Grand Rounds Presentation

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SUNY Downstate
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HPI

- 42 yr old AA female presented to ER c/o decreased vision in her left eye for the last 2 months. She reports mild waxing/waning of symptoms over the last 2 month with recent 3 day history of persistent worsening vision. She also reports very mild nonspecific left eye pain on/off during this time. She denies any recent illness or trauma.

ROS

- ROS: occasional palm and foot numbness, otherwise neg.
- PMH: No DM, No HTN, + 2 previous spontaneous abortions
- POH: Denies
- Social Hx: Denies x 3
- NKDA
- Meds/Gtts: none
- Fam Hx: No Glaucoma/blindness

Examination

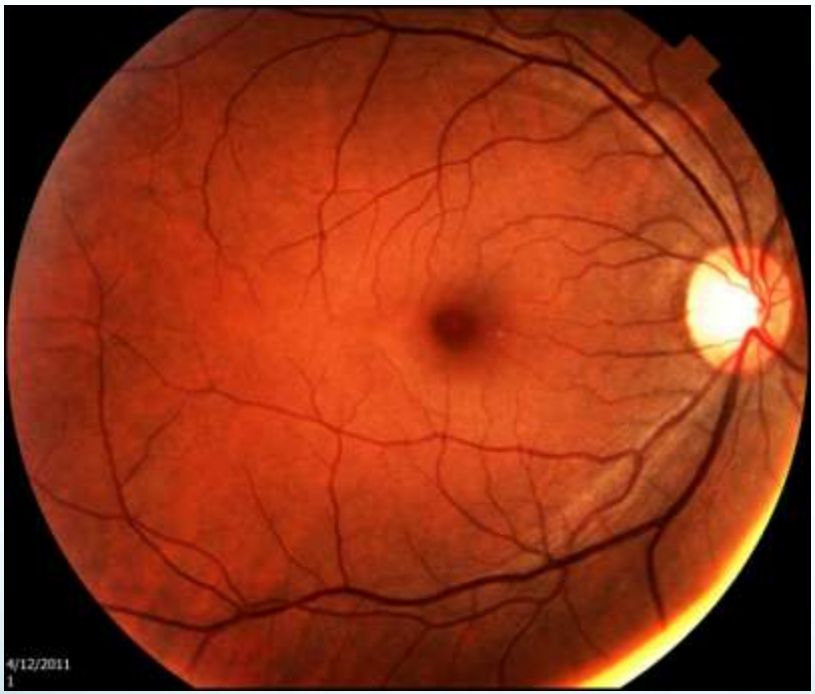
- BCVasc : 20/20 OD, CF OS
- EOM: full OU
- CVF: full OD, generalized restricted field OS
- P: 5-3 OU , + APD OS
- Tap: 16/12 @ noon

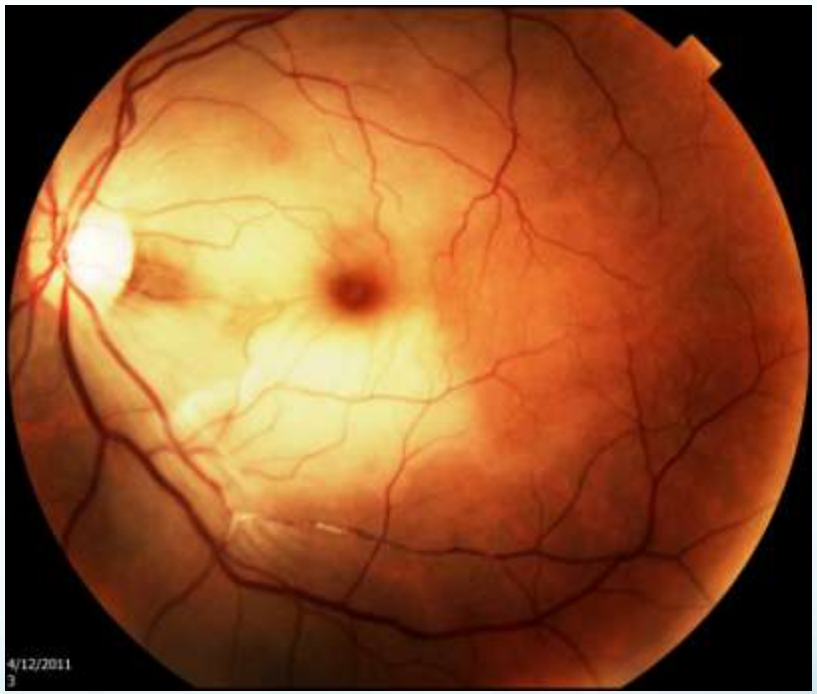
SLE

- LLA: wnl OU
- CS: w/q OD, trace hyperemia w/vascular sludging OS
- K : Dec TBUT OU
- AC: d/q OD, d/1+ mixed cell OS
- IP: RR OU , No NVI OU
- L: trace NS OU

- DFE:

DFE





DDx?

DDx?

- Vascular:
  - CRAO
  - BRAO
  - Ophthalmic artery occlusion
- Inflammatory
  - GCA
  - SLE
  - Syphillis

- Embolic
  - Carotid plaque
  - Mural thrombus
- Vasculitic / Inflammatory
  - GCA
  - SLE
  - Syphillis
- Neoplastic
- Hematologic
  - Hypercoagulable

What Next?

What Next?

