Myelodysplasia and Myelofibrosis

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Myelodysplastic Syndromes

- MDS – Group of clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective hematopoiesis in one or more of the major cell lines.
- Clonality is important in the definition of true MDS
- Increased risk of AML (24-45% pts)
- The “minimal” morphologic criteria for the diagnosis of MDS in the appropriate clinical setting, at least 10% of the cells of at least one myeloid BM lineage (erythroid, granulocytic, megakaryocytic) must show unequivocal dysplasia for the lineage to be considered as dysplastic

- Synonyms- Dysmyelopoietic syndromes, preleukemic syndromes, oligoblastic leukemia.

RBCs – dyserythropoiesis with nuclear budding, internuclear bridging, karyorrhexis, multinucleation, megaloblastoid changes, ringed sideroblasts, Per-iodic acid Schiff stain positivity

Granulocytes – small size, nuclear hypolobation (pseudo- Pelger-Huet cells, abnormal granulation with pseudo Chediak – Higashi granules, hypersegmentation.

Megakaryocytes – micromegakaryocytes, hyolobation, nonlobation, multiple seperated nuclei.

- ALIP - small groups of immature precursor cells are present in biopsies in central part of marrow away from vascular structures and trabeculae. ≥ 3foci is considered positive

- Cytopenia - hemoglobin <10g/dL, absolute neutrophil count <1.8 x 10^{9}/L, platelets <100 x 10^{9}/L, absolute monocyte count <1.0x10^{9}/L

- Ringed sideroblasts - ≥ 1/3 of nucleus is encircled by ≥ 10 siderotic granules on iron stain

Age – elderly, average 70 years, uncommon <50yrs.

Incidence – rises with increasing age. 3/1lac to 20/1 lac population over 70yrs.

Etiology –

- primary / de novo
- Secondary (therapy related, 2-8 yrs after exposure, or due to other malignancies)

Cytogenetics – deletions, trisomies. chr. 3,5,7, 17,20,etc . Complex abnormalities are seen esp. in therapy related MDS, with worse prognosis.

Clinical Features – 50% initially asymptomatic.

elderly patient

Weakness, anemia,

Bleeding tendency may/maynot be present.

Organomegaly +/-

Investigations

Blood –

RBC- normocytic normochromic or macrocytic anemia, anisopoikilocytosis, variable degree of dysplasia in red cells and erythroblasts, basophilic stippling, howell-jolly bodies, PAS positivity

Granulocytes – leukopenia, hypo/hpersegmented, abnormal granules,. Monocytosis, blasts very few

Platelets – thromocytopenia, abnormal forms

Bone marrow – variable cellularity, often hypercellular, disordered and dysplastic maturation of different cell types(unilineage or multilineage), ringed sideroblasts, variable % of myeloblasts, (<20%), ALIP

Cytogenetic studies using FISH,flow cytometry or karyotyping

WHO Classification

- Refractory anemia
- Refractory anemia with ringed sideroblasts
- Refractory anemia with excess blasts
- Refractory cytopenia with multilineage dysplasia
- MDS – unclassifiable
- MDS with isolated deletion(5q) syndrome

WHO Classification (2008)

- Refractory cytopenia with unilineage dysplasia – this includes refractory anemia, refractory neutropenia, or refractory thrombocytopenia
- RARS
- RAEB
- Refractory cytopenia with multilineage dysplasia
- MDS with isolated deletion of 5q
- MDS, unclassifiable
- Childhood MDS

The WHO classification also includes a provisional entity: refractory cytopenia of childhood.

Revised Classification(2016)

- MDS –SLD -- MDS with single lineage dysplasia
- MDS –MLD ----- MDS with multilineage dysplasia
- MDS –RS (with ring sideroblasts)
- MDS – RS – SLD (MDS with RS and SLD)
- MDS – RS – MLD
- MDS with isolated deletion 5q

- MDS with excess of blasts (MDS –EB) (EB 1 or EB 2 depending on whether blasts are 2-4% or 5-19% in peripheral blood respectively or 5-9% or 10 -19% in bone marrow respectively and auer rods are absent or present respectively)
- MDS –U (unclassifiable)
- MDS with SLD and pancytopenia
- MDSwith a defining cytogenetic abnormality
- RCC – refractory cytopenia of childhood

Revised International Prognostic Scoring System

To improve prognostic classification, the MDS Risk Analysis Workshop developed the Myelodysplastic Syndrome International Prognostic Scoring System (IPSS). The revised IPSS score includes

- cytogenetic abnormalities
- Percentage of bone marrow blasts
- HB and ANC count and platelet count
- The IPSS score is used to stratify patients into 5 risk groups.

Treatment –

- supportive
- RBC transfusions, platelets, tt of infection
- Cytotoxic drugs if progressing to AML
- Hematopoietic growth factors, EP, G-CSF retinoids, immunomodulators (thalidomide).
- Bone marrow transplant – limited role

