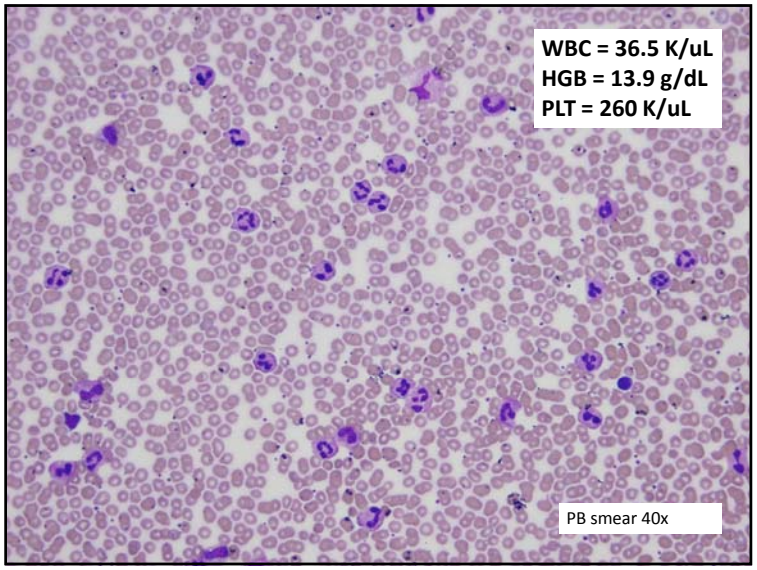
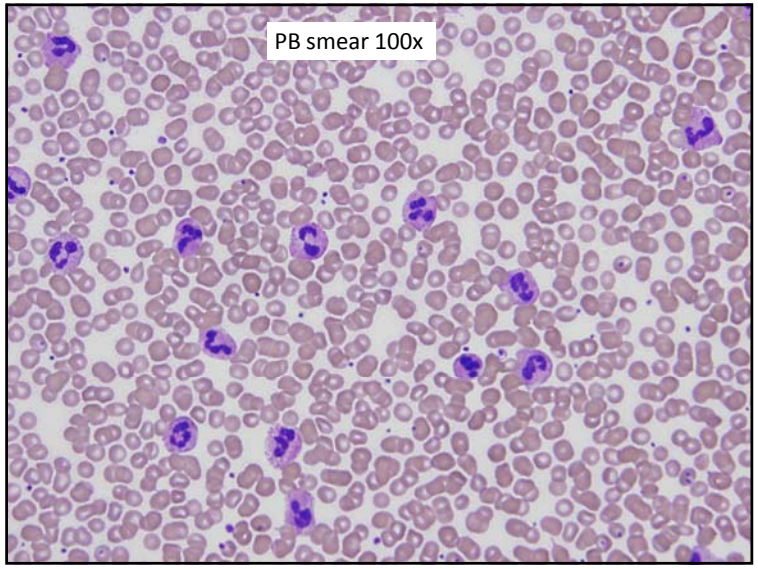
Case presentation

- 52 yo man
- Incidental finding of leukocytosis (36.5K/uL)
- No systemic Sx (fever, chills, night sweats)
- Mild splenomegaly





Classification of neutrophilia

Spurious
Platelet clumping
Mixed cryoglobulinemia
Primary (no other evident associated disease)
Myeloproliferative disorders (eg, CML, PV, ET)
Hereditary neutrophilia
Chronic idiopathic neutrophilia
Familial myeloproliferative disease
Congenital anomalies and leukemoid reaction
Down syndrome
Leukocyte adhesion factor deficiency
Familial cold urticaria and leukocytosis
Secondary
Infection
Stress (physical or emotional stress, vigorous exercise)
Cigarette smoking
Drugs
Glucocorticoids
Recombinant G-CSF or GM-CSF*
Catecholamines (epinephrine)
Lithium
All-trans retinoic acid
Isolated case reports for occasional other drugs
Nonhematologic malignancy
Heatstroke
Generalized bone marrow stimulation (as in hemolysis)
Asplenia and hyposplenism

Most commonly encountered causes of neutrophilia are shown in **bold**.

CML: chronic myelogenous leukemia; PV: polycythemia vera; ET: essential thrombocythemia; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.
* These agents are used therapeutically to raise the neutrophil count.