- Basic Lab workup:
  - CBC, BMP, Coags, Lipid Panel, Hbg A1C
- Inflammatory workup
  - ESR, CRP, ANA, ACE, ANCA, Lyme, FTA, RF, Lysozyme, HLA-B27, CXR
- Hypercoagulation workup
  - CH50, Prot S, Prot C, Uric Acid, C3, C4, lupus anticoagulant, homocysteine
- Imaging:
  - FA, Carotid Dopplers, Echocardiogram, MRI head/neck

Workup

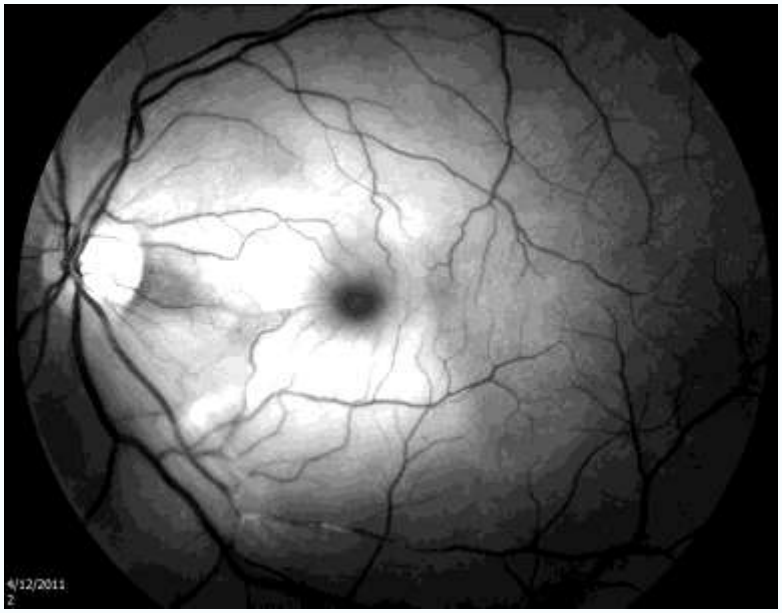
- CMP: wnl
- Lipid Panel: Chol and LDL slightly elevated
- Hgb A1c: 6.6
- Coags: wnl
- CBC**: Platelets 1080 K/uL** (130-400)
- CXR: wnl
- FTA : neg
- ACE: wnl
- ESR : 3
- CRP: 0.2
- ANA: neg
- Lyme: neg
- HLA b27: neg
- RF: neg
- Lysozyme: neg

Workup

- CH50: 48.9 (23-46)
- Prot C: wnl
- Prot S: wnl
- Uric Acid: wnl
- Lupus anticoag: neg
- Homocysteine: wnl
- C3 : 193 (90-180)
- C4: wnl

- Carotid Dopplers: no clinically significant stenosis
- Echo: mildly dilated left atrium, otherwise wnl. EF 55-60%

FA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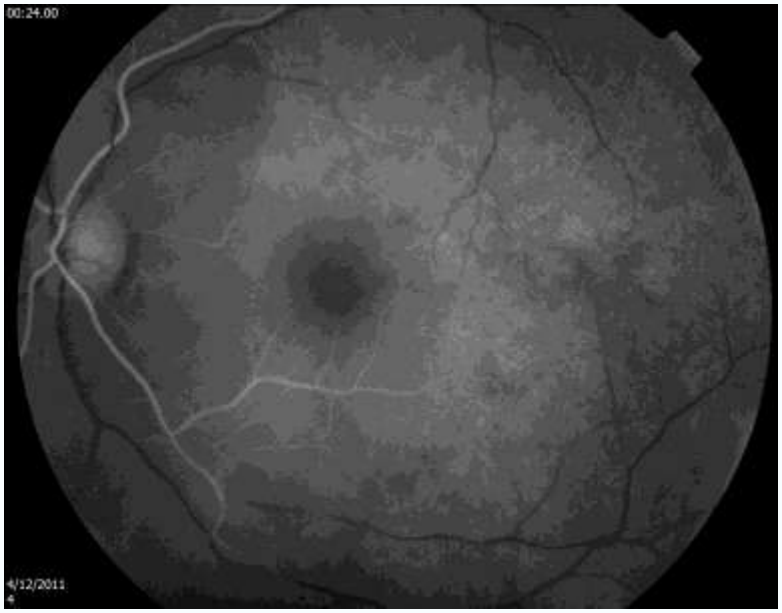
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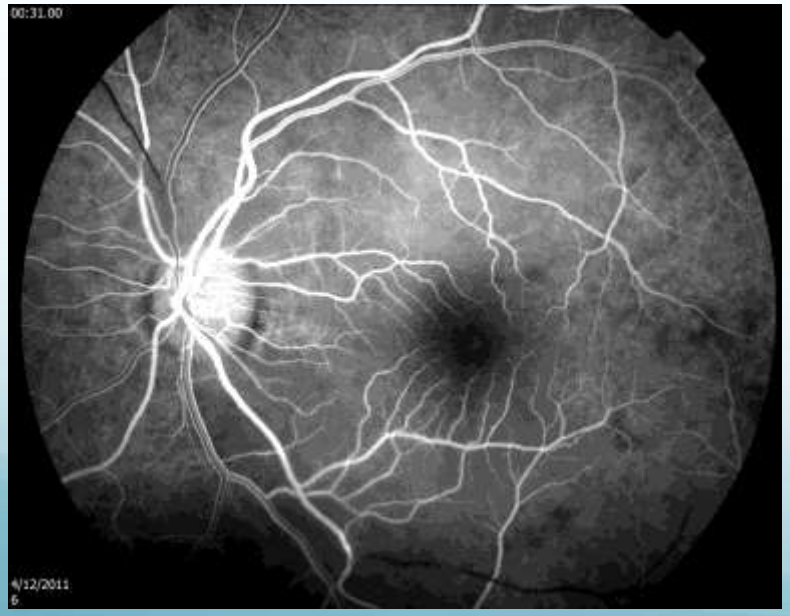
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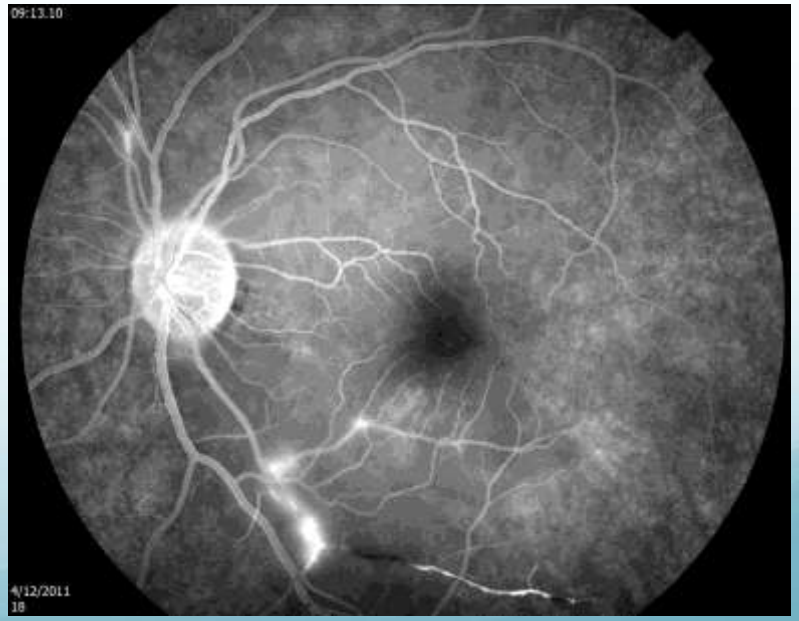
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Now What?