- Risk of iron overload

Complications – severe anemia, AML, intercurrent infection

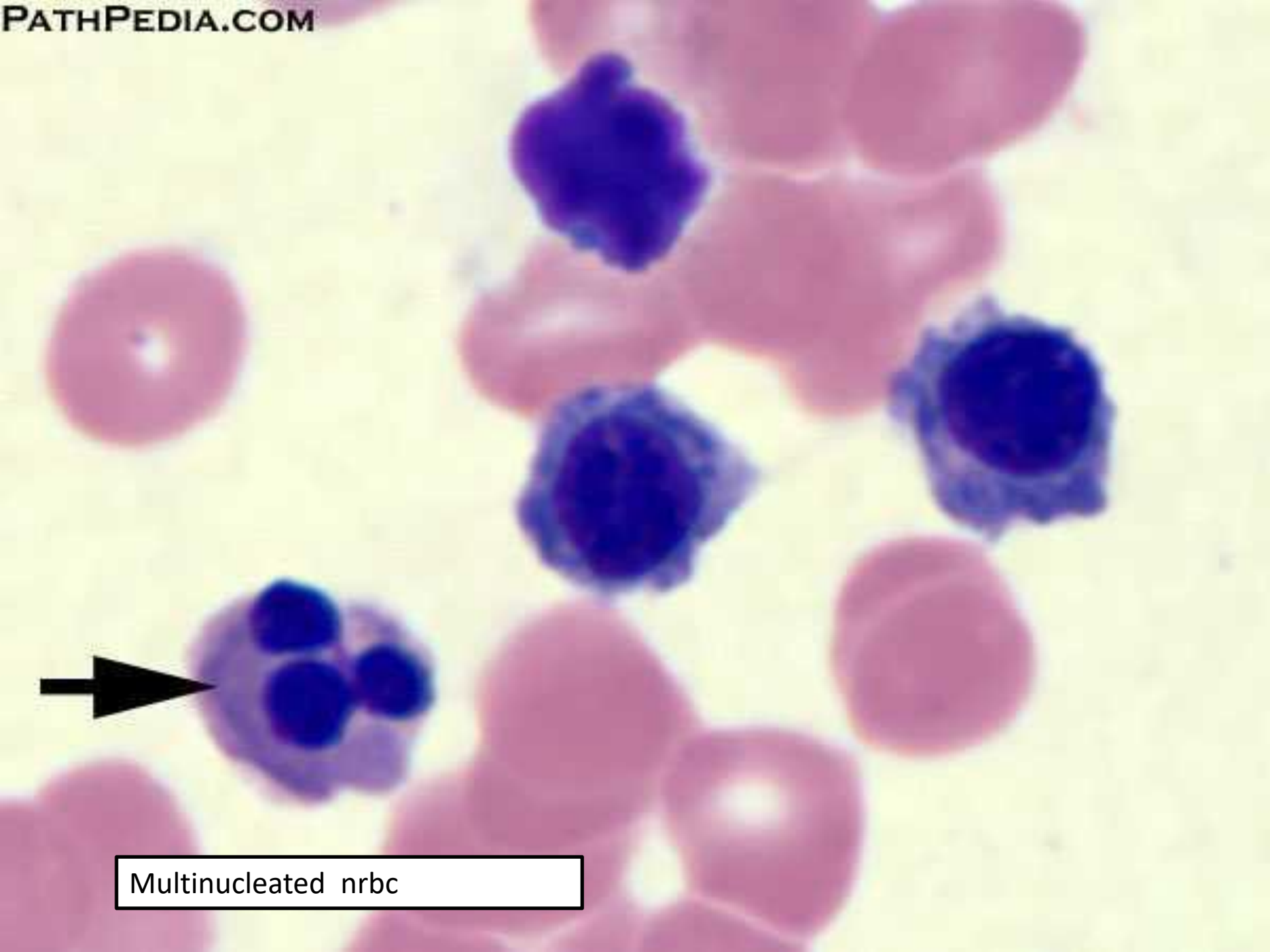
Interesting reads

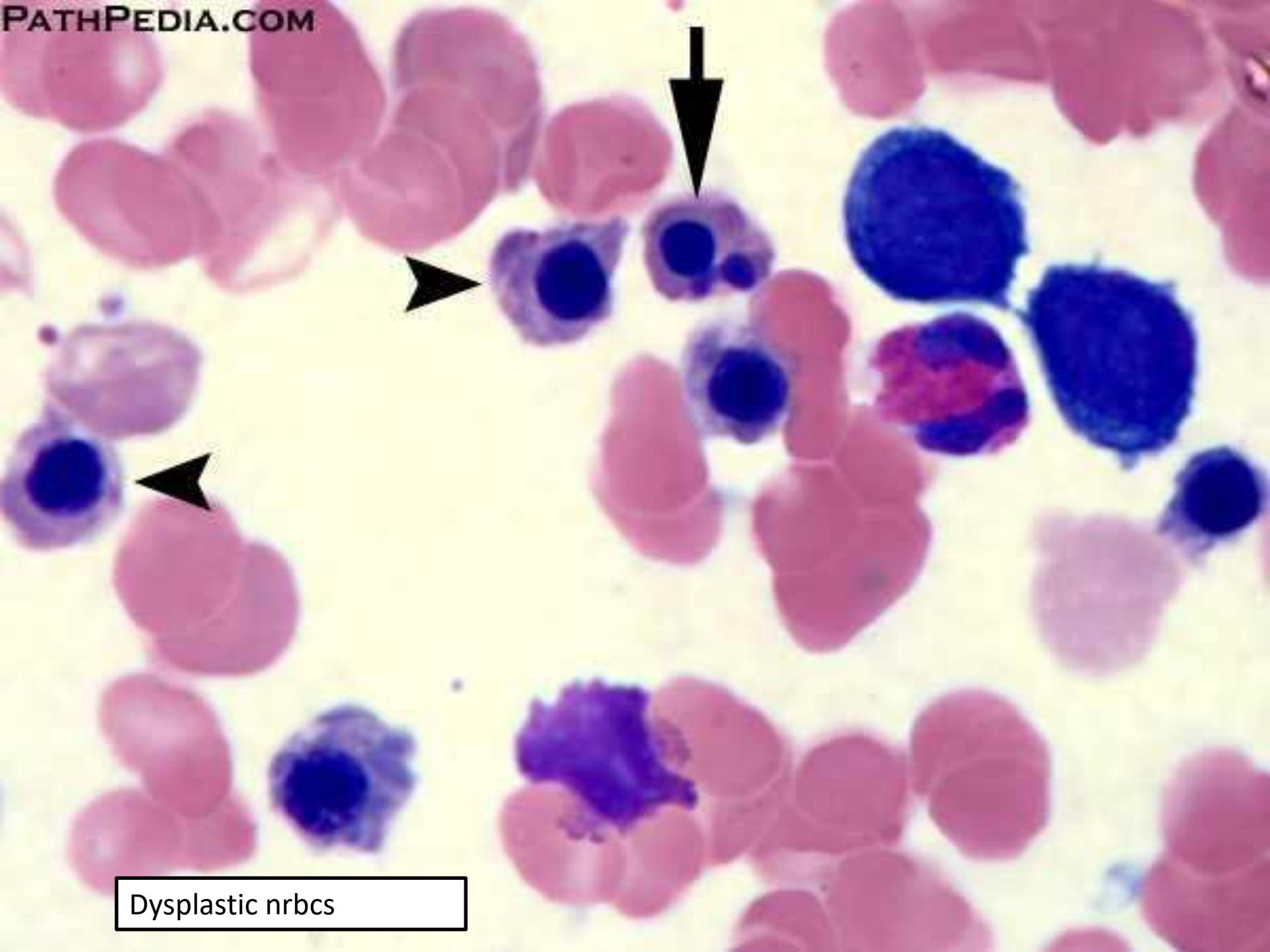
- Ming Hong and Guangsheng He. The 2016 revision to the world health organization classification of myelodysplastic syndromes. Journal of translational medicine 2017;5(3):139-143
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5655460/

- Sallman DA and List A. The role of innate immunity in MDS pathogenesis. Hemasphere 2019; 3(52): 136-37.

