, CD43, and lysozyme. MPO was noted only in scattered cells. The tumor cells did not express CD3, CD20, CD5, CD21, CD30, CD15, CD138, S100, CD1a, CD34, CD117, NPMc, nor CMV ag. The second biopsy showed similar immunoreactivity but failed to show any MPO staining and was positive for CD163.
PROPOSED DIAGNOSIS:
Myeloid sarcoma with histiocytic differentiation

PANEL DIAGNOSIS:
Differential diagnosis includes monocytic sarcoma and histiocytic sarcoma (possible differentiation).
Myeloid Sarcoma associated with or followed by AML

<table>
<thead>
<tr>
<th>Case number</th>
<th>Presenter</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>750042</td>
<td>Zukerberg L</td>
<td>MS with monocytic features and <strong>MLL rearrangement</strong> involving skin, with bone marrow suspicious for early involvement by AML</td>
</tr>
<tr>
<td>750135</td>
<td>Xie X</td>
<td>MS of bone manifesting clinically as <strong>AML-M3 with t(15;17)</strong> six months later</td>
</tr>
<tr>
<td>750129</td>
<td>Feldman AL et al.</td>
<td>AML with monocytic differentiation presenting as a mediastinal mass and acute cardiac tamponade</td>
</tr>
</tbody>
</table>
Case 750042
Submitter: L. Zukerberg

Clinical History: Eleven-month-old-girl who at the age of five months developed multiple 2-5 mm red-brown papules on the face, trunk and extremities. These lesions were asymptomatic and some appeared to regress spontaneously (biopsied twice).

PHENOTYPE:
Immunohistochemistry on the skin \( \text{CD117}^+, \text{CD34}^+, \text{CD68}^+ \) and lysozyme \(+\), CD1a \(-\), Tryptase \(-\) and MPO \(-\), Ki-67 90%.
Flow cytometry performed on the bone marrow aspirate revealed an abnormal population of blasts CD33 \(+\) and CD34 \(+\), with partial expression of CD 117 and CD14 \(-\) or MPO \(-\). These accounted for 4 - 6% of the total cells.
CYTOGENETICS:
FISH evaluation of the skin biopsy rearrangement at 11q13 (MLL); no abnormality was noted in chromosome 8.
Both marrow aspirates (performed 2 days apart) showed no clonal cytogenetic abnormalities

PROPOSED DIAGNOSIS:
Skin: myeloid sarcoma with monocytic features and MLL rearrangement by FISH.
BM: atypical population of blasts with monocytic and monoblastic features negative for MLL rearrangement, suspicious for early marrow involvement by AML.
It is puzzling that the MLL rearrangement was seen in the skin biopsies (initially and at recurrence) but never in the bone marrow biopsies (2 pre-treatment and 3 after treatment). Multiple hematopathologists reviewed the original bone marrow biopsies and all felt there was marrow involvement. However the lack of detectable translocation raises the possibility that the marrow blasts could be reactive and not leukaemic