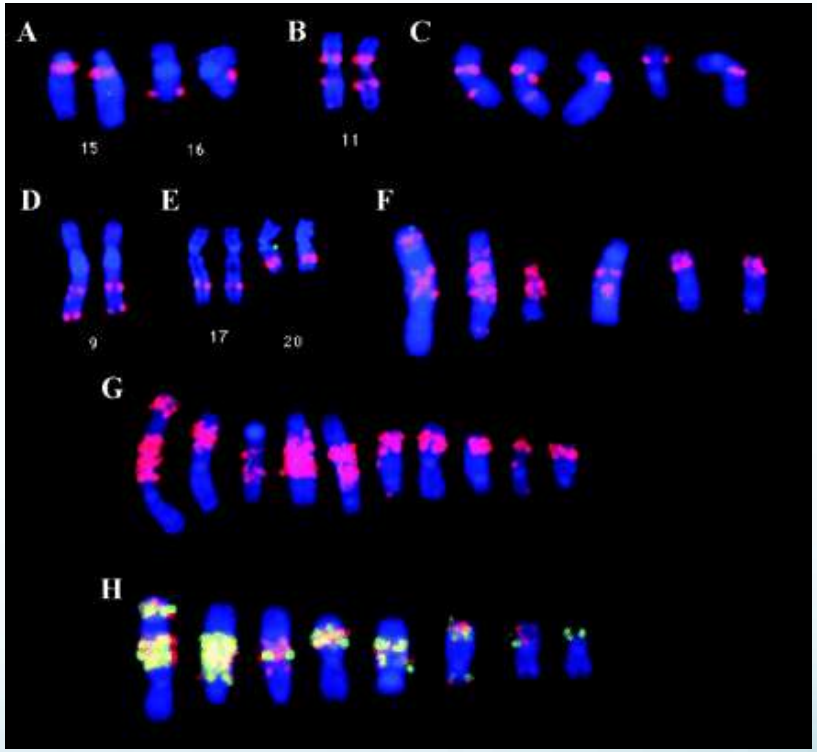
Now What?

- Review of previous records revealed a platelet level of 643 in 2005.
- Started pt on daily 81mg ASA
- Referred to Hematology
  - Recommended FISH chromosomal analysis
- Referred to Neurology
  - Agreed with starting asprin and recommended f/up after MRI studies.

Patient care, systems based practice

Fluorescence In Situ Hybridization (FISH)

- Patient DNA is denatured
- Flourescently labeled specific probes are introduced
- DNA is allowed to hybridize with probes
- Excess probe is washed off
- Chromosomes are analyzed under flourescent microscope

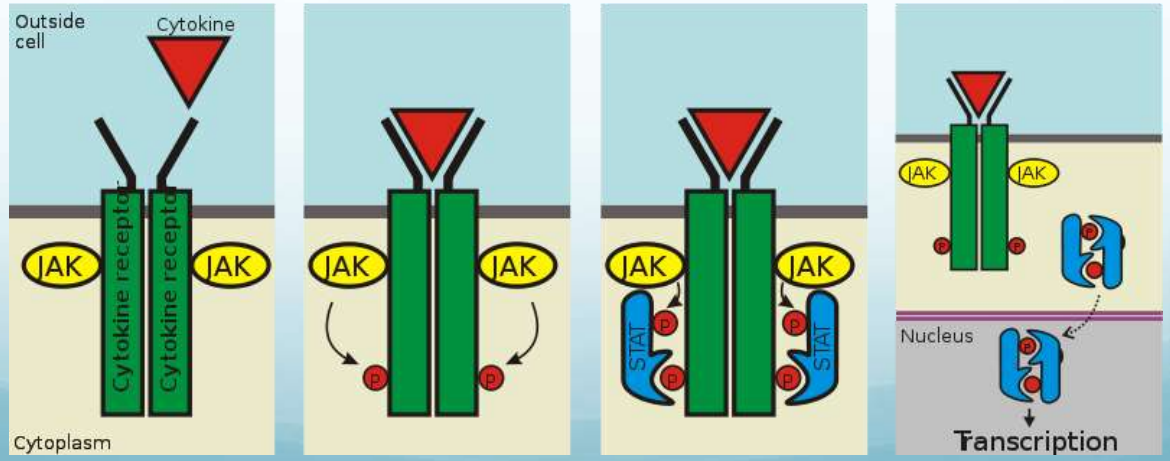


FISH

- FISH analysis revealed a Jak2+ gene mutation

Jak2+

- Located at chromosome 9p24
- Jak (Janus Kinase) proteins are a family of tyrosine kinases often associated with the “Jak/STAT” signal transduction cascade that is involved in regulation many basic cell processes such as cell growth, differentiation and death.
- Involved with signaling of:
  - Erythropoietin receptor, thrombopoetin receptor, and granulocyte colony-stimulating growth factor receptor.