UpToDate

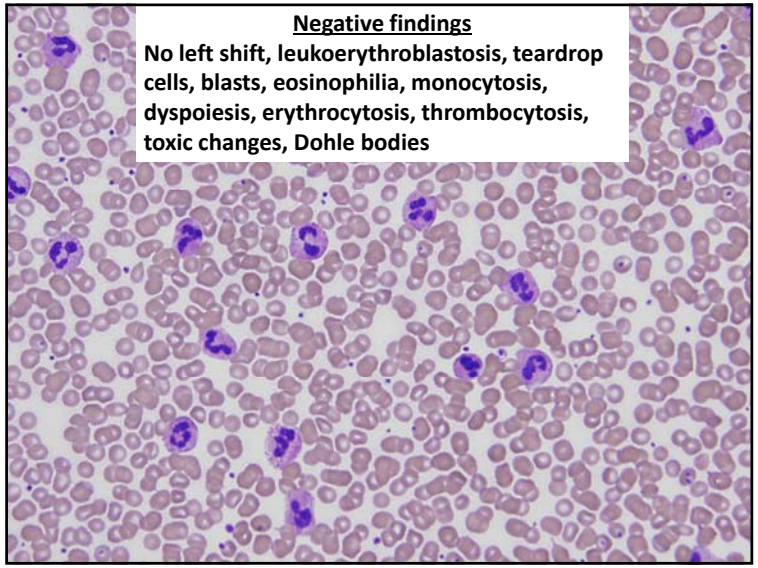
Clinical evaluation offers no explanation for persistent neutrophilia.

Which of the following should you NOT do?

A) Review peripheral smear
B) Bone marrow biopsy
C) Exclude plasma cell neoplasm
D) Molecular/genetic workup
E) Start pitcher in GAME 7 of World Series (*THE single most important game of the season)* who got completely shelled in Game 3 and didn't even last 2 innings !!!

Differential in our case…

- Reactive
  - Occult or undiagnosed infection, inflammation, stress, underlying tumor, drugs…etc.
- Myeloproliferative neoplasms
- MDS/MPN
- Myeloid/lymphoid neoplasm with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2