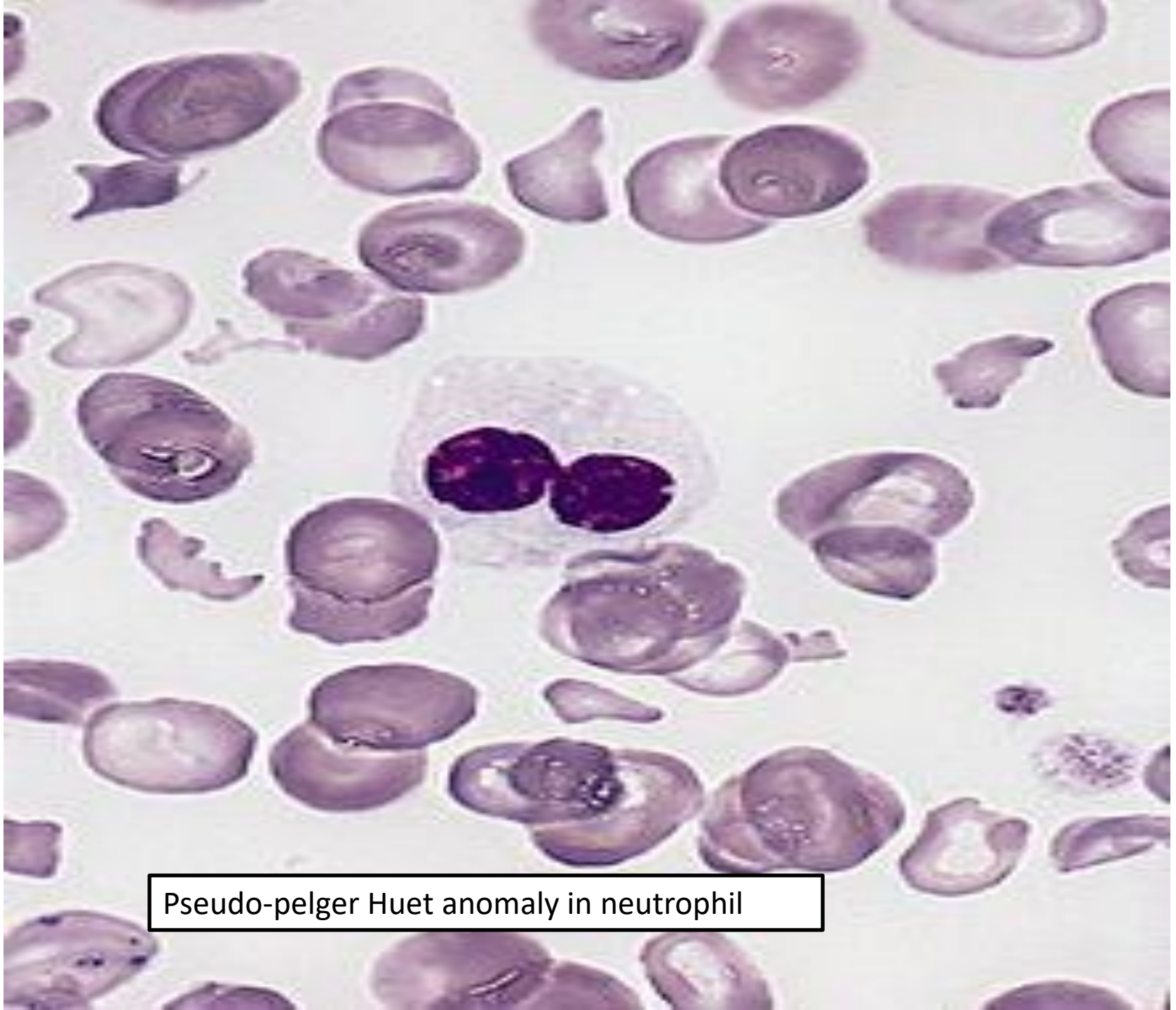
- Kast RE. Inhibiting the NLRP3 inflammasome with methylene blue as treatment adjunct in myelodysplasia.Frontiers in oncology 2018;8:280

