



Memorial Sloan Kettering
Cancer Center

SH2017-0159

Myeloid neoplasm with del(5q) and *SF3B1* and *MPL* gene mutations

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Patient Y.K.

77 year old male

Past Medical History:

Paroxysmal A fib

Diabetes

HTN

HLD

GERD

Social History:

Emigrated from South Korea in 1973

Retired architectural engineer

Former smoker

No exposures

Family History:

No hematologic disease

Medications:

Atorvastatin

Lisinopril-hydrochlorothiazide

Aspirin

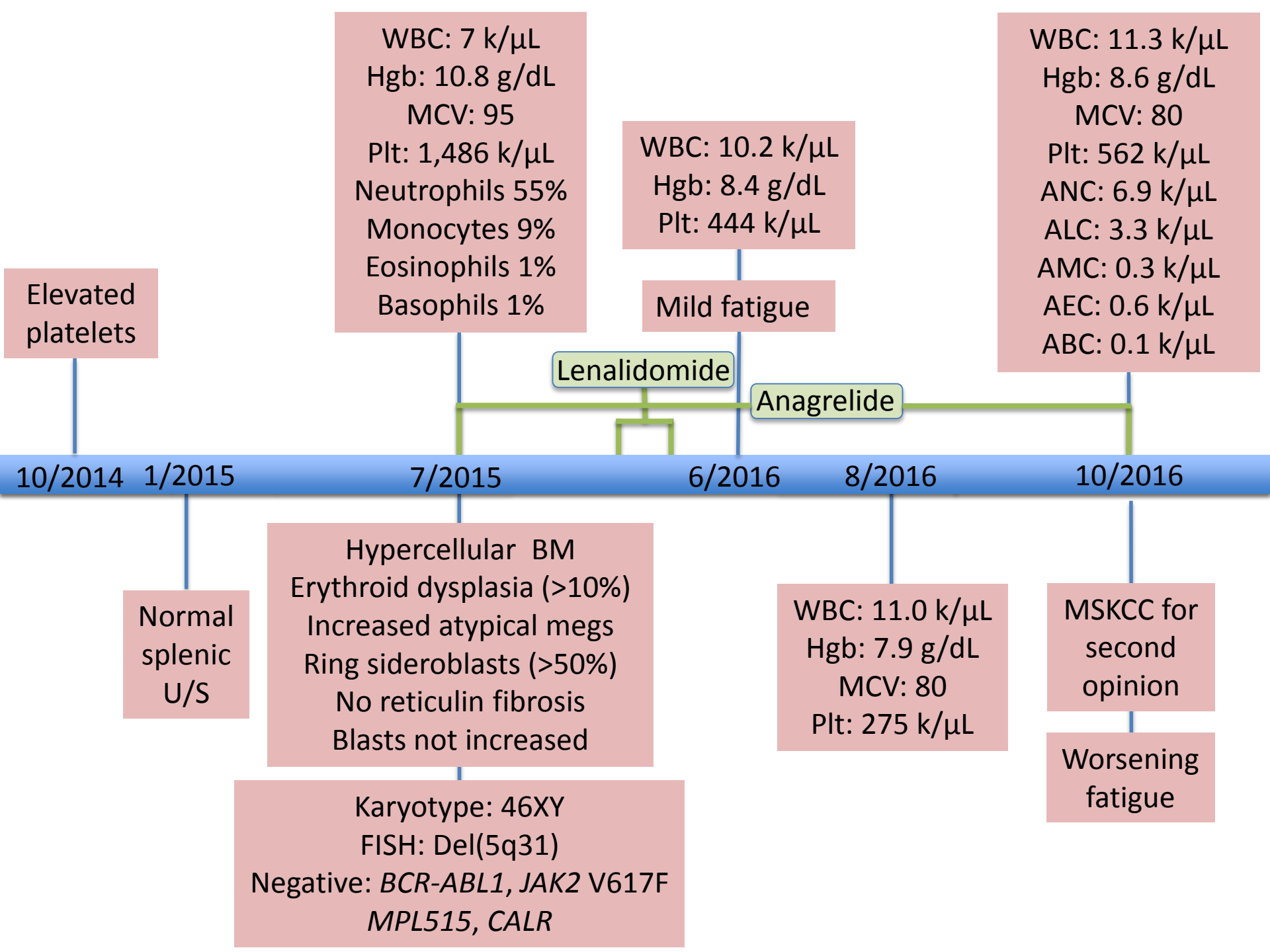
Metformin-sitagliptin

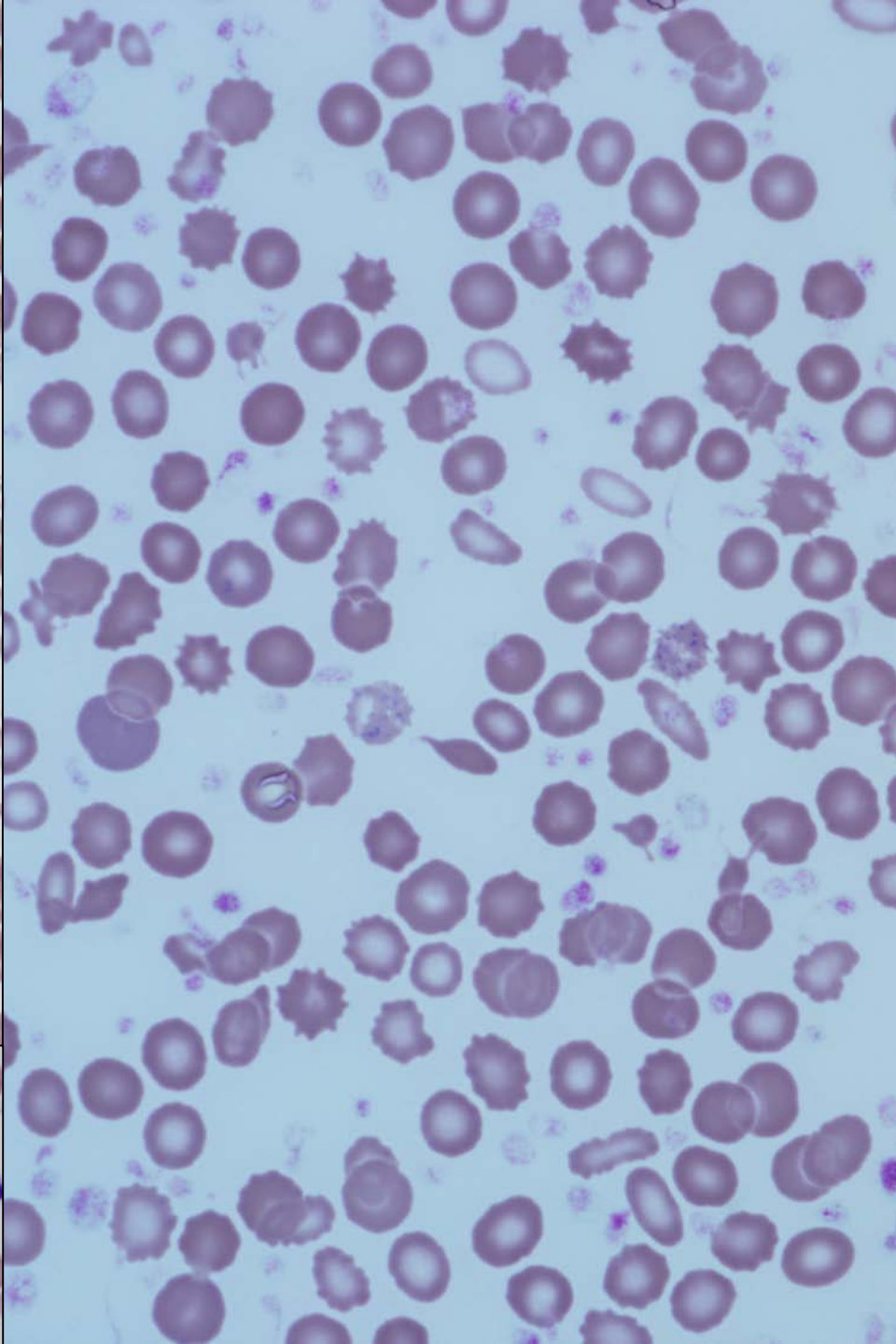
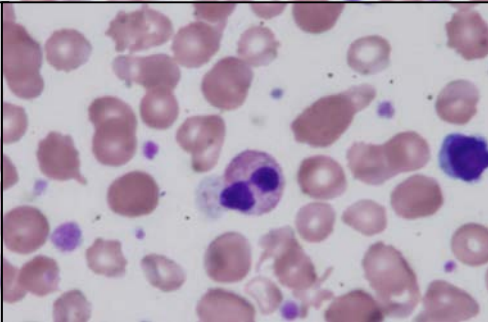
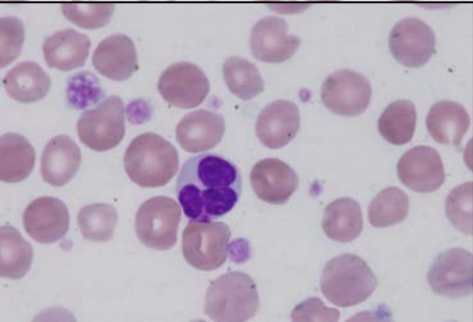
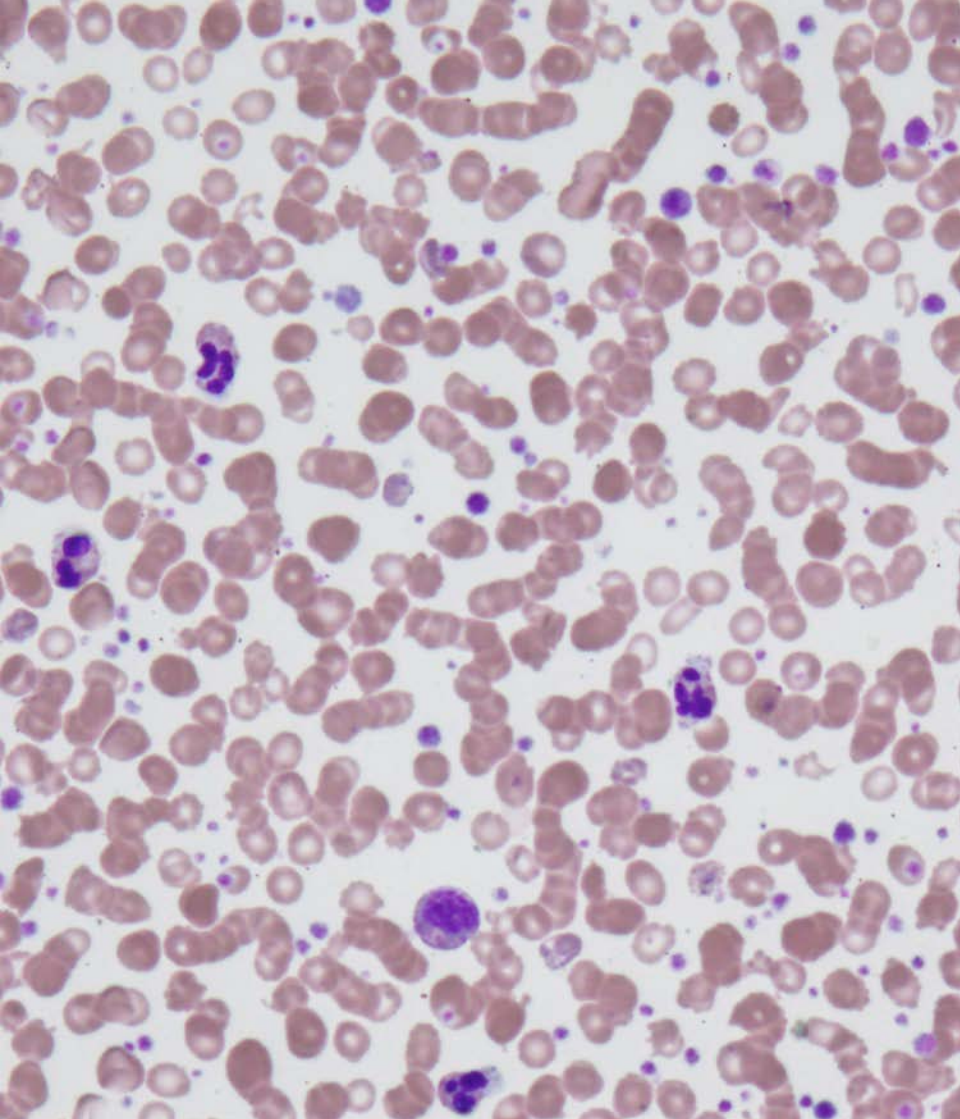
Esomeprazole

