Therapy-Related AML

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- After cytotoxic chemotherapy and/or radiation therapy
- Two types:

1. Alkylating agent and radiation therapy related
2. Topoisomerase II inhibitor related

Alkylating Agent/Radiation Therapy Related AML (MDS)

- Occur 5-6 years after initiation of treatment
- Range: 10-192 months
- Risk related to age and cumulative dosage
- Mutagenic effects of ionizing radiation and alkylating agents

Alkylating Agent/Radiation Therapy Related AML (MDS)

- Two-thirds of cases that present as MDS satisfy the criteria for RCMD
- MDS phase can evolve to higher grade MDS or AML
- A minority of cases present as overt AML

Alkylating Agent/Radiation Therapy Related AML (MDS)

- All myeloid cell lines affected
- Dyserythropoiesis
- Ringed-sideroblasts in 60% of cases (one-third in excess of 15% ringed-sideroblasts)
- Hypogranulation and nuclear hypolobation in granulocytes

Alkylating Agent/Radiation Therapy Related AML (MDS)

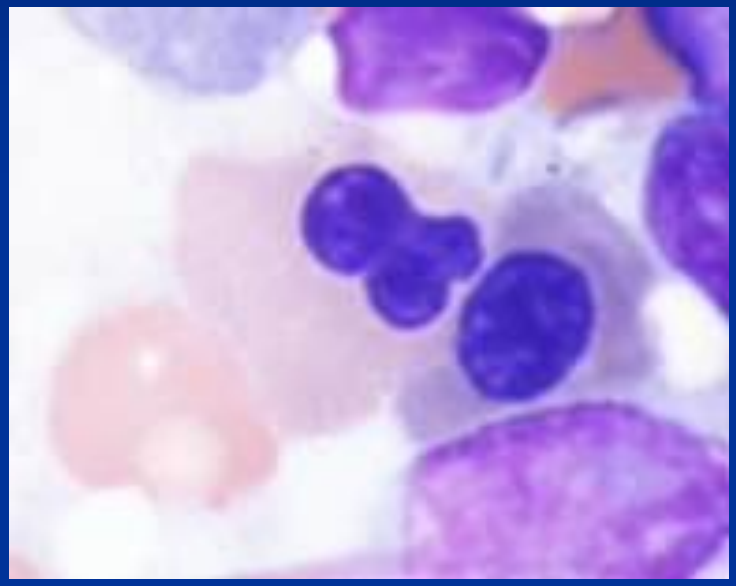
- Dysplastic megakaryocytes increased in 25%
- Basophils increased in 25%
- Occasional Auer rods

Alkylating Agent/Radiation Therapy Related AML (MDS)

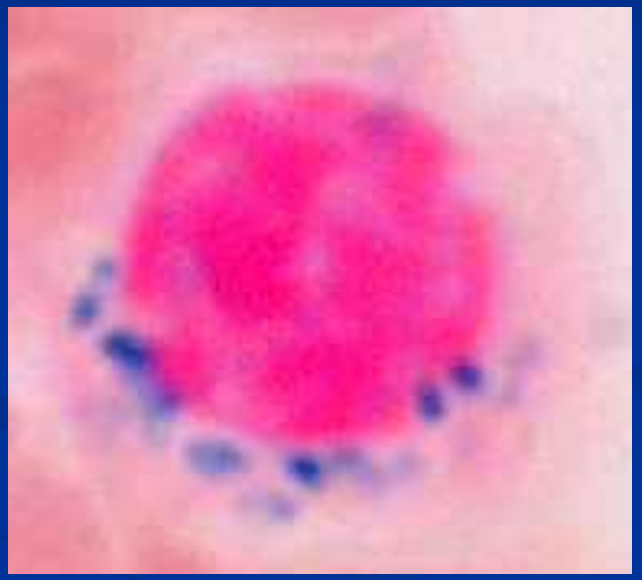
Bone marrow biopsy

- Hypercellular in 50%
- Normocellular in 25%
- Hypocellular in 25%
- Fibrosis in 15%

Alkylating Agent/Radiation Therapy Related AML (MDS)