https://www.ncbi.nlm,nih.gov/pmc/articles/PMC6072867/

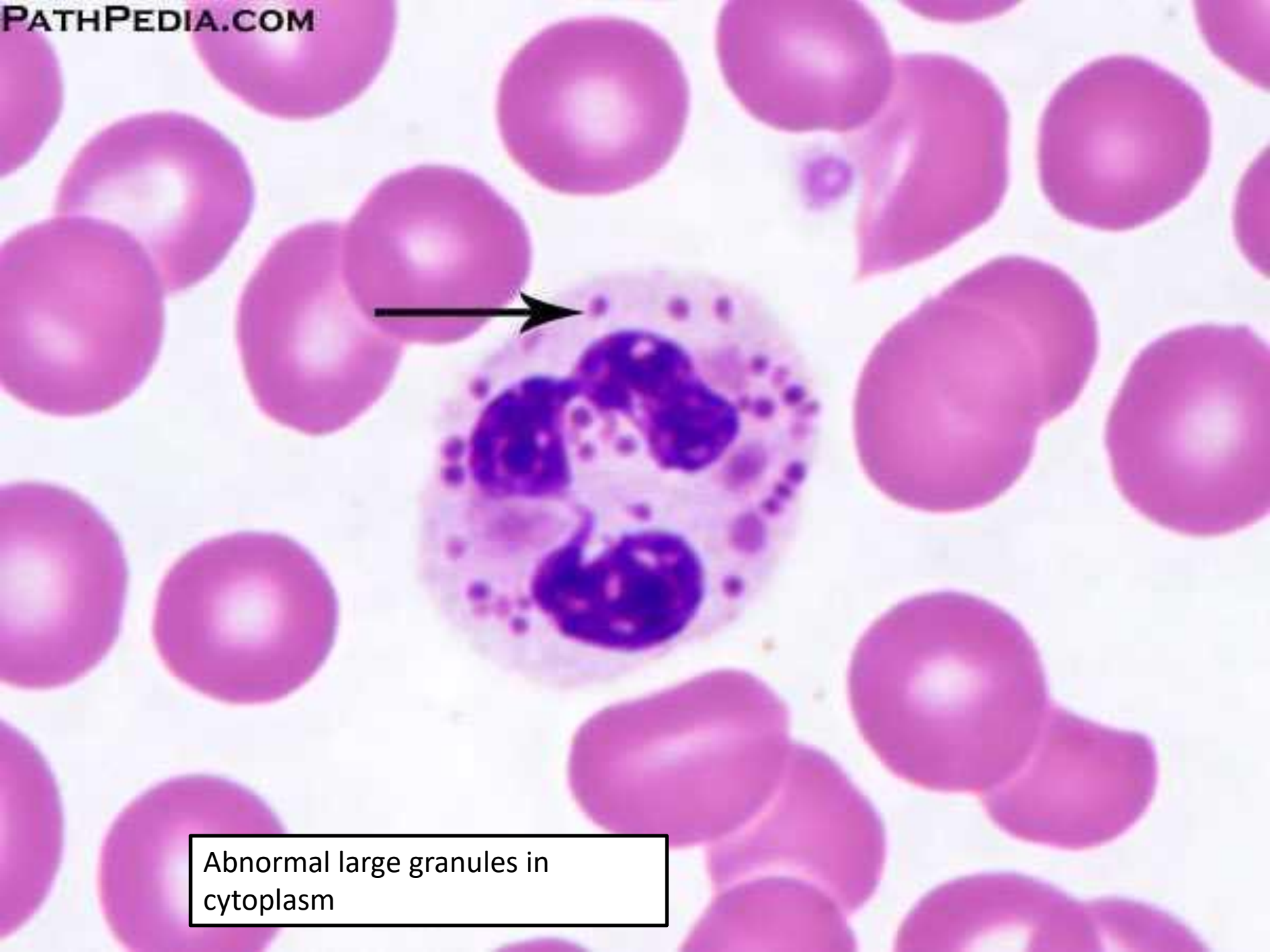

PATHPEDIA.COM
Multinucleated nrbc



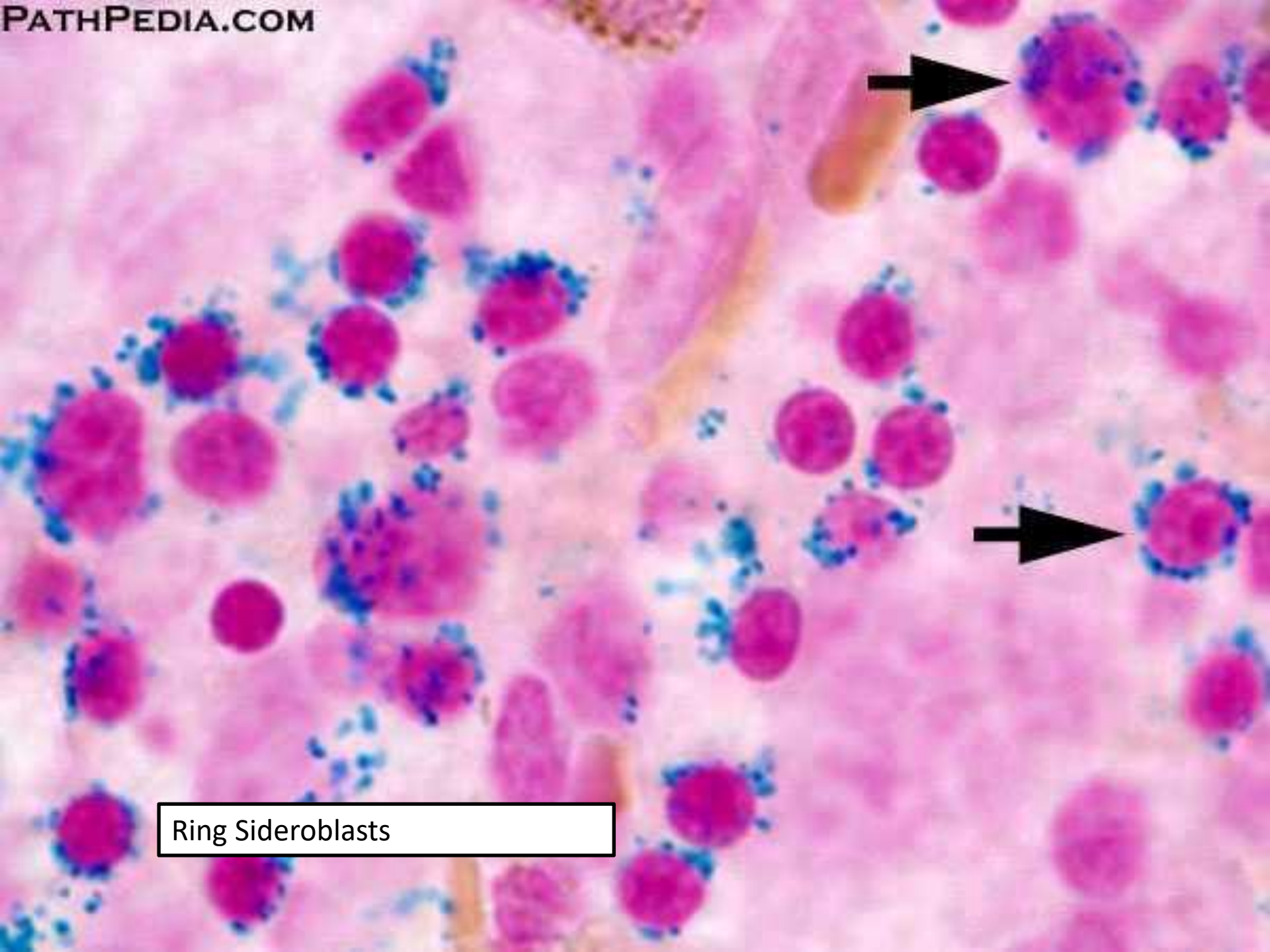
Dysplastic nrbcs



Pseudo-pelger Huet anomaly in neutrophil