Medical knowledge

JAK/STAT

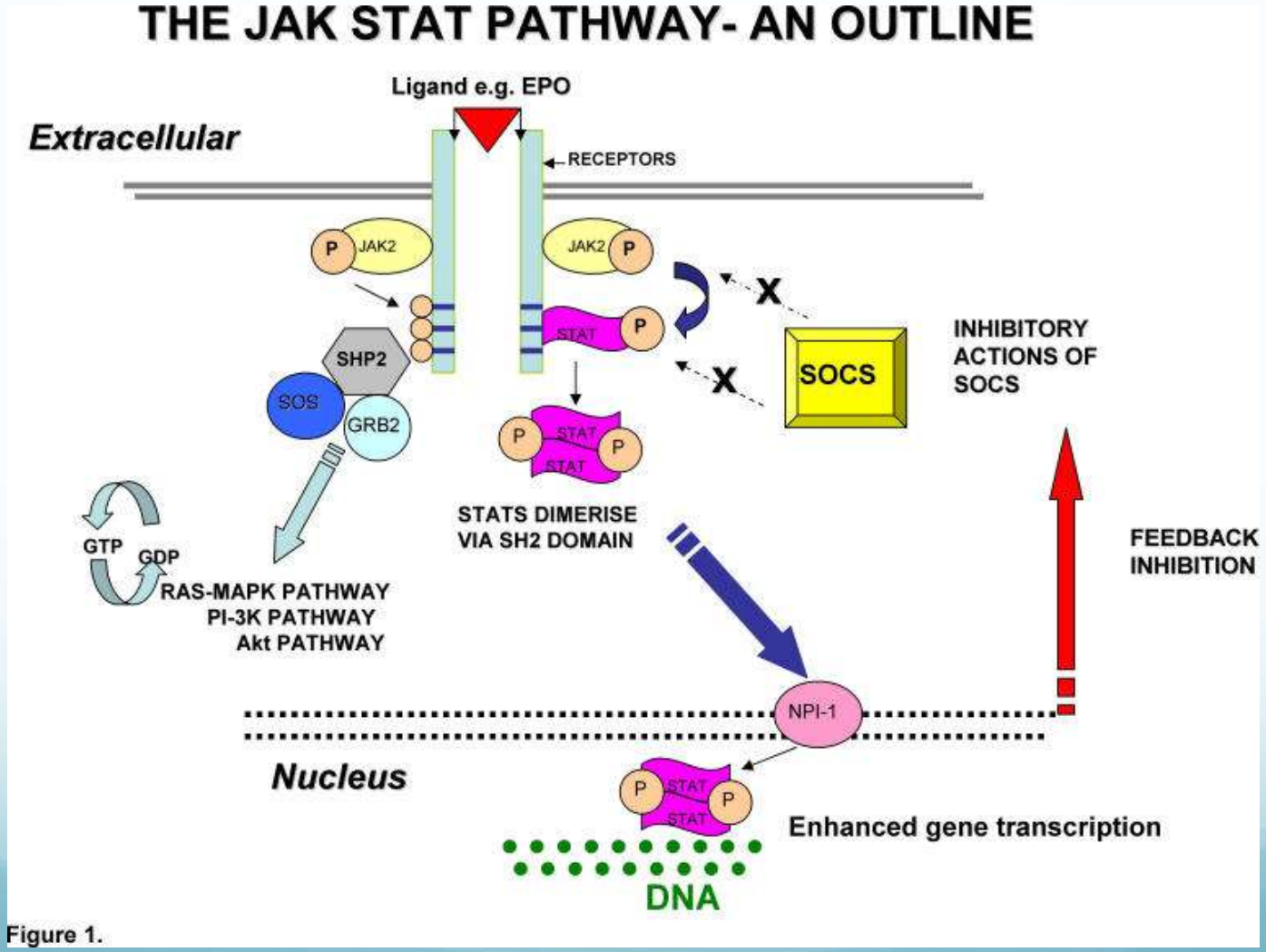


Figure 1.

Jak2+ V617F

- Gain-of-function mutation that leads to clonal proliferation of cell lines.
- Change from Valine to Phenylalanine
- Mutation occurs in JH2 domain of Jak2 protein
  - JH2 domain lies in an autoinhibitory domain that is active in the absence of ligand binding
    - Mutation causes disruption of autoinhibition
- Jak2+ V617F mutation is positive:
  - 95% -polycythemia vera
  - 50% -essential thrombocythemia
  - 50% - idiopathic myelofibrosis

Essential Thrombocythemia

- A member of a family of myeloproliferative disorders
  - Polycythemia Vera
  - Primary myelofibrosis
- Was previously a diagnosis of exclusion
- Has been reported to rarely transform into acute leukemia
- May actually represent a forme frust form of polycythemia vera
  - Share common genetic defect (V617F)

Essential Thrombocythemia

- Females 2x > Males
- Usually diagnosed in the 7^{th} and 8^{th} decade of life

Essential Thrombocythemia

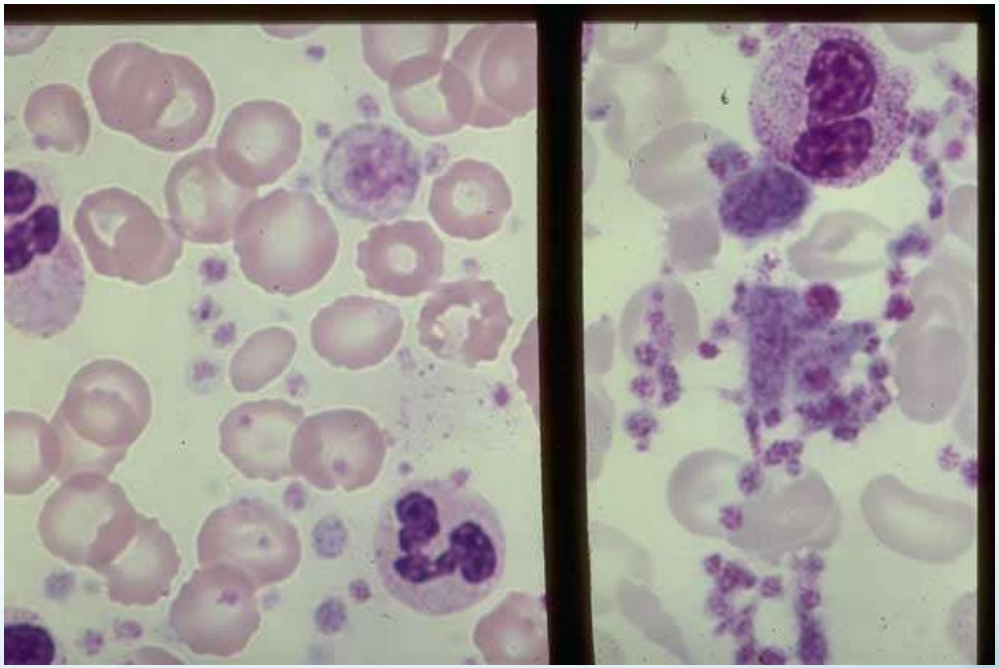
- Diagnostic Criteria:
  - Diagnosis requires A1-A3 or A1 + A3-A5
    - A1 Sustained platelet count >450 × 109/L.
    - A2 Presence of an acquired pathogenetic mutation (eg, in JAK2 or MPL).
    - A3 No other myeloid malignancy, especially polycythemia vera (PV), primary myelofibrosis (PMF), chronic myeloid leukemia (CML) or myelodysplastic syndrome (MDS).
    - A4 No reactive cause for thrombocytosis and normal iron stores.
    - A5 Bone marrow trephine histology showing increased megakaryo- cytes with prominent large hyperlobated forms; reticulin is generally not increased (≤ 2 on a 0-4 scale).