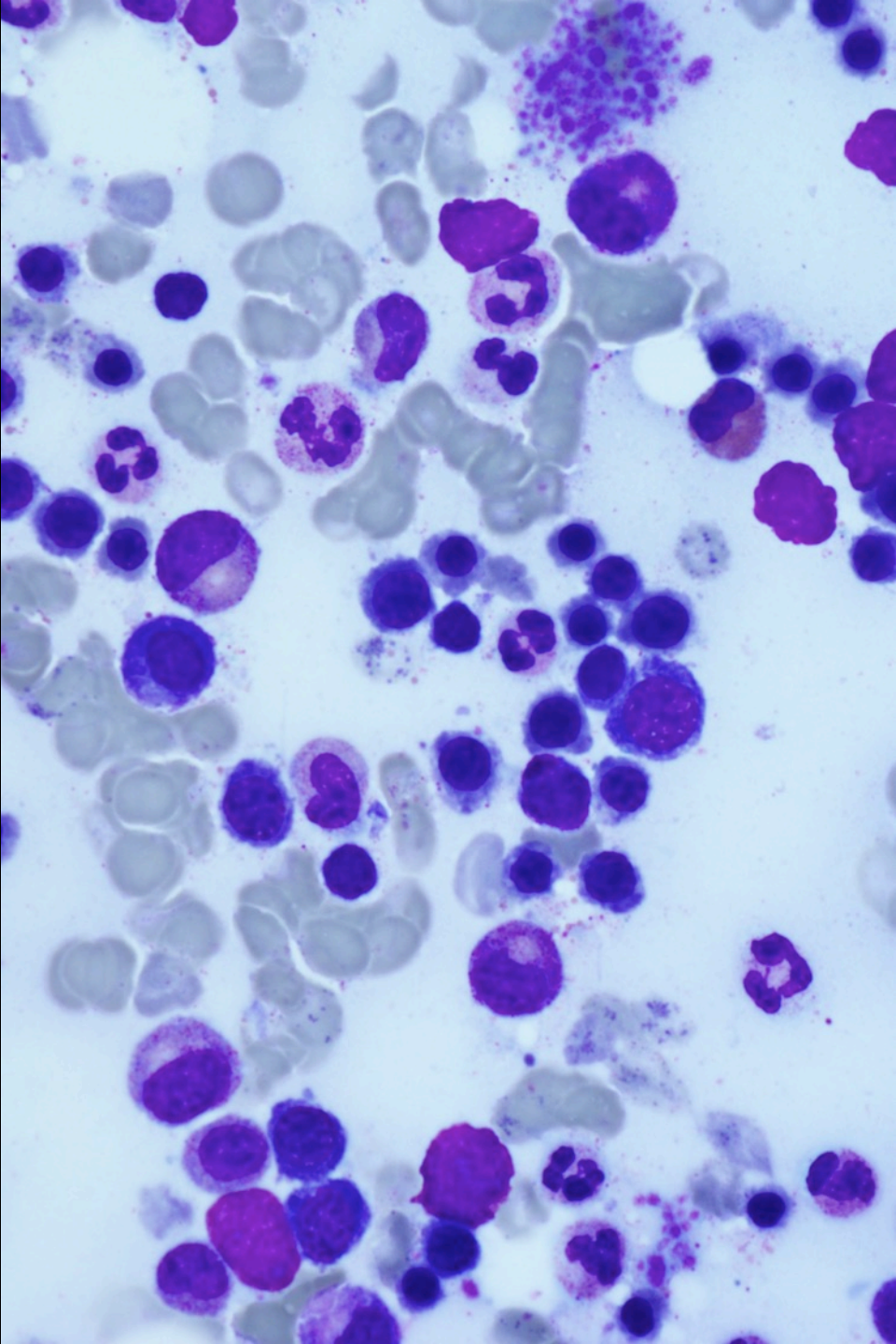
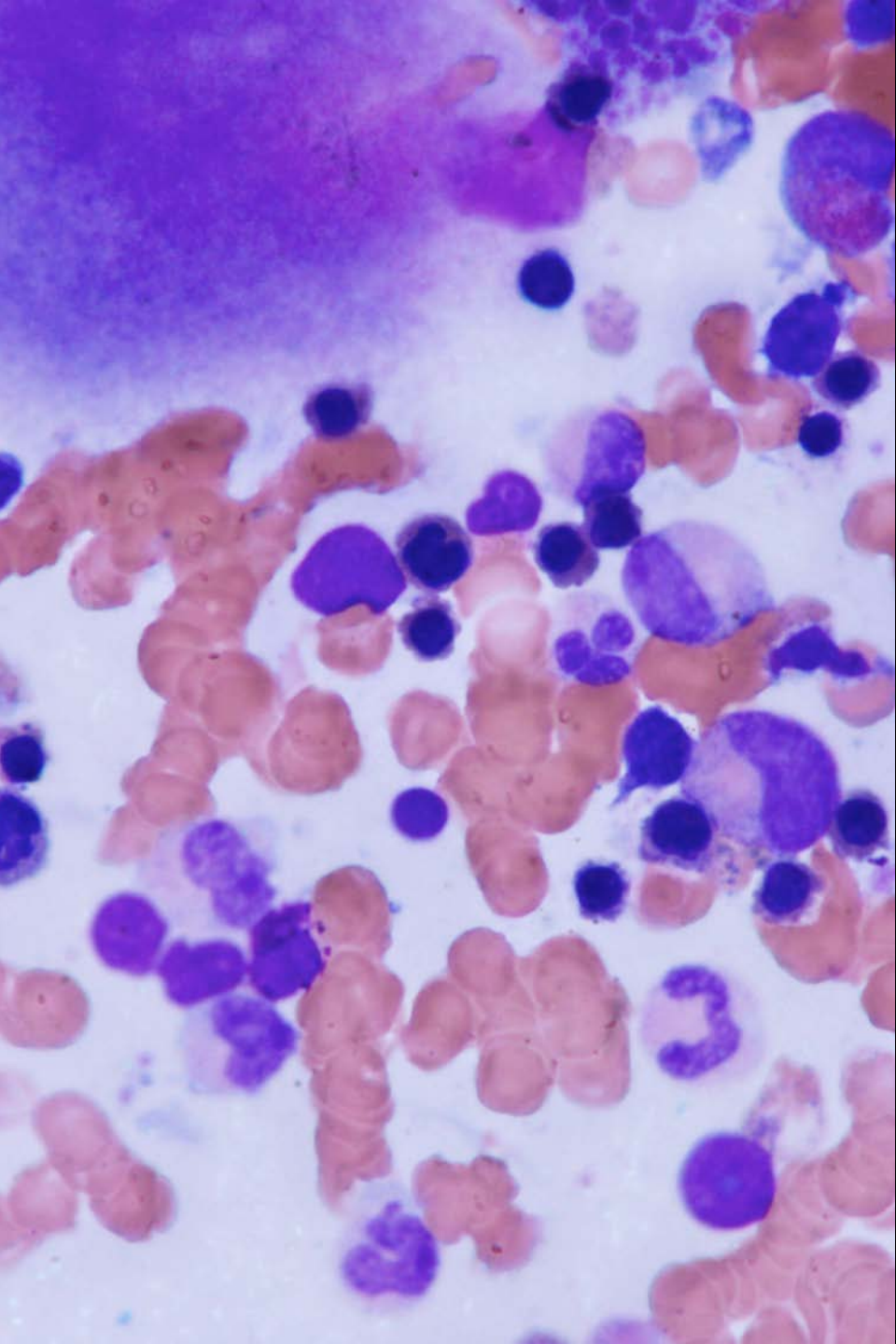
Multivitamin