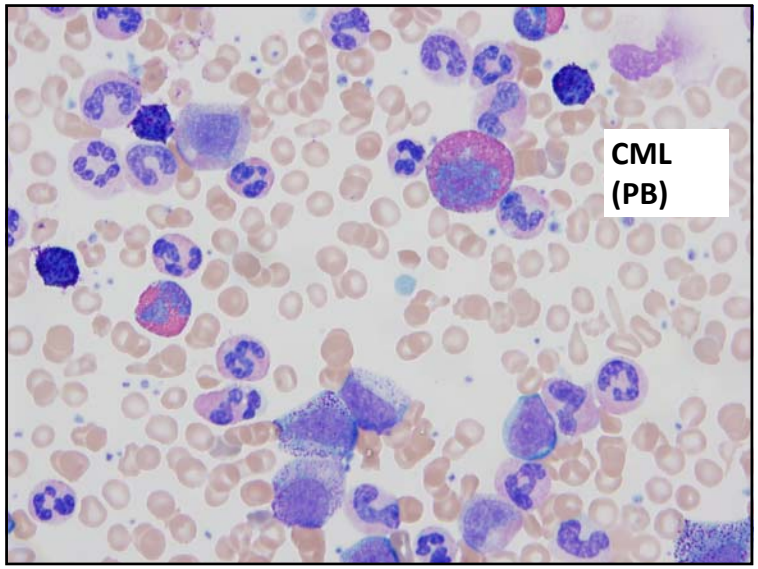


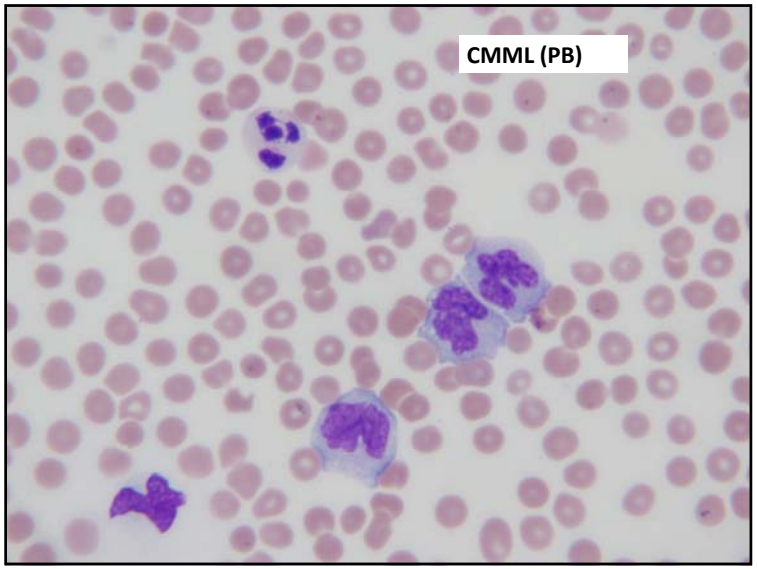
Negative findings

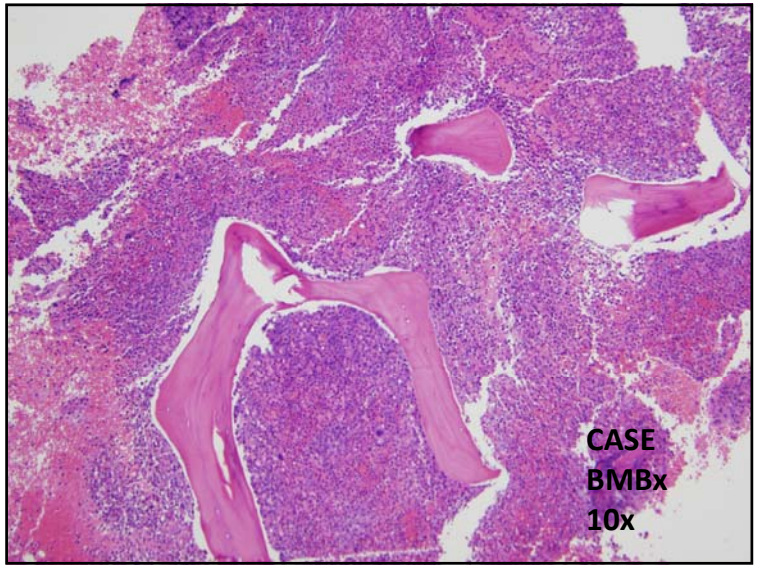
No left shift, leukoerythroblastosis, teardrop cells, blasts, eosinophilia, monocytosis, dyspoiesis, erythrocytosis, thrombocytosis, toxic changes, Dohle bodies

