Section 4
MDS

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Society for Hematopathology Workshop 2007
Myelodysplastic Syndromes

- Refractory cytopenias (RA, RN, RT)
- Refractory Anemia with Ring Sideroblasts
- Refractory Cytopenia with Multilineage Dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome, including Down syndrome
- Refractory cytopenia of childhood
- Refractory anemia with excess blasts in children
MDS:

• Cases Submitted: 16 (14 adults, 2 ped)
• Cases Moved to Other Category: 1
• Cases Moved into MDS Category: 1
• Submitter/ Panel Agreement: 13
• Submitter/ Panel Discordance: 3 (partial)
MDS/MPD: Key Problem Areas

• Impact of cytogenetics (5q- and other)
• MDS vs. AML
  RAEB-F versus APMF
  RAEB versus AML-M6b
• MDS in association with other diseases; true MDS versus reactive dyspoiesis
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5q- and its associations

Case 238 (AO) 5q- proliferative type moved to the MDS/MPD section

- Case 141 (Orduz) MDS with isolated del(5q) (classical)
- Case 036 (Sidhu) MDS with isolated del(5q) & CLL
- Case 061 (Porwit) Pediatric RAEB-2 vs. AML
- [Case 085] (Penn) MDS with isolated del(5q) & MGUS -- summarized later with case 007

Case 238 (AO) 5q- proliferative type moved to the MDS/MPD section
Chromosome 5q deletion

- Is seen across the spectrum of myeloid disorders including MPD
- Isolated deletions of the long arm of chromosome 5, del(5q), are observed in 10% of myelodysplastic syndromes (MDS)
- Associated with a more favorable prognosis, although the clinical course varies considerably
- If one or more additional chromosomal aberrations are present, this correlates with a significantly shorter overall survival
- Lenalidomide
Lenalidomide upregulates SPARC & Activin

- SPARC located at 5q31-q32, is a tumor suppressor gene with antiproliferative, antiadhesive, and antiangiogenic properties
- Activin A is a member of the transforming growth factor-beta superfamily has pleiotropic functions, including apoptosis of hematopoietic cells

Pellagatti A, et al. Lenalidomide inhibits the malignant clone and up-regulates the SPARC gene mapping to the commonly deleted region in 5q- syndrome patients. Proc Natl Acad Sci U S A. 2007;104:11406-11
MDS: role of cytogenetics

Case 158 (Chen): Clonal cytogenetic abnormality of uncertain clinical significance

Draft WHO 2008 MDS,

“Cases with chromosomal abnormalities compatible with a MDS associated with strong presumptive clinical evidence of a MDS but in which dysplastic features are <10 % of cells in one (unilineage) or more (multilineage) of the cell lineages”
MDS: role of cytogenetics

• Case 192 (Bhagat): MDS with t(6;9)(p23;q34)] aggressive MDS or AML. Concern for RAEB in this case. Follow up?

• [Case 161 (Kreisel): RCMLD with ring sideroblasts and isolated del 20q]

• [Case 158 (Isaacson): Pediatric MDS with dup (1) (ex Fanconi)]
Case 161 (Kreisel)
RCMLD with ring sideroblasts isolated del 20q


All 9 pts. were RA only
Follow up?
The most frequent chromosomal abnormalities noted in Fanconi anemia-associated leukemias are duplication of 1q and monosomy 7.

Alfaro R, et al. dup(1)(q21q32) as a sole cytogenetic event is associated to a leukemic transformation in Myelodysplastic Syndromes. Leuk Res. 2007 May 15; [Epub ahead of print]
MDS versus AML: difficulties with APMF and AML-M6

- Case 061 (Porwitt): RAEB-2 (Ped) vs. AML
- Case 075 (Montalvo): MDS-F vs. APMF
- [Case 191] (Gupta): RAEB-2-F vs. APMF
- Case 165 (Sasu): RAEB-2 vs. AML-M6b
Case 191 (Gupta, Alobeid, Bhagat): RAEB-2-F vs. AML (?APMF)
Presence of Mk-blasts  CD61 pos. / CD34 neg.
Acute Panmyelosis with Myelofibrosis

Acute onset / no splenomegaly / rapidly fatal

PB  Pancytopenia, no teardrops, non-leukemic

BM  Proliferative disorder of all three cell lines:
    • Small size Mks with disperse chromatin, non or hypolobulated nuclei
    • Blasts variably increased (median 22.5%)
    • **No or rare MK-blasts**
    • Degree of fibrosis is variable but usually 3+