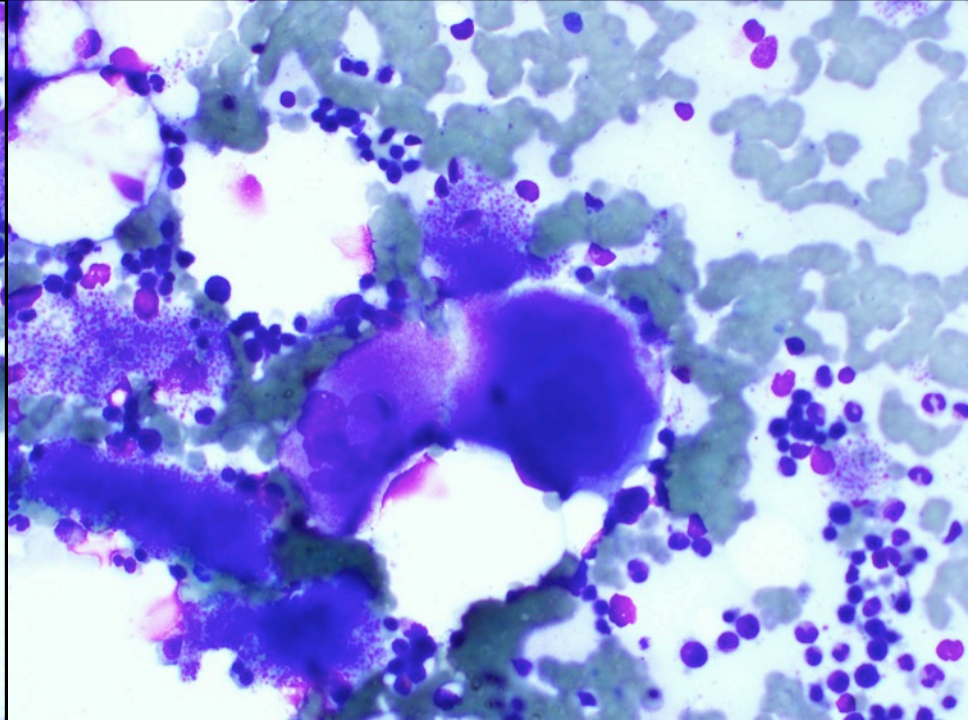
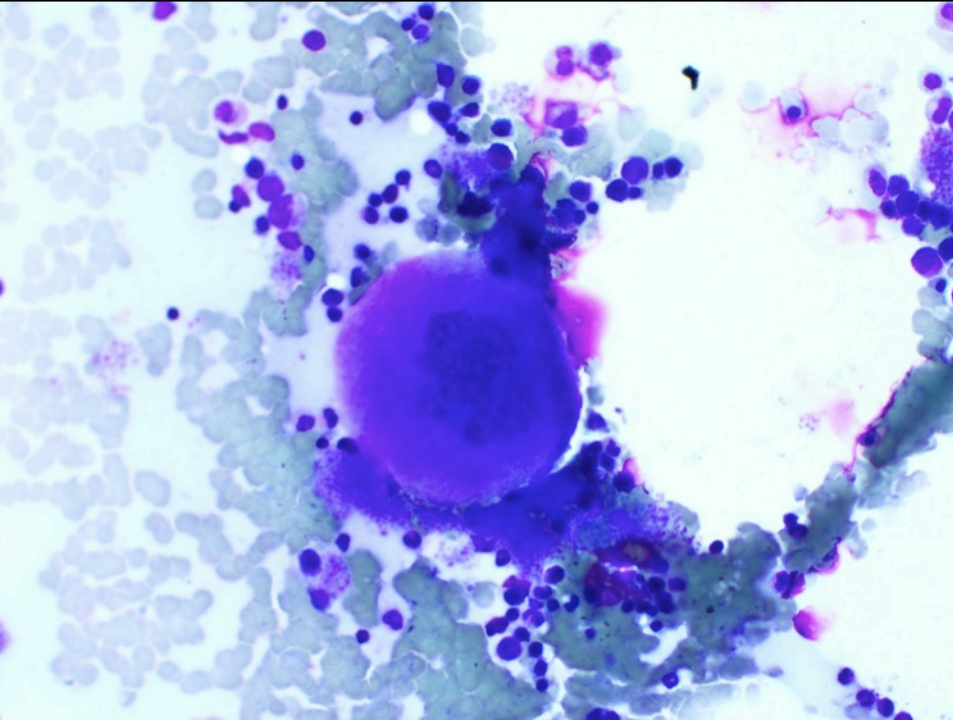