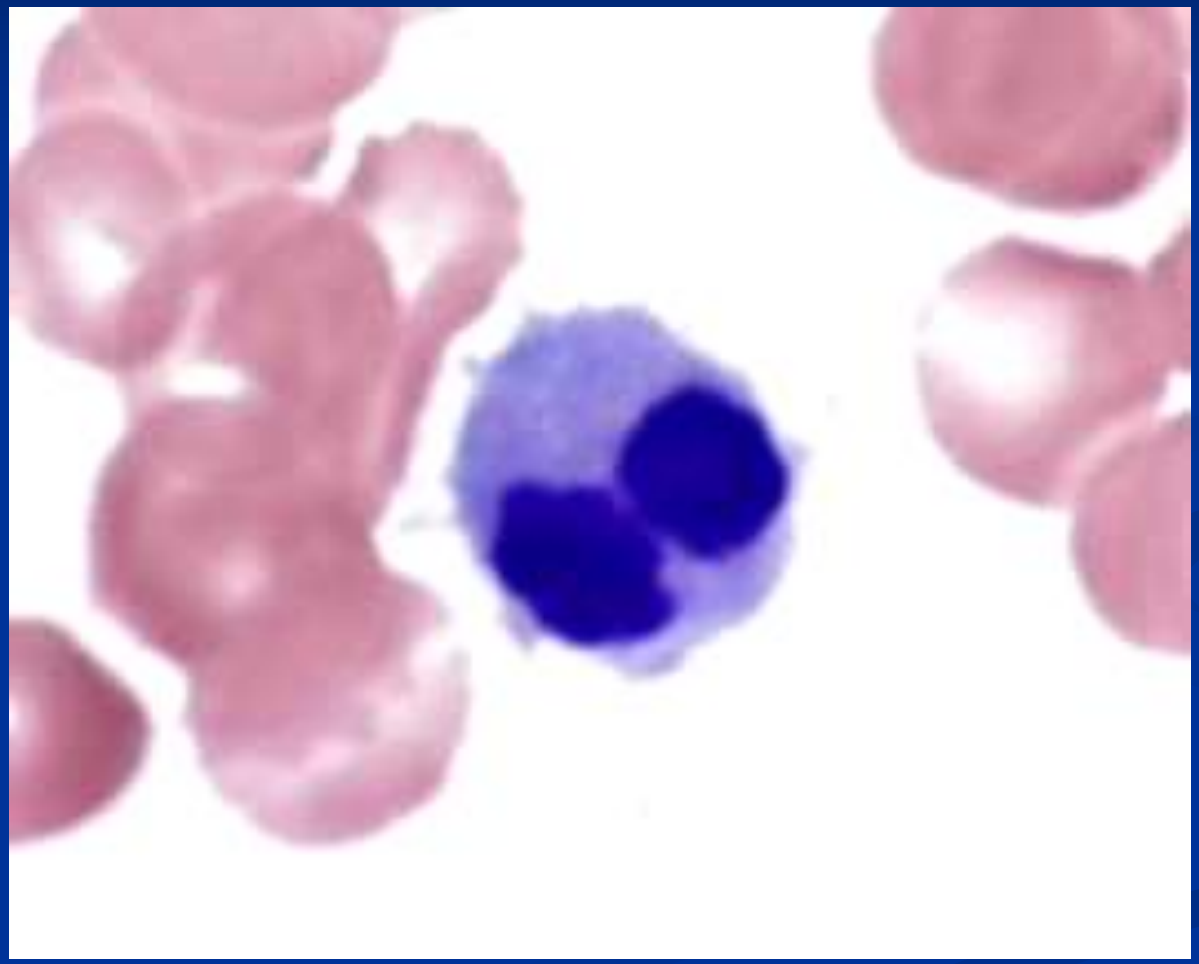


Dysplastic normoblasts



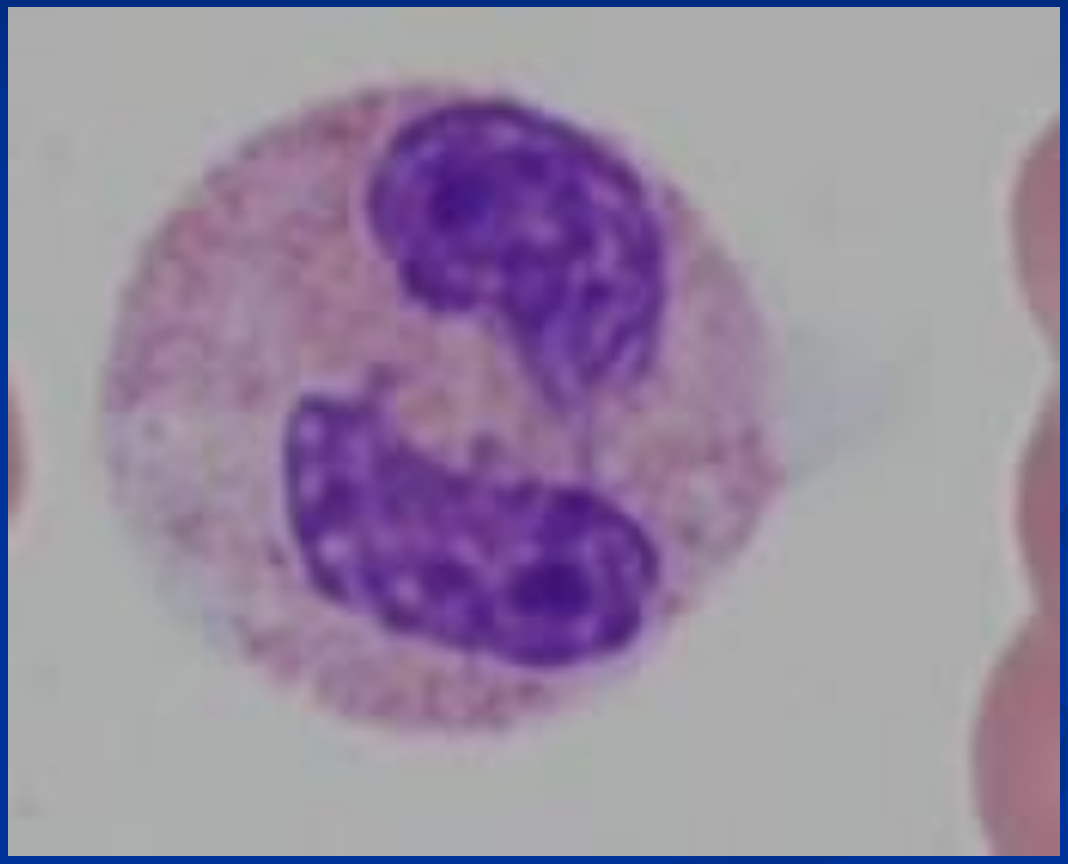
Ringed-sideroblasts

Alkylating Agent/Radiation Therapy Related AML (MDS)



Dysplastic normoblasts

Alkylating Agent/Radiation Therapy Related AML (MDS)



Pseudo Pelger-Huet cells

Alkylating Agent/Radiation Therapy Related AML (MDS)

Features

- AML with maturation
- Myelomonocytic
- Monocytic
- Erythroleukemic
- Megakaryoblastic

Alkylating Agent/Radiation Therapy Related AML (MDS) Immunophenotype

- Blasts often CD34+
- CD33+, CD13+
- Occasionally CD56+ and CD7+
- MDR-1 (multidrug resistance glycoprotein) expression

Alkylating Agent/Radiation Therapy Related AML (MDS): Genetics

- Increased cytogenetic abnormalities
- Similar to *de novo* MDS, RCMD, RAEB
- Unbalanced translocations
- Deletions of chromosomes 5 and 7 (long arms)
- Other chromosomes abnormalities: 1, 4, 12, 14, 18
- Complex chromosomal abnormalities

Alkylating Agent/Radiation Therapy Related AML (MDS) Prognosis

- Poor response to therapy
- Poor survival

Topoisomerase II Inhibitor Related AML (MDS)

- Epipodophyllotoxins and related compounds that target DNA-Topoisomerase II (gyrase)

  E.g., Etoposide and teniposide

- Also anthracyclines, such as doxorubicin and 4-epi-doxorubicin

Topoisomerase II Inhibitor Related AML (MDS)

- All ages
- Shorter latency 12-130 months (median: 33-34 months)
- Latency can be less than 6 months

Topoisomerase II Inhibitor Related AML (MDS)

- Usually presents as overt AML without a previous MDS phase
- Significant monocytic component
- Most are acute monoblastic or myelomonocytic

  (Acute promyelocytic leukemia in some as well as acute megakaryoblastic leukemia)
- Bone marrow usually hypercellular

Topoisomerase II Inhibitor Related AML (MDS)