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
<table>
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<td>Positivity</td>
<td>5/46 (10.8%)</td>
<td>Skin+testis</td>
<td>Testis</td>
<td>Pericardium</td>
<td>RAEB-1</td>
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<td></td>
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<td></td>
<td>Bone+soft tissues</td>
<td></td>
</tr>
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<td>Testis</td>
<td>+</td>
<td></td>
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<td>5/48 (10.4%)</td>
<td>Skin</td>
<td>Testis</td>
<td>Breast++</td>
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<td>Lymph node</td>
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<td>Uterus+breast</td>
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<td>Skin</td>
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<td>AML-M4</td>
</tr>
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<td>4/47 (8.5%)</td>
<td>Lung</td>
<td></td>
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<td>AML-M5</td>
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<tr>
<td></td>
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<td></td>
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<td>Breast++</td>
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<td></td>
<td>Lymph node+bone</td>
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<td></td>
<td>Ileum+bone+brain</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ileum</td>
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</tr>
<tr>
<td>CBF-beta splitting failure</td>
<td>12/56 (21.4%)</td>
<td>Kidney</td>
<td></td>
<td></td>
<td>AML-M4</td>
</tr>
<tr>
<td>Positivity</td>
<td>2/44 (4.5%)</td>
<td></td>
<td></td>
<td></td>
<td>CML</td>
</tr>
<tr>
<td>Trisomy 4 Failure</td>
<td>11/56 (19.6%)</td>
<td>Lymph node#</td>
<td>5q-- syndrome#</td>
<td>5q-- syndrome#</td>
<td></td>
</tr>
<tr>
<td>Positivity</td>
<td>2/45 (4.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monosomy 16 failure</td>
<td>12/56 (21.4%)</td>
<td>Testis</td>
<td></td>
<td></td>
<td>AML-M5</td>
</tr>
<tr>
<td>Positivity</td>
<td>1/44 (2.3%)</td>
<td>Skin$</td>
<td></td>
<td></td>
<td>AML-M5$</td>
</tr>
<tr>
<td>16q- Failure</td>
<td>12/56 (21.4%)</td>
<td></td>
<td></td>
<td></td>
<td>AML-M5</td>
</tr>
<tr>
<td>Positivity</td>
<td>1/44 (2.3%)</td>
<td>CNS</td>
<td>5q-- syndrome#</td>
<td></td>
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<tr>
<td>5q- Positivity</td>
<td>18/56 (32.1%)</td>
<td>Lymph node#</td>
<td>+</td>
<td>5q-- syndrome#</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>2/38 (5.2%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20q- Failure</td>
<td>15/56 (26.8%)</td>
<td>Skin$</td>
<td></td>
<td></td>
<td>AML-M5$</td>
</tr>
<tr>
<td>Positivity</td>
<td>1/41 (2.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AML/ETO fusion failure</td>
<td>12/56 (21.4%)</td>
<td>Skin+brain</td>
<td></td>
<td></td>
<td>AML-M5</td>
</tr>
<tr>
<td>Positivity</td>
<td>1/44 (2.2%)</td>
<td>Testis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 11 Failure</td>
<td>10/56 (17.8%)</td>
<td></td>
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</tr>
<tr>
<td>Positivity</td>
<td>1/46 (2.2%)</td>
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</table>
Case 750135
Submitter: X. Xie
Clinical History: 54-yr-old female with severe back pain. MRI of the lumbar spine: multiple focal bony lesions. CBC WBC 11.2. Biopsy of the L3 bone lesion (Biopsy #1) was performed at an outside hospital. At the time, it was classified as atypical myeloid infiltrate, d.d. included AML and MPD. BM: due to extremely low level and focal involvement by APL, a diagnosis of APL was not made at the time. It was elected to follow the patient closely clinically. At the meantime, BCR-ABL and JAK2 V617F were done and they were negative. Six months later, the patient presented with WBC 0.73, Hemoglobin 11.3, Plt 122. Lymph.s 48, Mono.s 11, Differential: Seg.s 41, Eos0, Baso.s 0. A bone marrow biopsy was repeated (Biopsy #2).

Phenotype:
Biopsy #1: MPO +, CD15 +, NPMc -
Biopsy #2: Flow cytometry: blasts express CD13, CD33, CD117, CD65, and dim CD19. A subpopulation of the blasts expresses CD34 and CD2
CYTOGENETICS:
Biopsy #2 Bone marrow: 46, XX, t(15;17)/46, XX

FISH ANALYSIS:
Biopsy #2: t(15;17) and RARα gene

PROPOSED DIAGNOSIS:
Biopsy #1: Granulocytic sarcoma, acute promyelocytic leukemia.
Biopsy #2: Acute promyelocytic leukemia (AML with t(15;17)(q22;q12))
Initial presentation of acute promyelocytic leukemia at an extramedullary site is extremely rare with only few cases have been reported in the literature. Majority of extramedullary presentation of APL reported in the literature are patients with relapse APL.