Lewis & Szur, 1963; Bearman et al, 1979; Sultan et al, 1981; Thiele et al, 2004; Orazi et al, 2005
• Clinically, APMF can be separated from MDS by its more abrupt onset with fever and bone pain

• Particularly difficult is the distinction between APMF and cases of MDS associated with both an excess of blasts and myelofibrosis since both share most of the morphological findings

• APMF shows more numerous megakaryocytes, and, on average, a higher number of blasts than RAEB

• However, cases of RAEB-2-F, except for their usually less acute clinical presentation, may be indistinguishable from APMF (case 191)
RAEB-2 vs. Erythroleukemia
Case 165 (Sasu)

- If the overall percentage of blasts is ≥20% and multilineage dysplasia is present, the diagnosis is AML (MLD)
- If <20% total blasts and the erythroid precursors are ≥50% of all cells, the differential count of non-erythroid cells should be calculated
- If blasts are <20% of non-erythroid cells, the diagnosis is usually myelodysplasia
- If blasts are ≥20% of non-erythroid cells, the diagnosis is erythroleukemia (erythroid/myeloid –M6a)
- Less reproducible the separation with M6b

WHO Tumors of the Hematopoietic and Lymphoid Tissues
MDS: associations with other diseases

- PNH - Case 131 (Wang)
- [Plasma cell neoplasms - Case 007 and 085 (Penn)]
- [Pure red cell aplasia - Case 124 (Yue)]
- [Hemophagocytic lymphohistiocytosis Case 115 (Pozdnyakova)]
• Abnormal morphological BM features reminiscent of MDS are common in PNH, regardless of the karyotype
• None of 46 patients developed excess blasts or leukaemia
• The authors conclude that in patients with PNH cytogenetically abnormal clones are not necessarily malignant and may not be predictive of evolution to leukaemia

Association of MDS with Plasma Cell Tumors
Case 085 (Penn): MDS with isolated del(5q) & MGUS

8/03

One orange, two green signals (x1,000).

Two orange and two green signals (x1,000).

Two orange signals (x1,000).

Two orange signals representing the 20q12 locus are present (x1,000).
Association of MDS with Plasma Cell Tumors

- Few cases documenting the coexistence of MDS and MM at diagnosis have been reported.
- In patients with MM, MDS have been reported after chemotherapy. These are clonally unrelated (MDS secondary to treatment with alkylating agents). The risk of both diseases has been estimated to be 10-20% after 10 years.
- MM and MDS may arise from a common stem cell, which may be characterized by a clonal cytogenetic.
- In one MGUS with del(20q), FISH showed its presence in CD34+CD38- (hematopoietic stem cells), CD34+CD38+ (progenitors), CD19+ (B cells), and CD15+ (myeloid cells) suggesting that del(20q) it might arise at a multipotent progenitor/stem cell level.

Pure red cell aplasia in MDS (RCMLD) Case 124 (Yue, Woda, Wang)
MDS with erythroid hypoplasia

- The incidence is probably underestimated
- May rarely be simulated by 5q-
- Mechanism unknown
- Steroids do not help
- An immunologic basis (similar to hypoplastic MDS) had been hypothesized
- Candidate for immunosuppressive treatment
Case 115 (Pozdnyakova, Wang, Woda, Hao)
RA (+8) & Hemophagocytic lymphohistiocytosis

Figure 2: Bone marrow cell hypercellular marrow with dysplastic megakaryocytes (Original Magnification x400)

Figure 6: Touch imprint: Phagocytic histiocyte and a budding erythroid (Original Magnification x600)

Figure 8: Touch imprint: Phagocytic histiocyte and a budding erythroid (Original Magnification x600)
MDS & HPL is very rare


• In case 115 the original MDS slides were not submitted

• MDS can be simulated by HPL!
  • Florena AM, et al. Bone marrow biopsy in hemophagocytic syndrome. Virchows Arch 2002;441:335-44
Acute bilinear leukemia ex. MDS (Andrei, Rabei, Mohamed, Palutke)
• Flow cytometric analysis showed two distinct populations of blasts:
  36% blasts lymphoid: CD19, CD10, CD34, TdT, HLA-DR
  23% blasts myeloid: CD117, CD34, HLA-DR, and MPO

• FISH: Blasts with both two and three signals for chromosome 8 suggests that the original stem cell did not have trisomy 8 and that this was acquired later by the myeloid but not the lymphoid line

• Trisomy 8 was found to be associated with a population of leukemic cells, characterized by CD34+ / HLADR+ / CD13+ / CD33+ / CD11b- / CD15- / CD14-

## MDS -- Cases Summarized with Panel Dx

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