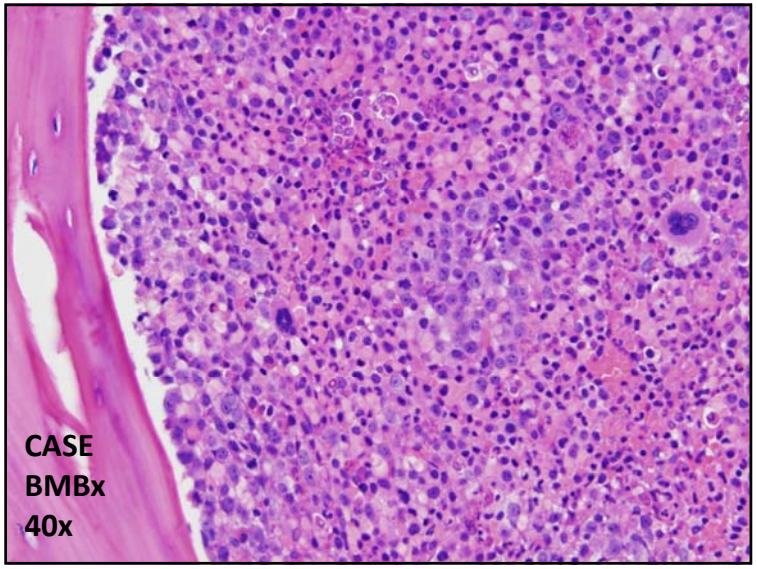
Differential – PB clues

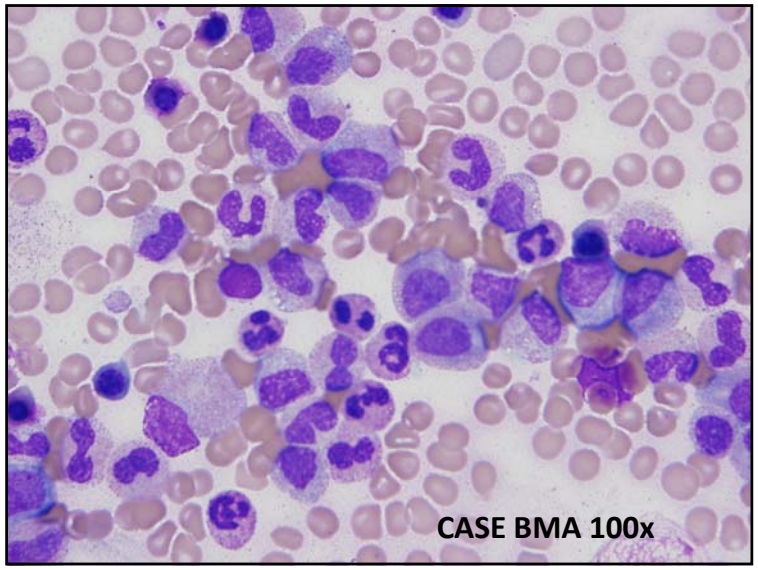
- Reactive
  - Toxic granules, Dohle bodies
- Myeloproliferative neoplasm
  - CML (left shifted granulocytes, basophilia)
  - PV (erythrocytosis)
  - PMF (leukoerythroblastosis, teardrops)
  - ET (thrombocytosis)
  - CEL (eosinophilia)
  - CNL
  - MPN unclassifiable
- Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2
  - Eosinophilia (variable other findings)
- MDS/MPN
  - Dysplasia
  - Monocytosis > 1000/uL (CMML)


CML
(PB)


CMML (PB)

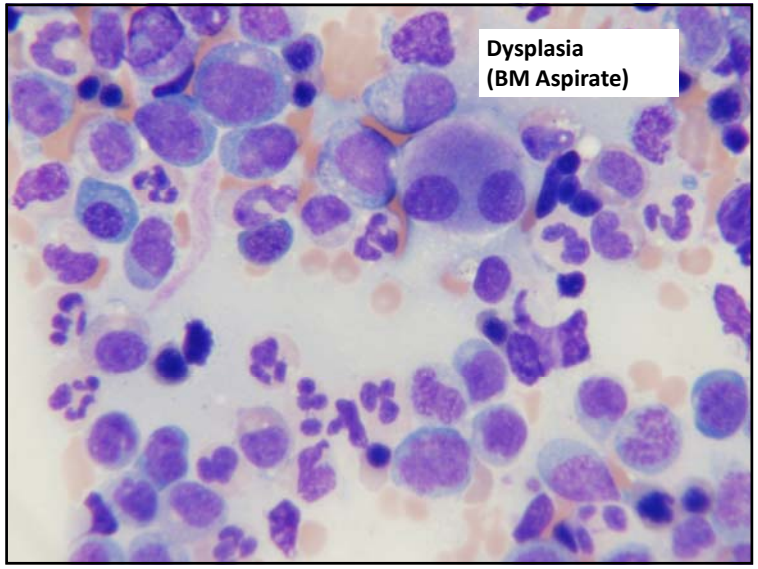

CASE
BMBx
10x


CASE
BMBx
40x



Differential – BM findings missing for certain diagnoses

- Reactive
- Myeloproliferative neoplasm
  - CML (dwarf megs)
  - PV (panhyperplasia)
  - PMF (clustered pleomorphic megs)
  - ET (numerous megs)
  - CEL (eosinophilia)
  - CNL
  - MPN, unclassifiable
- Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2
  - Eosinophilia, varied BM histology (CEL, CMML, LBL, ALL, AML)
- MDS/MPN
  - Dysplasia