Essential Thrombocythemia

- Complications
  - Headache, lightheadedness, atypical chest pains, distal paresthesias, transient occlusions of microcirculation, visual blurring or diplopia
  - Major source of mortality is thrombosis of large arteries (cardiac, DVT/PE, renal, cerebral).
  - Can get morbidity and mortality from associated hemorrhagic phenomenon (GI bleeds, secondary to trauma, epistaxis, gum bleeding, hematoma formation)
  - Acute leukemia and myelodysplasia are rare late-onset transformation events.

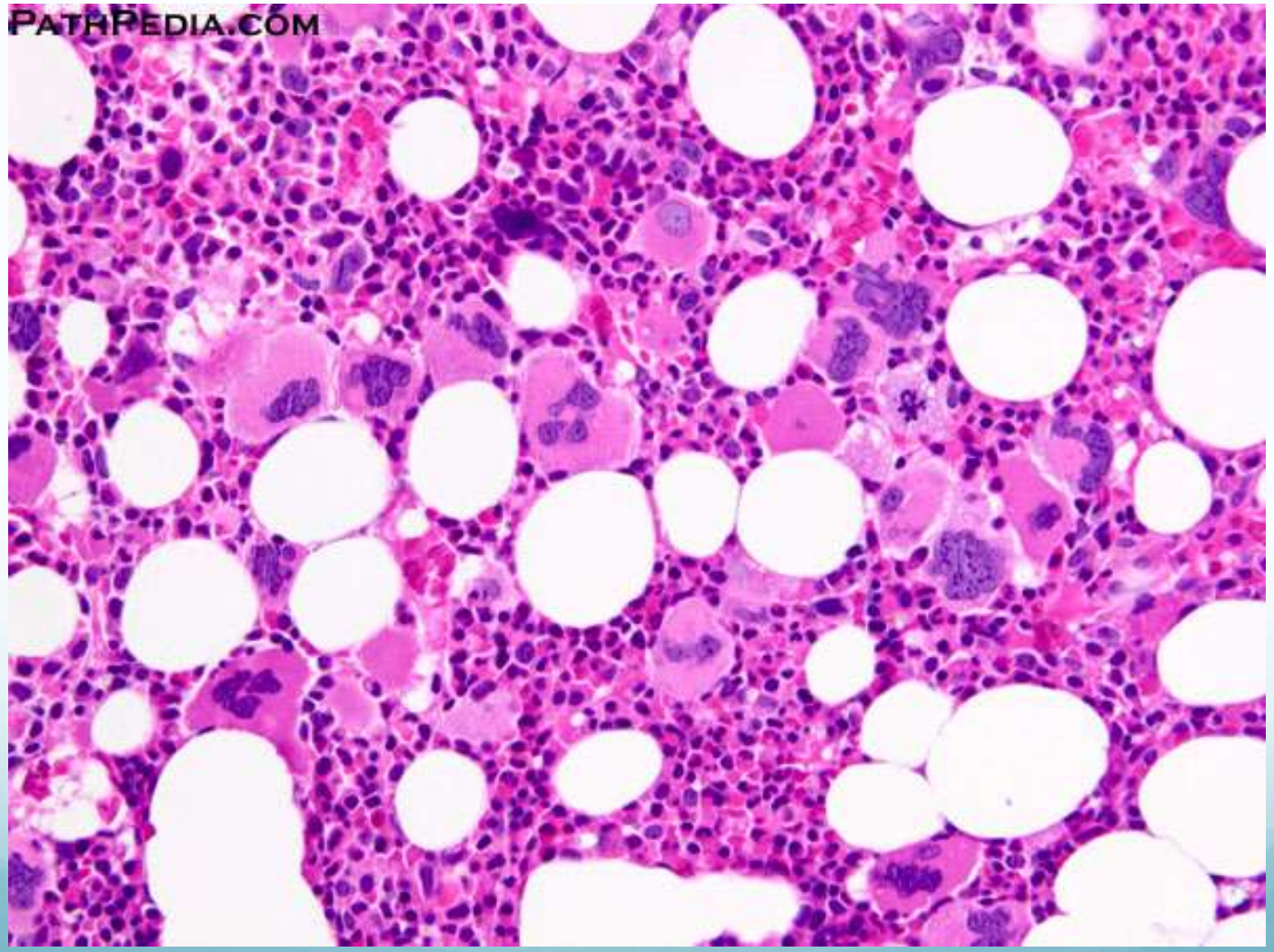
Peripheral Smear

- Increased Number of Platelets
- Increased Size of Platelets
  - Megathrombocytes



- Our patient's smear showed increased number of platelets with occasional large and giant platelets (megathrombocytes)