Abnormal large granules in cytoplasm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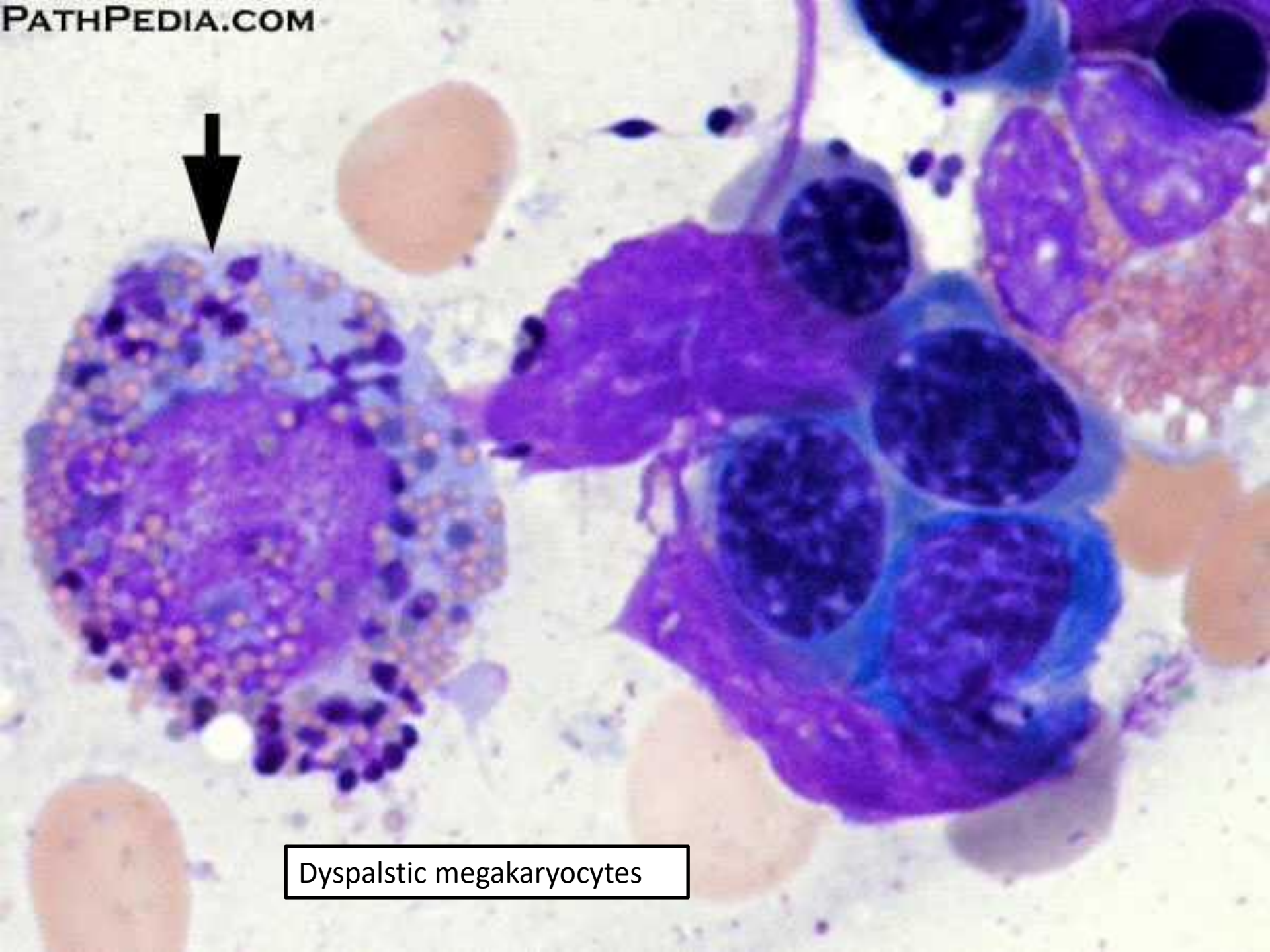
Ring Sideroblasts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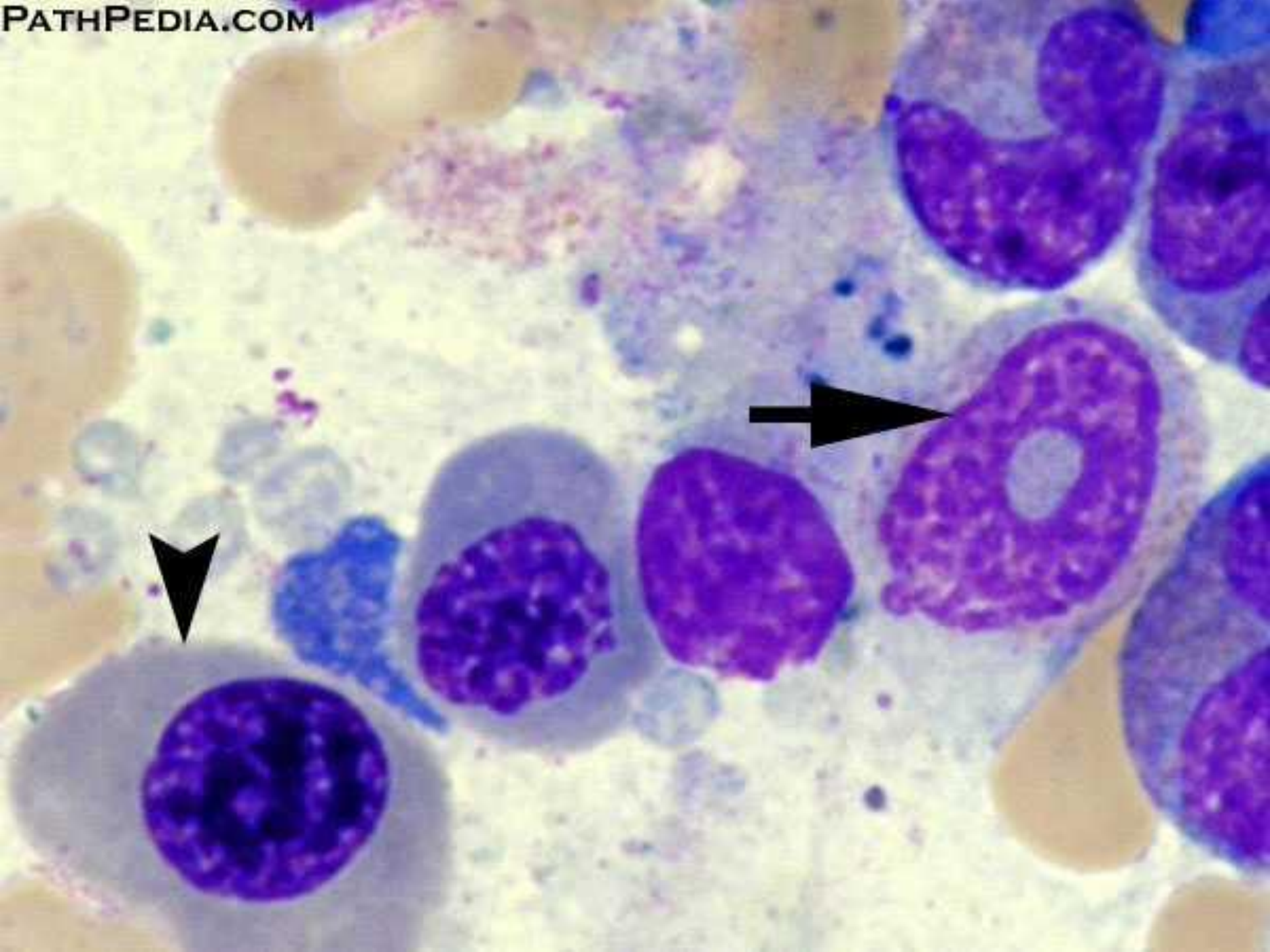
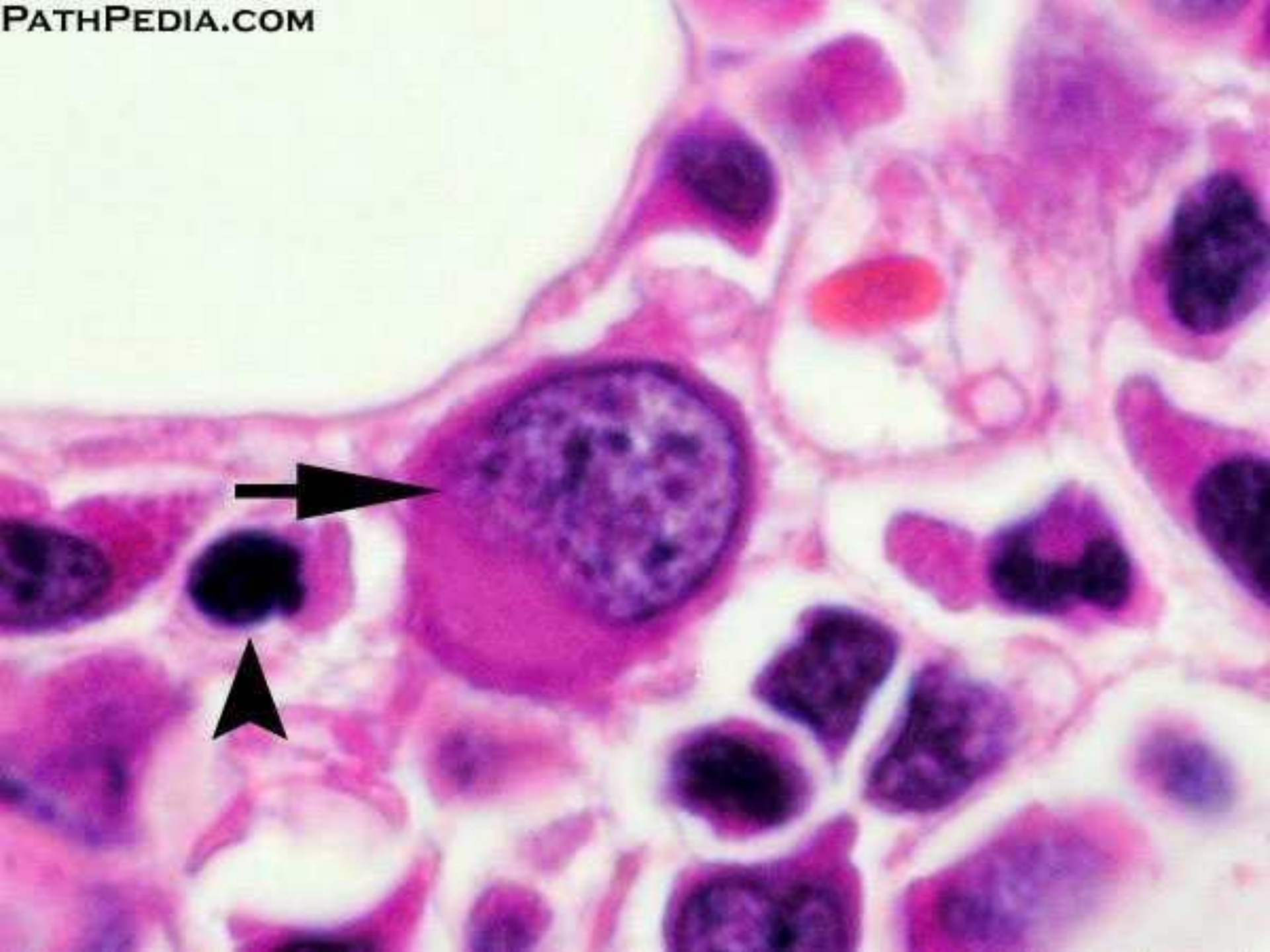
Dyspalstic megakaryocytes