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
Case 750129
Submitters: A.L. Feldman, C.A. Hanson, P.J. Kurtin

Clinical History: A 25-yr-male was admitted to a local hospital and felt to have an acute abdomen. Laparotomy revealed only ascites. He became hemodynamically unstable intraoperatively and a pericardial effusion was noted and drained. On transfer to our institution, WBC was 40.9, and BM biopsy was performed. CT revealed a large mediastinal mass. Emergency thoracotomy revealed a pericardial effusion with cardiac tamponade and anterior pericardiectomy was performed. The mediastinal mass was debulked. The patient received idarubicin and ARA-C, but had persistent disease and underwent BMT. He relapsed quickly and died.

Flow cytometry on mediastinal mass: CD33, CD34, CD38, CD13, HLA-DR, CD11b were +
CD2, CD3, CD5, CD7, CD56, CD10, CD19, CD20, CD22, CD14, CD41, CD61 were negative
IHC: CD45 +, CD33 +, CD163 +, Lys +; CD20, CD3, CD10, Pax5, CD4, CD7, CD68, CD117, CD123, CD34, MPO, NPMc were negative
CYTOGENETICS:
BM: 47-49,X,-Y,add(2)(p23),-4,+6,add(7)(p15),-9,-11,der(11)t(4;11)(q21;p15),
+13,add(17)(p11),add(19)(p13.3),add(22)(q11.2),+2-6mark[cp13]/46,XY

MOLECULAR ANALYSIS:
N/A

PROPOSED DIAGNOSIS:
Acute myeloid leukemia with monocytic differentiation, presenting as a mediastinal mass and acute cardiac tamponade

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
### Myeloid Sarcoma associated with CML

<table>
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<tr>
<th>Case number</th>
<th>Presenter</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>750136</td>
<td>Taddesse-Heath L</td>
<td>MS in a patient with CML in chronic phase in bone marrow</td>
</tr>
<tr>
<td>750210</td>
<td>Racke FK et al.</td>
<td>MS involving the breast</td>
</tr>
</tbody>
</table>
Case 750136
Submitter: L. Taddesse-Heath

Clinical History: 28-yr-old male with no significant past medical history, presenting with leukocytosis, splenomegaly and lymphadenopathy. CBC showed WBC of 371K, HB 10.3 g/dl, PTL 141K with a differential of 40% neutrophils, 10% bands, 20% metamyelocytes, 12% myelocytes, 5% promyelocytes, 7% myeloblasts, 4% basophils, 1% lymphocyte and 1% monocytes. LN, BM bx.s and BM aspirate were performed.

PHENOTYPE
Flow cytometry analysis of BM showed 94% of CD45 + cells showing a continuous spectrum of myeloid differentiation with 1% myeloblasts.
Flow cytometry analysis of LN showed 36% for CD34, CD13, HLA-DR, CD33 and MPO
IHC of LN: myeloblasts MPO +, CD34 +, CD68PGM1 - (weak+), NPMc -
CYTOGENETICS:
t(9;22)(q34;q11.2) was observed in all metaphases in the BM and LN

MOLECULAR ANALYSIS:
N/A

PROPOSED DIAGNOSIS:
Extramedullary manifestation of blast crisis (Myeloid sarcoma) in a patient with chronic phase of CML in the bone marrow at initial presentation

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
Case 750210
Submitters: F.K. Racke, W.L. Marsh

Clinical History: 55-yr-old-female diagnosed in Nov. 2006 with CML. In early January, 2007, the patient received a short trial of Decitabine (20mg/m2) for worsening counts. One month later, the patient reported the development of subcutaneous skin nodules, particularly evident on the breast. A bx. of the skin nodule was performed. CBC: WBC, 0.9; Hgb/Hct, 10.1/28.8%; plt, 190 k.

PHENOTYPE
Lysozyme +, CD68 +, CD43 +, MPO +, but negative for lymphoid markers. Interestingly, CD34 and c-kit highlight immature cells that are primarily centered around cytokeratin positive ducts with only scattered CD34 and c-kit positive cells within the more diffuse and differentiated areas of the infiltrate. Mib-1 (Ki-67) was also increased within the nodules.
CYTOGENETICS:
At diagnosis, in BM deletion of chromosome 7q22

FISH ANALYSIS:
N/A

MOLECULAR ANALYSIS:
N/A

PROPOSED DIAGNOSIS:
Myeloid sarcoma involving the breast.
The case illustrates an interesting example of tumor-environment interaction.