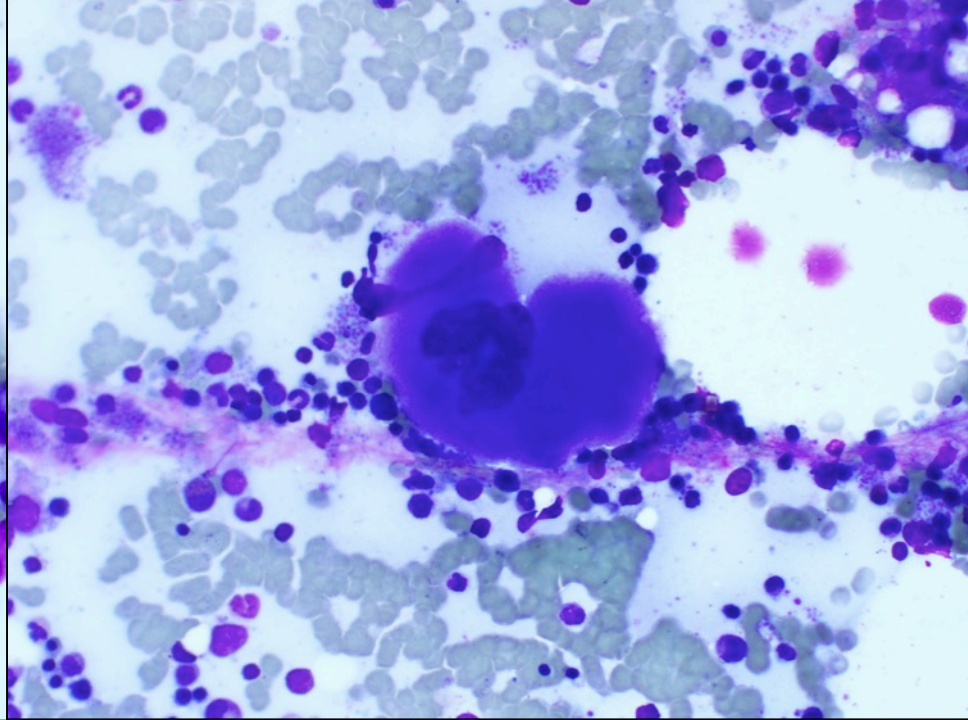
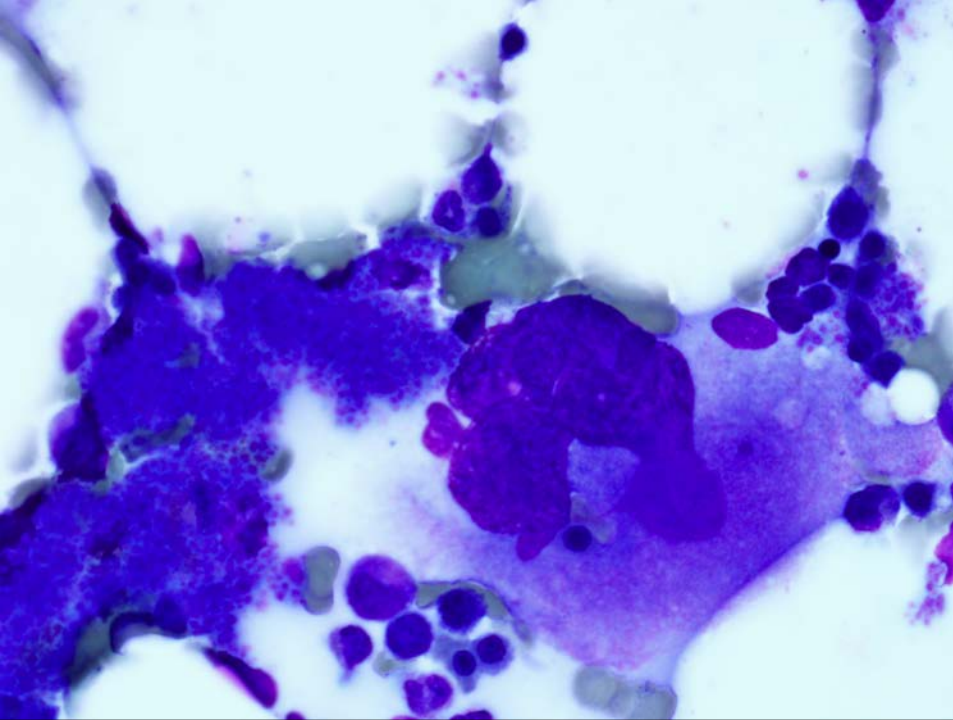
Fish oil