PathPedia.com

Megakaryocyte with nuclear lobation and fragmentation

- Next 3 slides show deletion 5q syndrome with numerous small megakaryocytes in bonemarrow with nuclear hypolobation

- Seen in middle aged females mostly
- Good prognosis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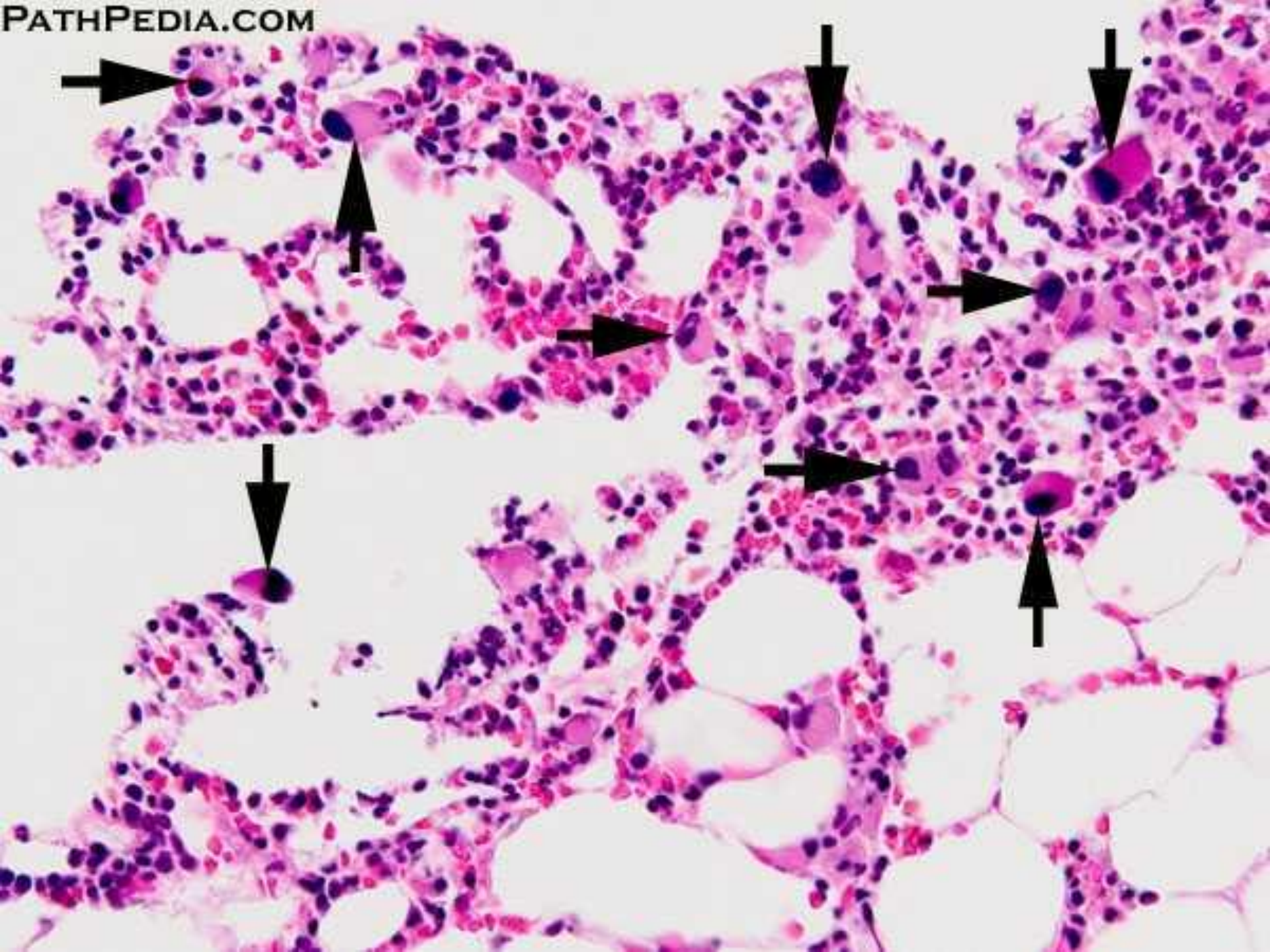
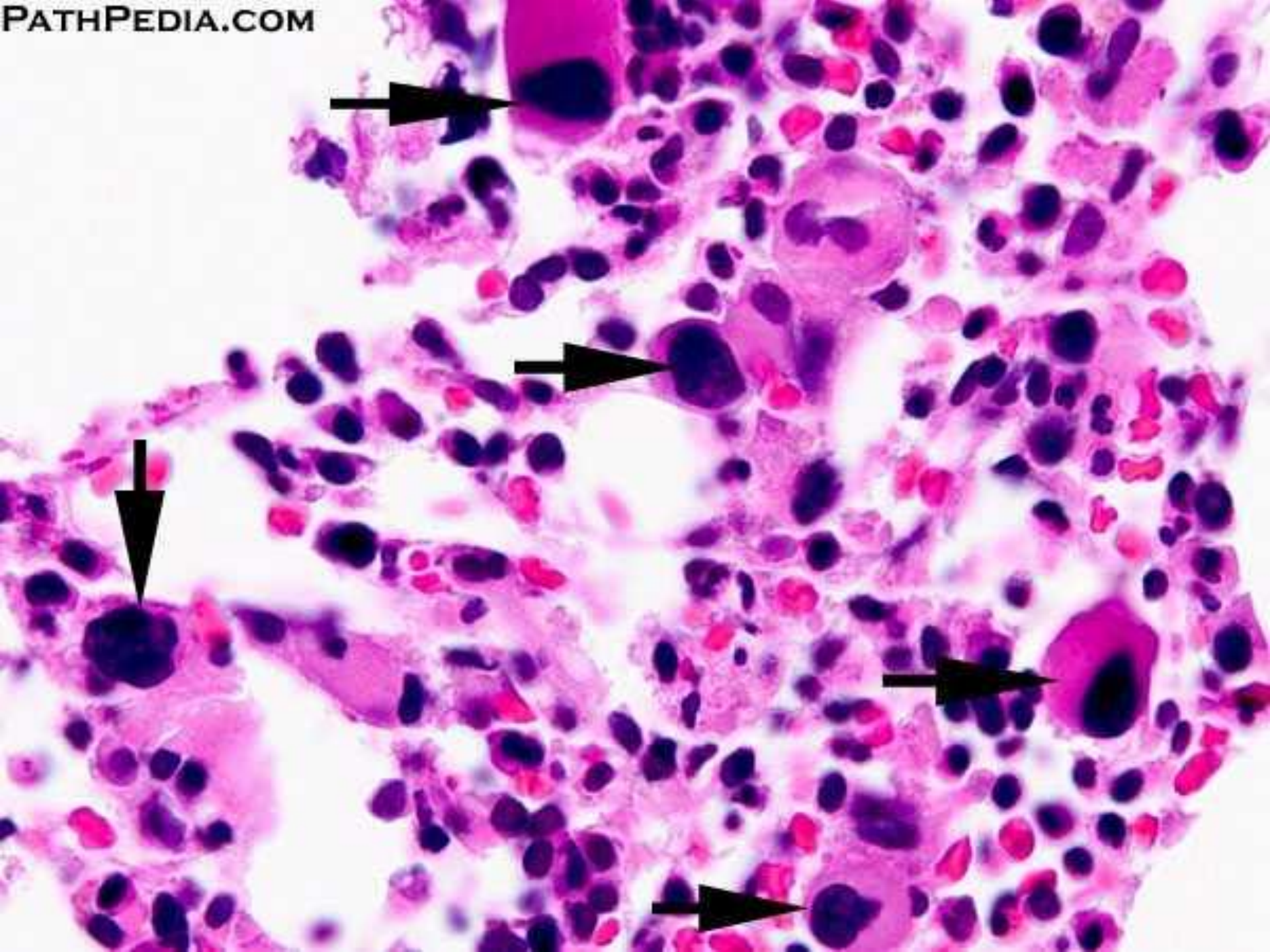