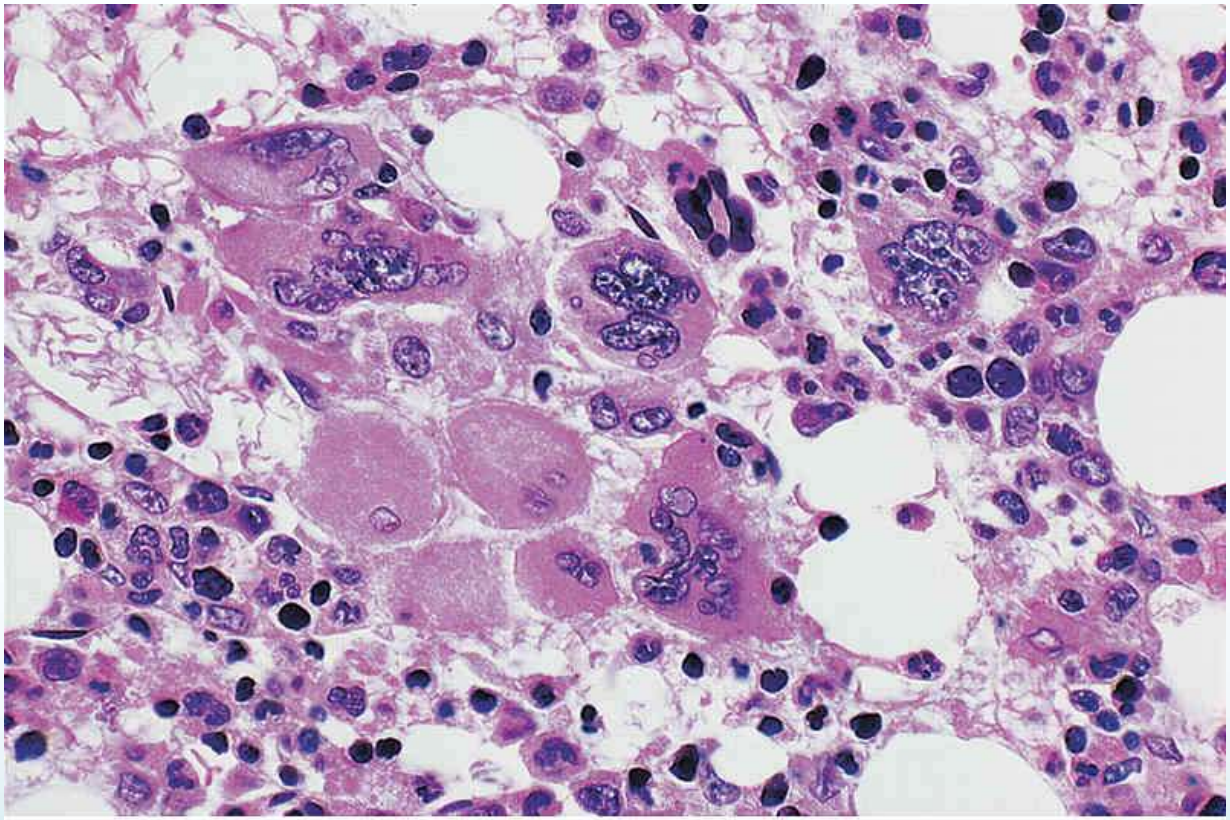
Bone Marrow Biopsy



Polycythemia Vera

- Member of group of myelodysplastic disorders in which largely (or solely) there is marked elevation in red blood cells (primarily)
  - Can also get elevation in platelets or wbc's
- Men>women
- Rare <40 yrs old
- Some symptoms: headache, SOB, dizziness, fatigue, bluish skin discoloration, itchiness, red skin spots, bleeding.

Polycythemia Vera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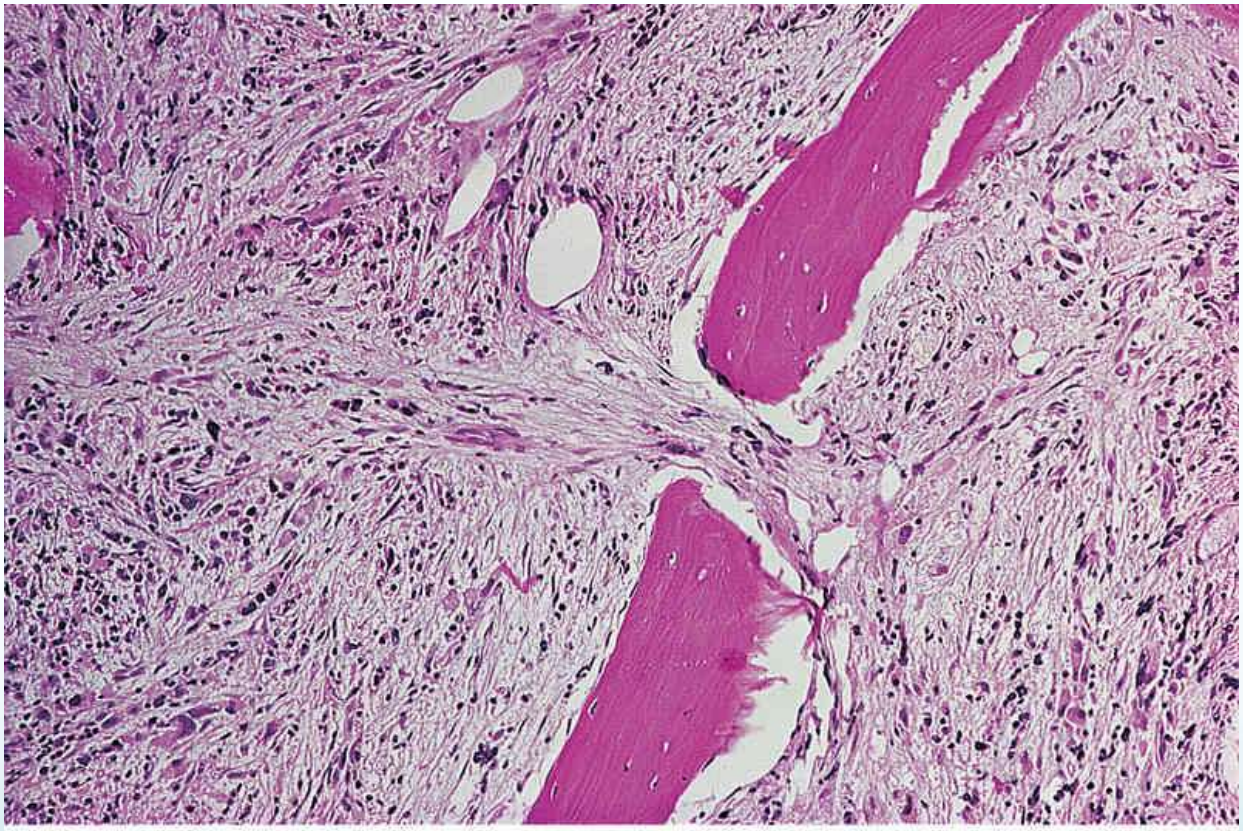
Hyperplastic bone marrow from a patient with polycythemia vera. All cellular elements are increased. Megakaryocytes are prominent and show considerable variation in size; many are unusually large with hyperlobulated nuclei.