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
Nothing is known concerning ABL/BCR.
### Extramedullary manifestations of MDS/MPN

<table>
<thead>
<tr>
<th>Reference</th>
<th>Author(s)</th>
<th>Case Description</th>
</tr>
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<tbody>
<tr>
<td>750010</td>
<td>Zhang K</td>
<td>Possibly <strong>CMML</strong> in bone marrow with extramedullary localization in lymph node and proliferation of plasmacytoid monocyte</td>
</tr>
<tr>
<td>750142</td>
<td>Kreisel FH</td>
<td><strong>CMML</strong> with extensive lymphadenopathy due to extramedullary hematopoiesis likely representing involvement by CMML</td>
</tr>
<tr>
<td>750204</td>
<td>Kovarik P et al</td>
<td><strong>MS</strong> with partial monocytic differentiation of soft tissue and <strong>CMML</strong> with excess of blasts in BM</td>
</tr>
<tr>
<td>750212</td>
<td>Fan G et al</td>
<td><strong>MPD/MDS</strong> with lymph node involvement and transformation to acute myeloid leukemia</td>
</tr>
</tbody>
</table>
**Case 750010**

**Submitter:** K. Zhang

**Clinical History:** 38-yr-old male with leukocytosis (CBC:15.5K/ul with 17% monos) and progressive cervical lymph node enlargement. BM and cervical lymph node bx.s obtained.

**Phenotype on lymph node:** CD4 +, CD68 +, Lysozyme +, CD123 +, HECA weakly+, CD56 -, CD34 -, weakly + for CD45, CD43, CD7, CD10; some precursors CD34 +, MPO +, CD99 +.
CYTOGENETICS
BM aspirate: normal, XY

MOLECULAR ANALYSIS
LN: negative for TCR (gamma by PCR)

PROPOSED DIAGNOSIS
LN: uncommon case of MPD with tumor proliferation of plasmacytoid monocytes (PDC)
BM: Chronic myeloproliferative disorder (possibly CMML)

PANEL DIAGNOSIS
Agreed with the proposed diagnosis. NPMc − (+ in nuclei).
Nodules of PDCs can be observed in MDS and AML carrying the same chromosomal abnormality as the primary disease

Similar lesions have been noted in myeloid sarcoma along with inv16 (Pileri SA et al, Leukemia 2007, 21: 350-60).
Müller-Hermelink HK, Steinman G, Stein H, Lennert K.
Malignant lymphoma of plasmacytoid T-cells. Morphologic and immunologic studies characterizing a special type of T-cell.

• Elderly patients.
• Hepato-splenomegaly.
• Generalized lymphadenopathy.
• Various forms of acute and chronic myeloid neoplasms (esp. myelo-monocytic leukaemia).
• Outcome is usually rapidly fatal and appears to be related to the associated disorders rather than to progressive expansion of PM.
Case 750142  
Submitter: F.H. Kreisel  
Clinical History: 86-year-old female with abdominal pain and bilateral axillary and retrocrural lymphadenopathy. Spleen normal. CBC: 20.4x103/mcl with 47% mono.s, anemia and thrombocytopenia. LN and BM bx.s were obtained. The patient died one year later for acute melena. Family history was significant for an identical twin sister who died one year earlier of some sort of leukemia.

PHENOTYPE (LN): maturing myeloid elements Leder +, CD43 +, MPO +, CD34 -, with small subset CD117 +; CD68/KP1, CD68/PG-M1, CD163, lysozyme highlighted mature histiocytes within sinuses and monocytic cells in EMH aggregates; CD4 and CD56 were negative
CYTOGENETICS:
BM normal female karyotype

MOLECULAR ANALYSIS:
N/A

PROPOSED DIAGNOSIS:
CMML with extensive lymphadenopathy due to extramedullary hematopoiesis likely representing involvement by CMML

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis. NPMc− (⁺ in nuclei).
NPM mutations and MDS & MPN/MDS

• Not one of 50 patients with myelodysplastic syndrome and normal karyotype (including pediatric patients) of the GIMEMA protocol, had an \textit{NPM1} gene mutation. Moreover, one should be extremely cautious in reporting a case as "myelodysplastic syndrome expressing \textit{NPM1} mutations", since AML carrying \textit{NPM1} mutations is frequently associated with multi-lineage involvement and dysplastic features (Blood 108:4146-4155, 2006).