Primary Myelofibrosis

Myelofibrosis

- As name suggests, signifies deposition of fibrous tissue in bone marrow
- Can be primary or secondary to other causes such as bone marrow infiltration(myelophthisic anemia), multiple myeloma, metastatic carcinoma, radiation, tubercular infection, other myeloproliferative neoplasms, drugs etc.

Primary myelofibrosis

- Clonal myeloproliferative neoplasm characterised by abnormal bone marrow cell proliferation (megakaryocytes and granulocytes), marrow fibrosis and extramedullary hematopoiesisalso k/a chronic idiopathic myelofibrosis, agnogenic myeloid metaplasia

Etiopathogenesis

- Idiopathic
- ???Exposure to chemicals/radiation
- Can be familial
- Abnormal stem cell signalling and increased inflammatory cytokines and growth factors along with abnormal JAK/STAT pathway signalling favour fibrosis

Clinical features

- Elderly usually
- An be asymptomatic initially
- Fatigue, weakness, bleeding, infections, etc

- Has initial cellular phase and followed by fibrotic or burnt out phase where marrow is replaced by fibrous tissue/collagen/bone deposition with consequent cytopenia

- Cellular phase is characterised by normal or increased cell counts, thrombocytosis, and immature granulocytic precursors along with nrbc and anisopoikilocytosis in peripheral **blood(leuco-erythroblastic blood picture}**

- Fibrotic phase shows pancytopenia including anemia with many tear drop cells on GBP.

- Bone marrow aspirate – failed tap due to fibrosis in later stages
- Trephine biopsy- loss of marrow cellularity with fibrous tissue deposition of varying degree
- Fibrosis is assessed under light icroscopy on special stains(Reticulin silver stain or other connective tissue stain)
- Graded accordingly

.

New WHO Criteria - Primary Myelofibrosis

Diagnosis requires meeting all 3 major criteria and 2 minor criteria

Major criteria

1. Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin or collagen fibrosis,
or,
in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)