Idiopathic Myelofibrosis

- AKA: primary myelofibrosis, agnogenic myeloid metaplasia
- Bone marrow fibrosis and production of abnormal blood cells
- Men and women
- Usually ages 50-70 yrs old
- Symptoms: splenomegaly, fatigue, unexplained bleeding, night sweats, weakness, weight loss

Idiopathic Myelofibrosis



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Biopsy from an adult with a 7-year history of chronic idiopathic myelofibrosis (agnogenic myeloid metaplasia). There is extensive marrow fibrosis with marked reduction in hematopoietic tissue.

Treatment Options

- Daily low dose Asprin (81mg)
- Hydroxyurea
- Interferon-alpha
- Anagrelide
- Pipobroman
- Busulfan
- Melphalan
- Radioactive Phosphorus (^{32}P)

Medical knowledge

Treatment Algorithm

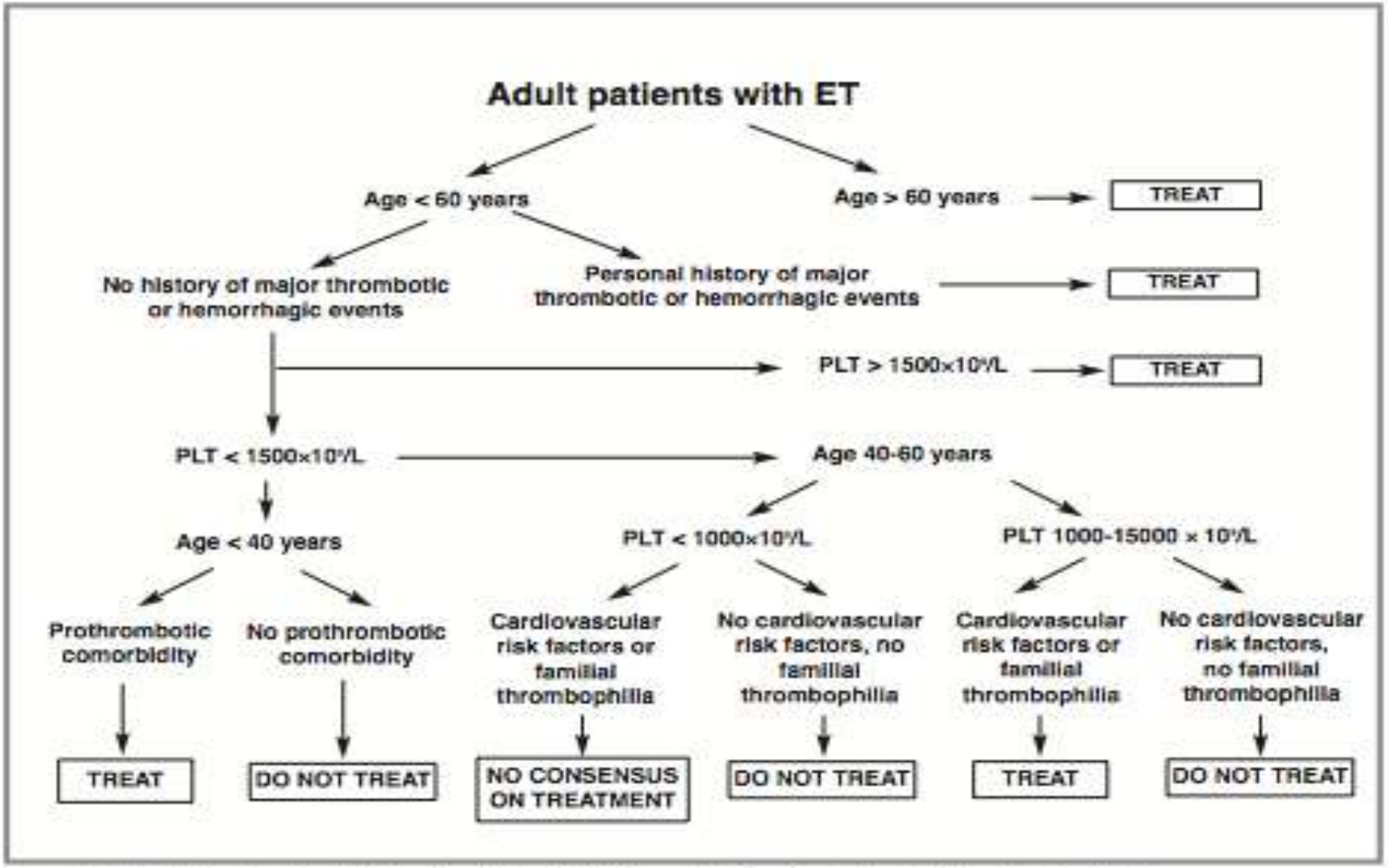


Figure 1. Algorithm for the decision to start platelet-lowering treatment in adult patients with ET.

Treatment

- Target of therapy is to lower platelets to a level of 400.
- A level of 600 may be an apropriate target for pts who require high doses of medication/ high risk of toxicity.
- Should be followed every 3-4 mo by PCP for the first year then twice yearly.
  - Should monitor CBC with diff, cardiovascular risk factors, signs/symptoms of embolic and hemorrhagic events.