• In the past, cases of AML with t(8;21) were also misdiagnosed as MDS (Leuk Res 18:761-765, 1994; Ann Hematol 76:279-282; Ann Hematol 80:763-766, 2001).
Case 750204

Submitters: P. Kovanik, C. Kohnli, S. Nathan, R. Catchatourian

Clinical History: 64-yr-old male who presented to the emergency room with a left foot ulcer which developed after a spider bite four months prior. At examination on the left foot, there was a firm lobulated lesion with no radiographic evidence of bony destruction. CBC WBC 4,800/mm, Hemoglobin 8.5 g, Platelets 121,000/mm. Following examination of the debrided tissue, the patient also underwent bone marrow biopsy and aspirate.

PHENOTYPE:
IHC demonstrated that the large cells were positive for LCA and partially for both CD68 and CD15, thus suggesting both granulocytic and monocytic differentiation.
**CYTOGENETICS:**
BM : 47,XY, +8

**FISH ANALYSIS:**
FISH analysis did not detect evidence of BCR/ABL gene rearrangement

**PROPOSED DIAGNOSIS:**
Soft tissue of left foot: Granulocytic sarcoma with partial monocytic differentiation.
Bone marrow: Myeloproliferative/myelodysplastic disorder compatible with CMML with excess of blasts

**PANEL DIAGNOSIS:**
Possible but additional immunostains are essential for definitive diagnosis; absolute monocyte count not provided.
Case 750212

Submitters: G. Fan, R. Braziel, K. Gatter, M. Loriaux, J. Huang

Clinical History: 46-yr-old woman, HCV+, presented with right axillary and right inguinal lymphoadenopathy. Patient had one bone marrow biopsy done in 1996 due to leukocytosis and pathology report stated normal cellular BM. The right axillary node biopsy was done at 5/2005. BM biopsy showed refractory anemia without increase in blasts. 5/06 BM biopsy revealed RAEB-II (12% blasts). 11/06 and 12/06 BM bx.es showed same feature. Patient received chemotherapy. 1/07 severe pancytopenia with AML in BM

Phenotype:

LN: The myeloid precursors are positive for MPO, CD68/PGM1, CD43, and partial CD45; negative for CD117, CD34, NPMc.

BM blasts by flow: CD45 dim, CD34, CD117, HLA-DR, CD13 dim, CD33 dim
CYTOGENETICS:
Normal

MOLECULAR ANALYSIS:
JAK2 and Kit mutations were negative

PROPOSED DIAGNOSIS:
Myeloproliferative/myelodysplastic syndrome with lymph node involvement and final transformation to acute myeloid leukemia.

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis.
### Extramedullary Manifestations of Neoplastic Myeloid Disorders with Accessory Cell Differentiation

<table>
<thead>
<tr>
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<th>Description</th>
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<td>750108</td>
<td>Hasserjian RP</td>
<td>Atypical CML with differentiating extramedullary MS and Langerhans cell histiocytosis, involving skin and lymph node clonally related to atypical CML</td>
</tr>
<tr>
<td>750130</td>
<td>Grogg KL et al</td>
<td>AMML, with extramedullary differentiation to interdigitating dendritic cell tumor</td>
</tr>
</tbody>
</table>
Case 750108
Submitter: R.P. Hasserjian

Clinical History: 80-yr-old female presenting for management of Langerhans cell histiocytosis diagnosed on a skin biopsy one month prior. Inguinal, axillary, and occipital lymphadenopathy noted on exam as well as diffuse morbilliform skin rash. WBC 29.3 x 10^9 (69% polys, 8% bands, 6% lymphs, 2% atyps, 4% monos, 5% myelos, 6% metas) HGB 9.4 gm/dl, PLT 174 x 10^9. LN and BM bx.s and BM aspirate were performed.