2. Demonstration of *JAK2 V617F*or other clonal marker

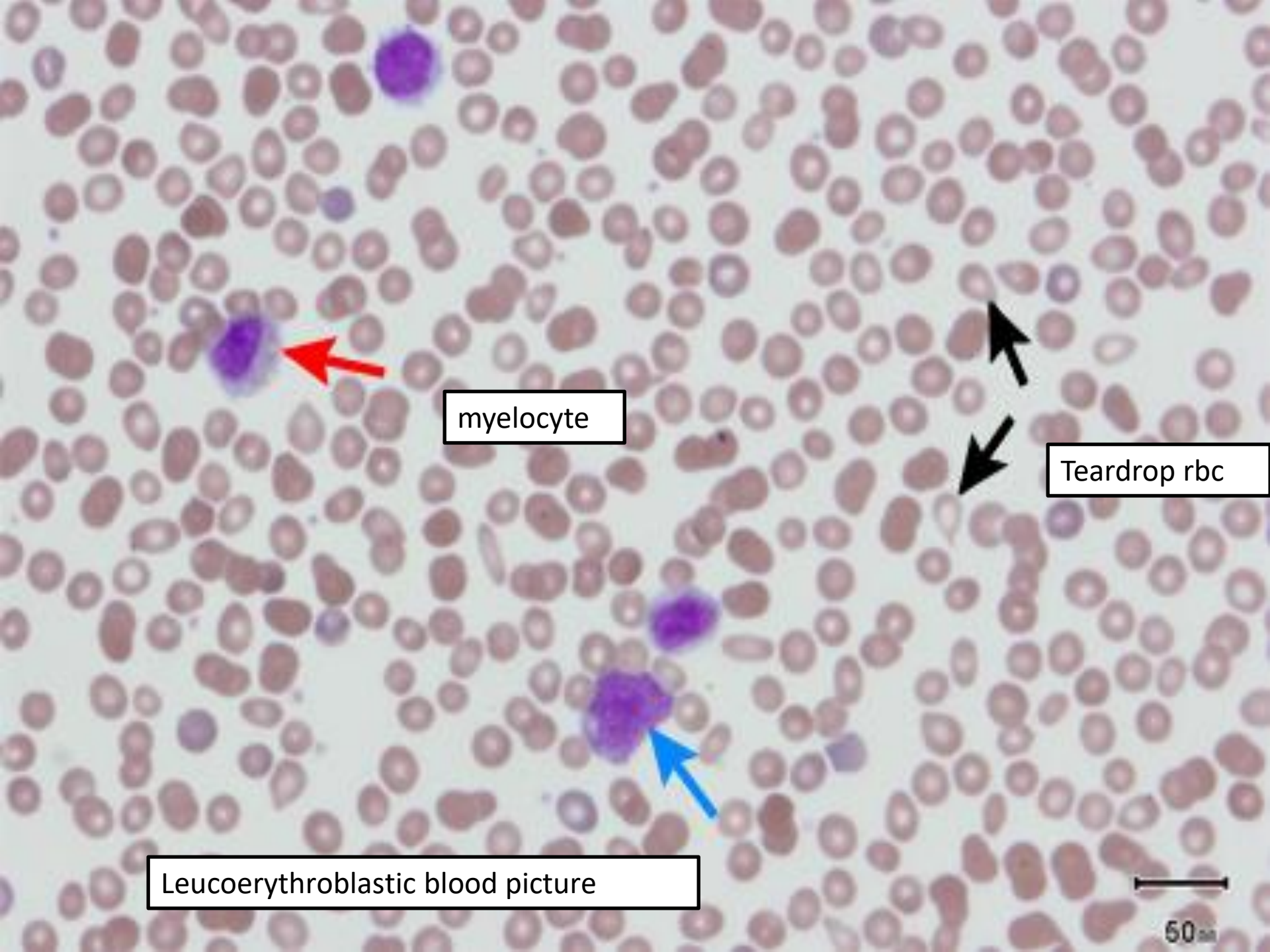
- 3. Not meeting WHO criteria for polycythemia vera, *BCR-ABL1–positive chronic* myelogenous leukemia, myelodysplastic syndrome,or other myeloid disorders

or,in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm,metastatic malignancy, or toxic (chronic) myelopathies

- **Minor criteria**
- 1. Leukoerythroblastosis
- 2. Increase in serum lactate dehydrogenase level
- 3. Anemia
- 4. Palpable splenomegaly

- Treatment –supportive, splenectomy, JAK2 inhibitors

- D/D – other myeloproliferaive neoplasms


myelocyte
Teardrop rbc
Leucoerythroblastic blood picture
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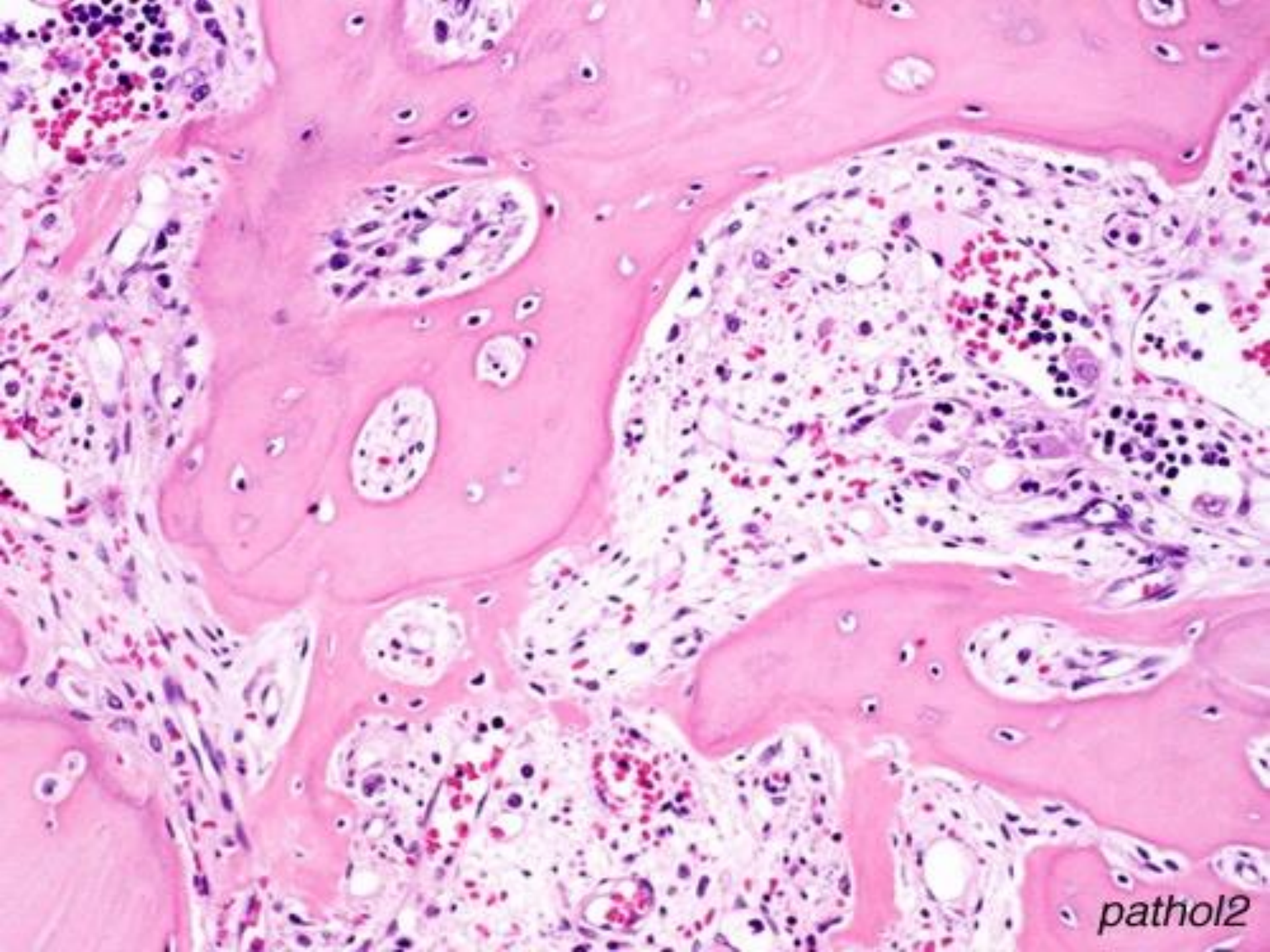
pathol2

Severe myelofibrosis – reticulin stain

What else to read……

- Zahr AA, et al. Bone marrow fibrosis in myelofibrosis, pathogenesis, prognosis and targeted strategies. Hematologica 2016; 101(6): 660-671.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013940/

- The WHO classification of tumours of hematopoietic and lymphoid tissue – Primary myelofibrosis . ((Abutalib SA and Medeiros LJ, The Asco post,)

https://ascopost.com/issues/may-10-2019/the-who-classification-of-tumors-of-hematopoietic-and-lymphoid-tissues/