Hydroxyurea

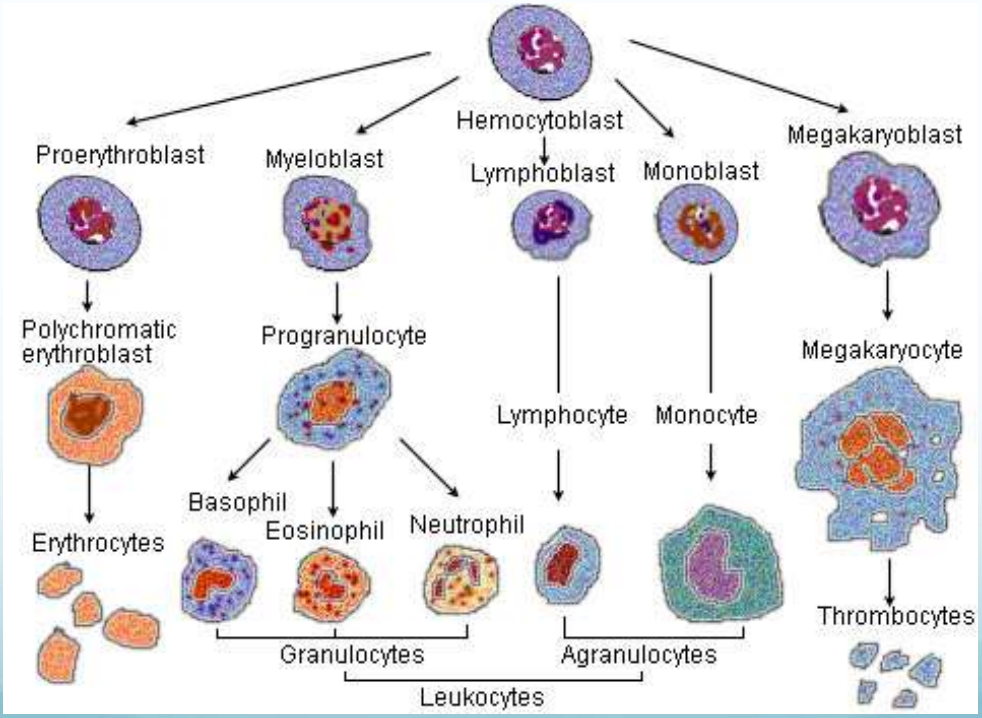
- Inhibits ribonucleosidase reductase.
  - Inhibits DNA synthesis
- Causes generalized myelosupression of all myelogenous cell lineages
- Can cause increased risk of malignancy when used in conjunction with other myelosupressive agents (eg. Busulphan)
- Generally accepted as first line therapy for essential thrombocythemia.

Interferon-alpha

- Direct acting cytokine that can inhibit hematopoeic progenitor cells and megakaryocytic forming units.
- Main side effect is flu-like symptoms upon induction of therapy

Anagrelide

- Acts by inhibiting megakaryocyte maturation
- Phosphodiesterase inhibitor with unknown exact mechanism of action



Other Treatments

- Pipobroman – alkylating agent. Has been shown to carry a aprox. 2.5% risk of leukemic transformation.
- Busulfan –alkylating agent used commonly in CML. Has been shown to have higher incidence of secondary malignancy in pt's treated with busulfan and hydroxyurea.

CRAO Interventions and Prognosis

Beatty S, Au Eong KG. Acute occlusion of the retinal arteries: current concepts and recent advances in diagnosis and management. J Accid Emerg Med. 2000 Sep;17(5):324-9

- Systematic review of the acute CRAO literature
- Showed a lack of evidence to support visual improvement with any intervention
  - Ocular massage
  - Iop lowering medication
  - Inhalation of carbogen
  - Ac paracentesis
  - Systemic anticoagulation
  - (Selective intra-arterial fibrinolysis (tPA) has shown promise but serious complications can occur and access to neuroradiological support is limited)

CRAO Interventions and Prognosis

- 62.5-66% of cases have a final visual acuity of counting fingers or worse
- 18-21% of cases will have good visual outcome as defined by 20/40 or better
- Major cause of mortality is cardiovascular disease
  - Arterial occlusion patient population survival prognosis is similar to age/sex matched cohort
  - Those with visible emboli have statistically higher mortality
    - 26% died with mean f/up of 9.7 yrs.

Our Patient

- After the Jak2+ lab result our patient returned to Hematology clinic
  - Recommended:
    - Continuing daily ASA
    - Starting daily hydroxyurea
    - No need for further anticoagulation at this time other than daily ASA
    - Return to Hematology clinic in 1 mo

Systems based practice, patient care

Our Patient

- Continue to closely follow at KCH eye clinic
- Has had no clinical deterioration in her vision OU
- Va continues to be 20/20 OD and CF OS
- Will obtain MRIs soon and continue to follow with Hematology and Neurology

Patient care, professionalism

Reflective Practice

- Here we have presented a rare case of Jak2+ Essential Thrombocythemia induced retinal arterial occlusion. I believe that the patient was evaluated, and treated apropriately. Additionally It highlights the necessity and advantage of a well coordinated multidisciplinary approach to patient care.

Practice based learning, professionalism

Core Competencies

- Patient Care – throughout the patient encounters the patient was appropriately treated with compassion and the patient's best interest in mind.
- Interviewing and Communication Skills- A thorough ROS and history was obtained from the patient and open communication between consulting services was maintained at all times.
- Professionalism – the patient was treated with kindness and in a respectful professional manner at all times.
- Medical Knowledge – The scientific literature was reviewed and then was applied to the patient encounter.
- Systems Based Practice – The ophthalmologists were able to work within the framework of the hospital system to call upon proper consult services and arrange to get certain testing done while the patient was in the hospital.
- Practice Based Learning – The patient was monitored closely and interval changes were noted at each visit. Changes in patient care were made based on patient performance and testing results.

Practice based learning

References

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- http://www.pathconsultddx.com – images

Thank You

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