**PHENOTYPE:** IHC on the LN, the myeloid elements are CD68^+, MPO^+, rare CD117 and CD34 positive blasts. Hb and Glycophorin highlight scattered erythroid elements. The nodules of large cells are strongly positive for S-100 and CD1a. NPMc^-.
**CYTOGENETICS:**
BM: 47, XX, +8

**FISH ANALYSIS:**
BM: BCR-ABL is negative
LN: trisomy 8
LN: CD1a (green immunofluorescence) and FISH was then performed for the chromosome 8 centromere (red). This reveals several CD1a positive cells showing three chromosome 8 signals, consistent with presence of trisomy 8 in the Langerhans cells

**PROPOSED DIAGNOSIS:**
Atypical CML with differentiating extramedullary myeloid sarcoma. Langerhans cell histiocytosis, involving skin and lymph nodes, clonally related to the atypical CML

**PANEL DIAGNOSIS:**
Agreed with the proposed diagnosis
**Case 750130**

**Submitters:** K.L. Grogg, J.D. Hoyer, W.G. Morice

**Clinical History:** 74-yr-old woman presented with diffuse lymphadenopathy and progressive pancytopenia. An axillary lymph node was excised. Over the next four weeks, the patient was treated with prednisone. Follow-up CBC then showed WBC $84 \times 10^9$/L, Hgb 10 g/dL, plt $42 \times 10^9$/L. White blood cell manual differential (%): Neutrophils 18, Lymphs 12, Monos 20, Metamyelocytes 1, Myelocytes 4, **Blasts/promonocytes 45.** A bone marrow biopsy was performed.
**CYTOGENETICS:**
BM aspirate specimen showed a normal female karyotype (46, XX)

**MOLECULAR ANALYSIS:**
N/A

**PROPOSED DIAGNOSIS:**
Acute myelomonocytic leukemia, with extramedullary differentiation to interdigitating dendritic cell tumor

**PANEL DIAGNOSIS:**
Agreed on the proposed diagnosis, but the final maturation step remains matter of discussion.
Progenitors

Blood Precursors

Interstitial DC

CD14+ CD11c+ CD1a-CLA- monocyte

GM-CSF
IL-4

CD34+

CD14+ CD11c+ CD1a-CLA- monocyte

GM-CSF
TNF-a

CD14- CD11c+ CD1a+CLA+

GM-CSF
IL-4
TGF-b

CD14+ CD11c- CD1a- CD123+

CD14- CD11c- CD1a- BDCA2+ CD123+

FLT3L
TPO

PDC

Plasmacytoid DC

Mature DC

IL3
CD40L
Bacteria
Viruses

Immature DC

IDC

IDC – S100+

CD1a-

Langerhans DC

Interstitial DC
Plastic downregulation of the transcriptional repressor BCL6 during maturation of human dendritic cells

Serafino Pantano*, David Jarrossay, Simona Saccani, Daniela Bosisio, Gioacchino Natoli

Institute for Research in Biomedicine, Via Vela 6, Bellinzona CH6500, Switzerland

Dendritic cell (DC) maturation links peripheral events initiated by the encounter with pathogens to the activation and expansion of antigen-specific T lymphocytes in secondary lymphoid organs. Here, we describe an as yet unrecognized modulator of human DC maturation, the transcriptional repressor BCL6. We found that both myeloid and plasmacytoid DCs constitutively express BCL6, which is rapidly downregulated following maturation triggered by selected stimuli. Both in unstimulated and maturing DCs, control of BCL6 protein levels reflects the convergence of several mechanisms regulating BCL6 stability, mRNA transcription and nuclear export. By regulating the induction of several genes implicated in the immune response, including inflammatory cytokines, chemokines and survival genes, BCL6 may represent a pivotal modulator of the afferent branch of the immune response.
Miscellanea
Case 750172  
Submitters: S.K. Gurbuxani, E.M. Hyjek, J.I. Dickstein, Y. Zhang, J. Anastasi  
Clinical History: 70-yr old male who presented to an outside hospital in 4/05 with right flank skin lesion, diagnosed as DLBCL (CD20 +, CD10 +). CR achieved with R-CHOP. In 9/06 diagnosis of AML of ambiguous lineage with blood and BM blasts CD13 +, CD33 +, CD4 +, CD7 + and but lacking CD19 and CD56; AML protocol administered. Relapse within 4 months with blasts in blood and numerous skin lesions, anemia, thrombocytopenia, CBC 15.4K/ul.