- Acute lymphoblastic leukemia also possible
- Usually associated with t(4;11)(q21;q23) chromosome abnormality

Topoisomerase II Inhibitor Related AML (MDS)

Genetics

- Usually balanced translocation involving 11q23 (MLL gene) and chromosomes 6, 9, and 19
- t(8;21), t(3;21), t(6;9)
- t(4;11)(q21;q23) (associated with ALL)
- t(15;17)(q22;p21) (APL)

Topoisomerase II Inhibitor Related AML (MDS)

Prognosis

- Good initial response to therapy, but relapses are frequent (especially with 11q23)
- Survival variable (but poor in 11q23)
- Insufficient data of long-term follow-up

AML with multilineage dysplasia

Definition

- AML plus dysplasia
- Dysplasia: >50% of cells of 2 or more myeloid lines in a pre-treatment specimen.
- May occur de novo or following MDS or MDS/MPD.

Epidemiology and clinical features

- Mainly in elderly and rare in children
- Often severe pancytopenia

Morphology

Specimen needed: well-stained, pre-treatment smears of blood or bone marrow

Dysgranulopoiesis

- Hypogranular cytoplasm
- Hyposegmented nuclei (pseudo Pelger-Huet anomaly)
- Bizarrely segmented nuclei

Dyserythropoiesis

- Megaloblastic nuclei
- Karyorrhexis
- Nuclear fragments
- Multinucleation
- Ringed sideroblasts
- Cytoplasmic vacuoles
- PAS positivity

Dysmegakaryopoiesis

- Micromegakaryocytes
- Monolobated
- Multiple separated nuclei

Differential diagnosis

- M2
- M6

Immunophenotype

- Generally: CD34 and pan-myeloid markers (CD13 and CD33)
- Frequently: aberrant exp of CD56 and CD7
- Increased incidence: MDR-1

Genetics

- Similar to MDS
- Often: -7/del(7q), -5/del(5q), +8, +9, +11, del(11q), del(12p), -18, +19, del(20q), +21
- Less often: t(2;11), t(1;7), 3q21, and 3q26

Prognosis

Multilineage dysplasia: adverse effect on achieving remission