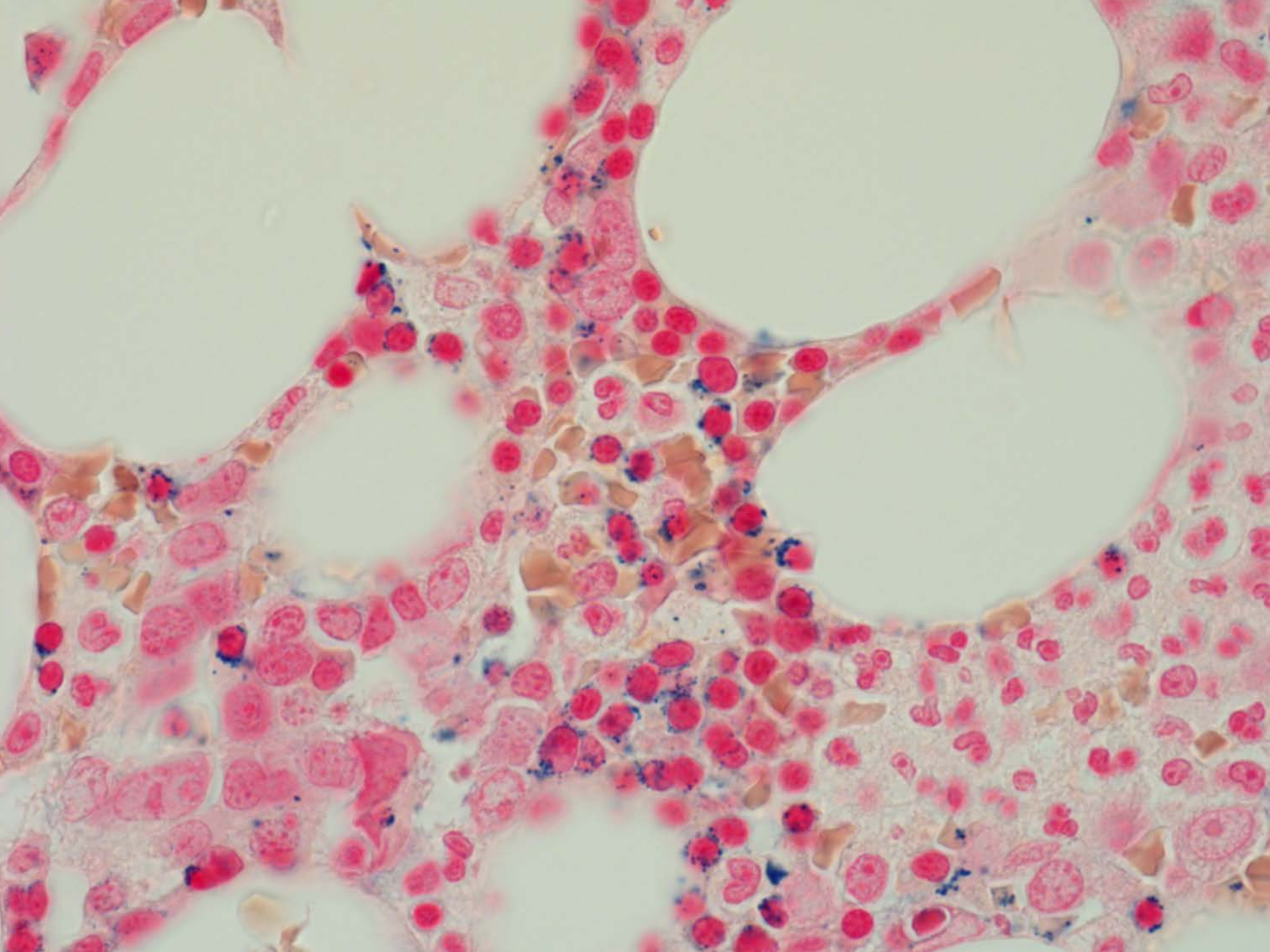
Probiotic

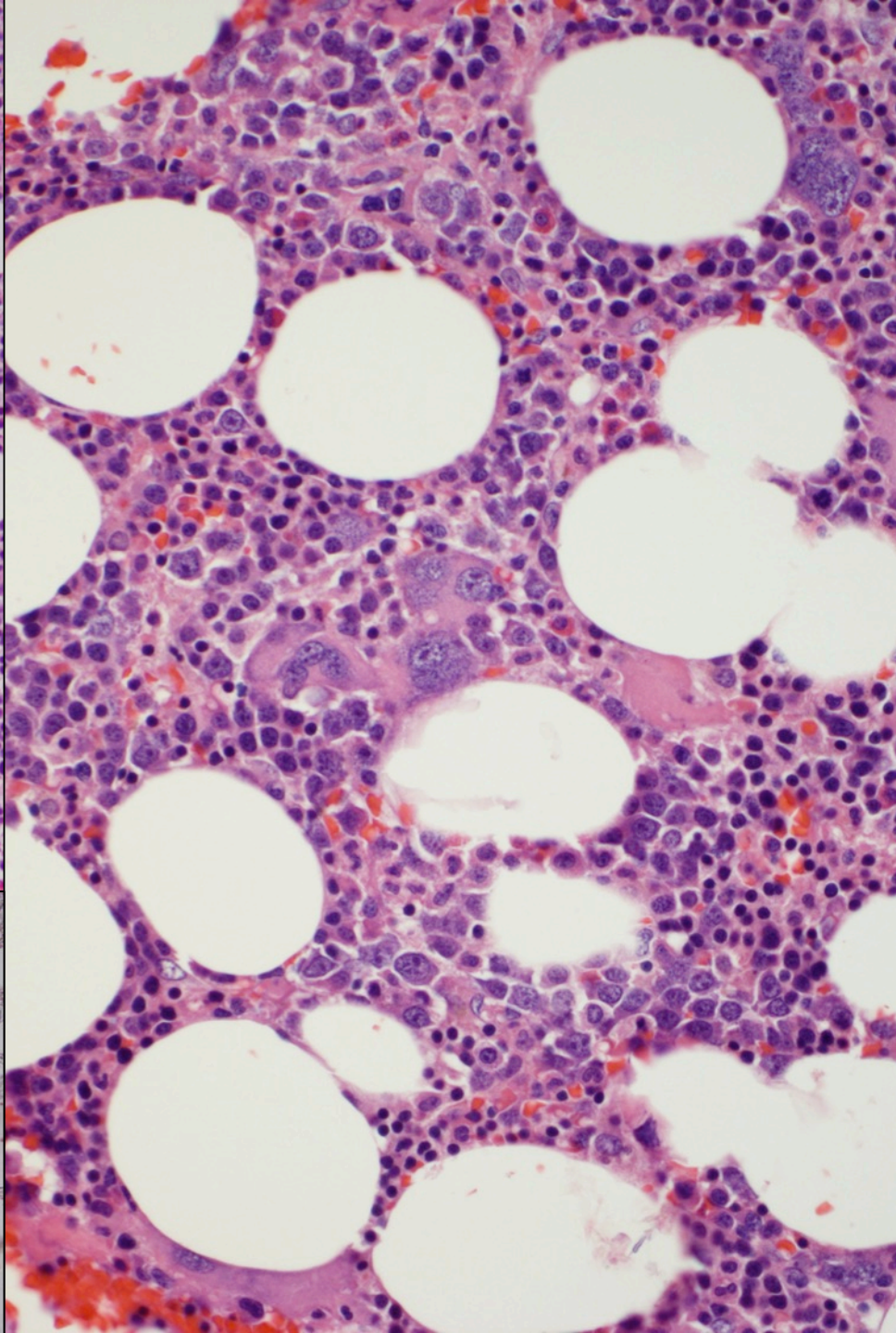