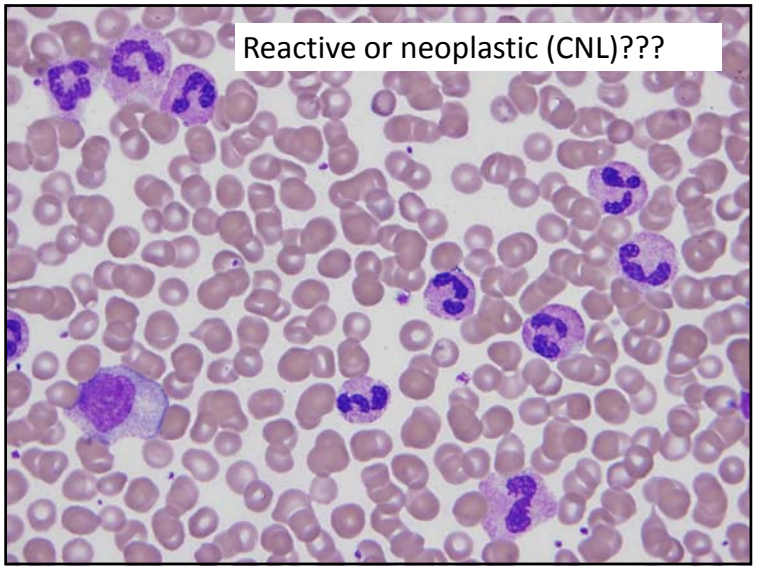


Our case: Molecular/genetic results

- Karyotype – Normal male 46,XY
- FISH
  - Negative BCR/ABL
  - Negative PDGFRa, PDGFRb, FGFR1
- Molecular
  - Negative JAK2 V617F, JAK2 exon 12-14, CALR, MPL

Differential

- Reactive
- Myeloproliferative neoplasms
  - CML (BCR/ABL -)
  - PV (JAK2 V617F and JAK2 exon 12 -)
  - PMF and ET (JAK2-/CALR-/MPL-; 10% "triple neg"; morphology and CBC)
  - CEL (no eos)
  - CNL
  - MPN unclassifiable
- Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2
  - PDGFRa-/PDGFRb-/FGFR-; no eos
- MDS/MPN
  - Normal karyotype; No monocytosis (CMML); No dysplasia



Chronic neutrophilic leukemia (CNL)

2008 WHO criteria

- PB leukocytosis (WBC>25x10^9/L)
  - Segmented/bands represent >80% of WBCs
  - Neutrophilic precursors <10% of WBC. Blasts rare.
  - Monocytes <1x10^9/L
- No dysgranulopoiesis
- BM hypercellular with granulocytic hyperplasia and blasts <5%
- Hepatosplenomegaly
- No identifiable cause for physiologic neutrophilia, or, if present, demonstration of clonal myeloid cells (molecular/genetic studies)
  - No infectious, inflammatory process or underlying tumor
- Does not meet criteria for CML, PV, ET, PMF
- No rearrangement of PDGFRa, PDGFRb, FGFR1 or PCM1-JAK2
- No evidence of MDS or mixed MDS/MPN
  - No granulocytic or other lineage dyspoiesis, no monocytosis

Diagnosis of Exclusion

Chronic neutrophilic leukemia (CNL)

Updated 2016 WHO criteria

- PB leukocytosis (WBC>25x10^9/L)
  - Segmented/bands represent >80% of WBCs
  - Neutrophilic precursors <10% of WBC. Blasts rare.
  - Monocytes <1x10^9/L
  - No dysgranulopoiesis
- BM hypercellular with granulocytic hyperplasia and blasts <5%
- Does not meet criteria for CML, PV, ET, PMF
- No rearrangement of PDGFRa, PDGFRb, FGFR1 or PCM1-JAK2
- Presence of CSF3R T618I or other activating CSF3R mutation
  - If no CSF3R mutation, then persistent neutrophilia (>3 mos.), with splenomegaly and no identifiable cause of reactive neutrophilia, including plasma cell neoplasm, or, if present, myeloid clonality demonstrable by molecular/genetic studies.