PHENOTYPE: Skin lesion at diagnosis: TdT +, CD123 +, CD45 +, CD4 +, CD7 +, CD43 +, BCL2 +, CD20, CD79a, CD10 focally +, CD56 -.
CYTOGENETICS:
t(6;8)(p21;q24.1), del(13)(q12q14)

MOLECULAR ANALYSIS:
Both the peripheral blood (at relapse) and initial skin specimen showed clonal IgH rearrangements of the incomplete (DJH) type. TCR gene rearrangement showed no clonality.

PROPOSED DIAGNOSIS:
Plasmacytoid dendritic cell tumor initially misdiagnosed as DLBCL, followed by an acute leukemia of ambiguous lineage due to initial lack of CD56 and partial expression of B cell markers and TdT. The case also points to the likely multipotentiality of the precursor cell involved which seems capable of giving rise to plasmacytoid/myeloid dendritic/B-lineage cells.

PANEL DIAGNOSIS:
Agreed with the proposed diagnosis
Case 750221
Submitter: S.D. Popov, M. Palutke

Clinical History: A 5-yr-old boy presented with pallor, fatigue, fever, chest and joint pain. CT scans showed multiple bone lesions in ribs, scapula, sternum and skull. The CBC showed moderate anemia, a white count of 7,200 with 6% blasts, 1% metamyelocytes, 22% band forms, 32% PMNs, 7% monocytes, 1% eosinophils, 29% lymphocytes. Platelet count was 260,000. A BM aspiration was performed and showed 47% blasts. The patient was treated for AML. After second course CT scans demonstrated healing of all bone lesions. BM smears were hypercellular and showed mononuclear blasts with a high N/C ratio, fine chromatin, nucleoli, and cytoplasmic pseudopod formation. BM bx was not performed.

Phenotype: Flow cytometry showed that blasts were CD13, CD33, CD117, CD61 positive. They were CD2, CD3, CD5, CD19, CD79a, HLA-DR and TdT as well as MPO negative.
CYTOGENETICS:
46 XY

MOLECULAR ANALYSIS:
N/A

PROPOSED DIAGNOSIS:
Acute megakaryocytic leukemia.

PANEL DIAGNOSIS:
No consensus.

Comments:
Neither bone lesion nor BM biopsy.
Case 750159
Submitter: C.P. Soupir, N.L. Harris, R.P. Hasserjian

Clinical History: 31-year old female with enlarged supra-clavicular and cervical lymph node one week post partum. A LN and BM biopsies were performed. Splenectomy 19 years prior for massive splenomegaly and thrombocytopenia with mononucleosis; spleen with extramedullary hematopoiesis and a “CD45 negative blast like infiltrate”; BM biopsy was felt to be consistent for MPD, but she received no treatment and remained clinically well.

PHENOTYPE (LN): Glycophorin C +, MPO -, CD117 weak+, CD43 +, CD45 -, CD2 -, CD3 -, CD20 -, Pax-5 -, CD30 -, MUM1 -, CD79a -, CD21 -, CD34 -, CD68 -, Lys -, CD56 -, S100 -; proliferation Index/MIB1 100%.
**CYTOGENETICS:**
BM: 46,XX

**FISH ANALYSIS:**
FISH negative for BCR-ABL

**MOLECULAR ANALYSIS:**
Negative for JAK2 mutation

**PROPOSED DIAGNOSIS:**
LN: extramedullary hemopoiesis with marked pronormoblast proliferation, likely non-neoplastic.
BM: markedly hypercellular marrow with marked pronormoblast proliferation, likely non-neoplastic.

**PANEL DIAGNOSIS:**
Agreed with the proposed diagnosis
Haematopathology is challenging!