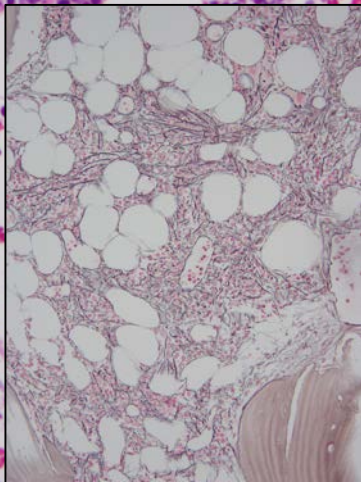
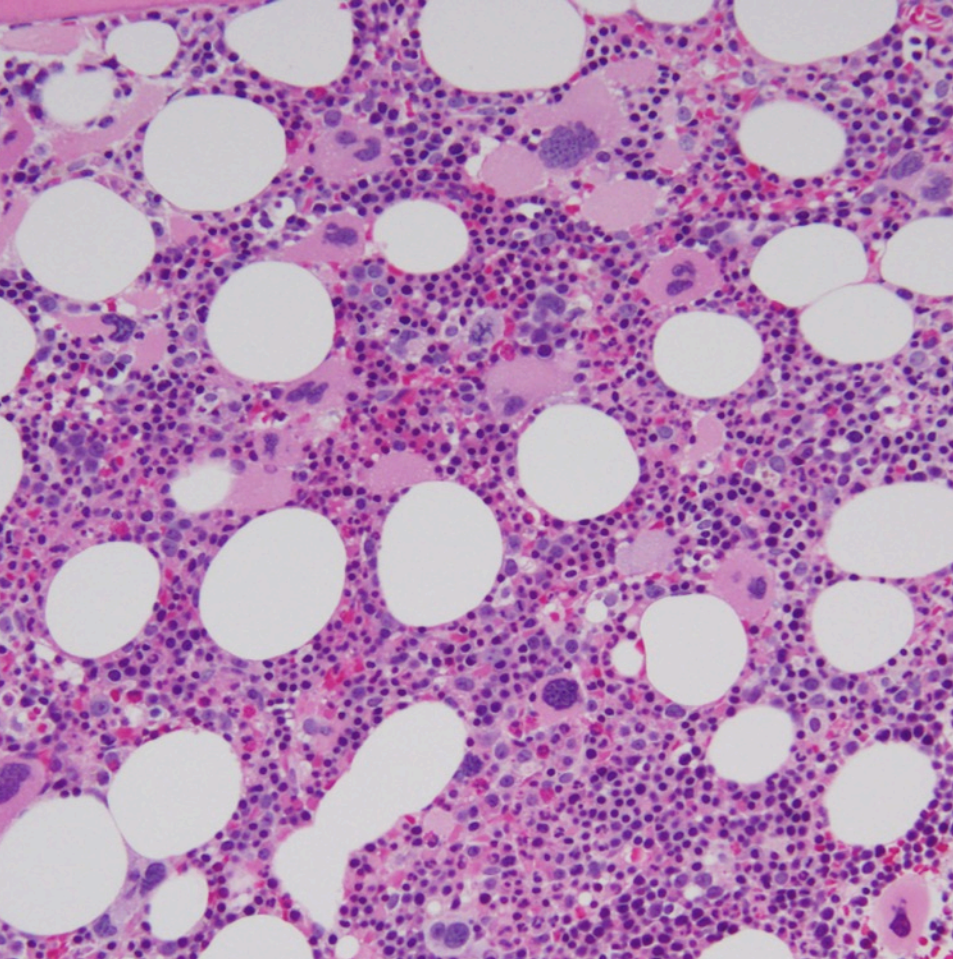