MOLECULAR- ONCOHEME COMPLETE

Date Ordered: 4/25/2017 **Status:** Signed Out

INTERPRETATION
Specimen: PERIPHERAL BLOOD

Test Requested: Comprehensive mutation and fusion analysis by Next Generation Sequencing

Tumor Type: Myeloproliferative neoplasm (chronic neutrophilic leukemia)

Genomic Alterations Detected	Allele Frequency
CSF3R (c.1853C>T; p.T618I)	45%
CSF3R (c.2337T>A; p.Y779*)	44%

INTERPRETATION:

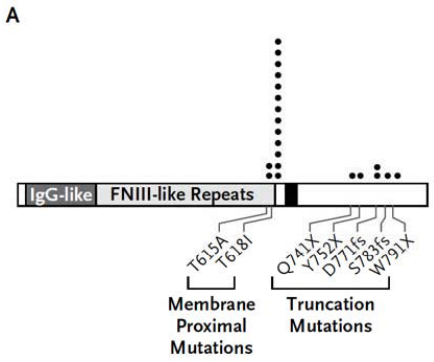
CSF3R: Two alterations of the *CSF3R* gene were detected. The *CSF3R* gene encodes the receptor for colony-stimulating factor 3. Mutations of the CSF3R gene are often found in myeloproliferative neoplasms (MPN), particularly in chronic neutrophilic leukemia (CNL) [1-3]. One alteration detected is a missense mutation at codon 618 of the *CSF3R* gene. The T618I mutation is the most common hotspot alteration of *CSF3R* and has been suggested as a driver mutation of leukemic transformation in congenital neutropenia progressing to acute myeloid leukemia (AML) [4, 5]. Preclinical studies have suggested the association of T618I mutation with increased sensitivity to JAK1/2 inhibitor therapies [1, 6].The other alteration detected is a nonsense mutation at codon 779 and has been prevously reported in CNL cases [7]. Furthermore, nonsense mutations result in premature termination and likely loss of function of the gene.

CSF3R mutations

- 80-90% in WHO defined CNL
  - Membrane proximal mutations common (Maxson NEJM 2013)
  - T618I mutation appears quite Sensitive and Specific for CNL
    - Ligand independent activating mutations of JAK-STAT pathway (ruxolitinib responsive)
  - Others types of mutations (intracytoplasmic truncation) occur in CNL but usually along with T618I or T615A mutations
- Variable % reported in atypical CML
  - Very low if strictly WHO defined (*Wang et al, Blood 2014*)
- Rare in other myeloid disorders
  - 1-2% AML
  - Rare in CMMoL (different mutations than CNL)
  - Severe congenital neutropenia (mostly acquired truncation type), Hereditary chronic neutrophilia

Maxson 2013; Pardanani 2013

CSF3R mutations in CNL



Plasma cell neoplasm with CNL-like changes

- CNL-like findings associated with MG
- Secondary to aberrant CSF3 production by PC
  - CNL-like changes remit with treatment of PC disorder
  - Neutrophils shown to be polyclonal
- Lack CSF3R activating mutations (T618I)
- Prognosis much more favorable than CSF3R+ CNL

CNL vs Atypical CML

CNL	Atypical CML (MDS/MPN)
• PB granulocytosis – Only rare left shifted forms	PB granulocytosis - Left shifted forms in PB (>10% metas, myelo, pro) - dysgranulopoiesis
• BM myeloid hyperplasia	BM myeloid hyperplasia - dysgranulopoiesis
• Activating CSF3R mutations (80-90%)	CSF3R mutations variably reported (probably very low incidence if WHO criteria applied strictly) *Wang et al Blood 2014; 123(17):2645-2651.*

CNL disease features (T618I +)

- Often incidentally discovered (asymptomatic)
- 1/3 have splenomegaly
- Mild anemia, variable PLT count
- Normal karyotype
  - 20-25% have nonspecific clonal findings del20q, +21, del 11q, del 12p
- Molecular
  - SETBP1 mutations (35%), ASXL (50%)

CNL (T618I +) disease features

- Chronic phase → Accelerated phase → Blast crisis
- 20% progress to AML at 21 mos.
- Median survival <2 years
- Ruxolitinib (JAK inhibitor) limited experience
  - Effect may be abrogated by other mutations (SETBP1)
- Hydroxyurea or interferon to control WBC
- Bone marrow transplant

Chronic neutrophilic leukemia Key points

- Requires comprehensive correlation of clinical, morphologic and molecular/genetic findings
- Activating CSF3R mutations represent new diagnostically helpful finding

THANK YOU!!!