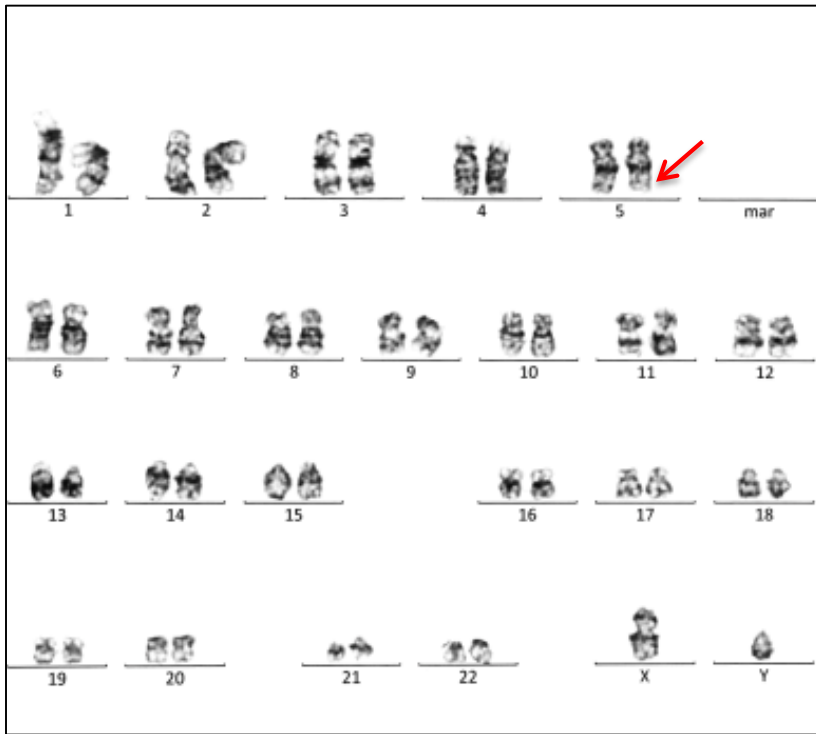




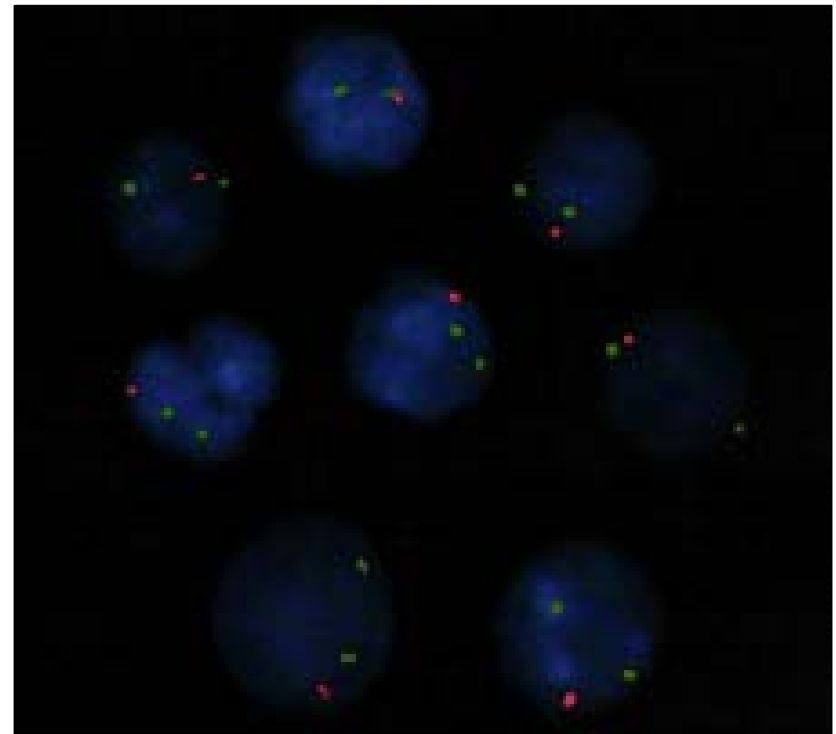








46,XY,del(5)(q31q31)[9]/46,XY[11]



Deletion of 5q31 (83% of the cells)

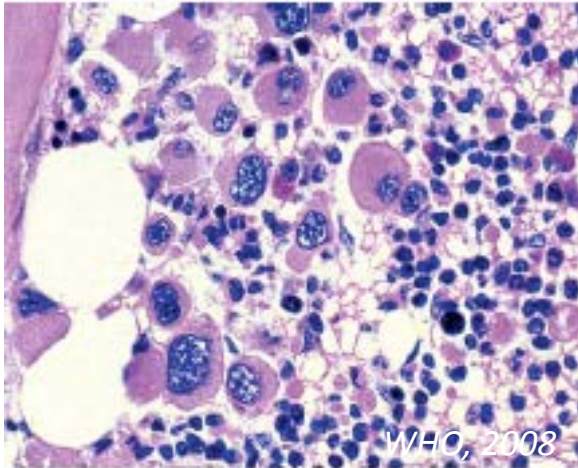
Molecular Analysis

<p><i>SF3B1</i> p.K666Q (c.1996A>C) VAF 46%</p>	<p><i>MPL</i> p.W515S (c.1544G>C) VAF 39%</p>
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Expert Panel Proposed Diagnosis

Myeloid neoplasm with features of both myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis and myelodysplastic syndrome with isolated del(5q)

MDS with Isolated Del(5q)

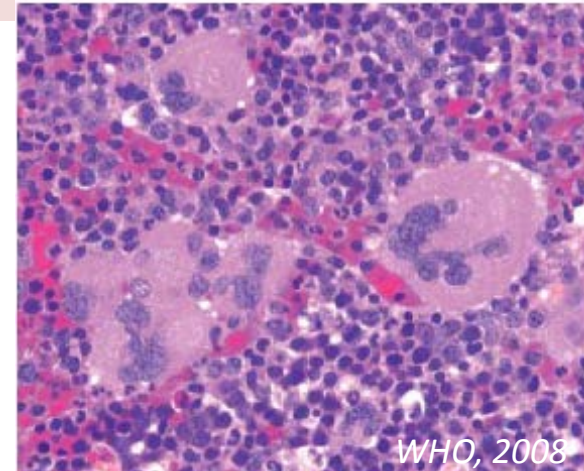


- Erythroid hypoplasia
- Hypolobated megs
- Myeloid/erythroid dysplasia uncommon

- Del(5q) + 1 cytogenetic abnormality (except -7 or del(7q))

Anemia
Thrombocytosis
Hypercellular BM

MDS/MPN-RS-T



- Erythroid hyperplasia
- Large, atypical megs
- Dyserythropoiesis + >15% ring sideroblasts
- +/- Myeloid dysplasia

- *SF3B1* (~85%)
- *JAK2* V617F (~50%), *MPL* (<10%), *CALR* exon 9 (<10%)
- ~50% *SF3B1* and *JAK2* V617F
- Isolated del(5q) excluded

	MDS with Isolated Del(5q)	MDS/MPN-RS-T
Median age	67	71-75
Median OS	145 mo (<i>WHO, 2008</i>)	76 mo (<i>Broseus et al, 2012</i>)
AML transformation	<10% (<i>WHO, 2008</i>)	1.8/100 patients/year (<i>Broseus et al, 2012</i>) 2% (<i>Patnaik et al, 2011</i>)
Complications	Transfusion-dependent anemia	Transfusion-dependent anemia Thrombosis - 3.6/100 patients/year (<i>Broseus et al, 2012</i>) - 20% (<i>Patnaik et al, 2011</i>) - Risk of vasomotor symptoms
Treatment	Transfusion/ESA Lenalidomide	Transfusion/ESA Aspirin/Anti-platelet agents Cytoreductive agents (Hydroxyurea) Lenalidomide

69 yo Male
Generalized weakness
Pallor, splenomegaly

CBC

WBC: 19.1 k/ μ L
Hgb: 9.3 g/dL
MCV: 67
Plt: 650 k/ μ L
PB: Mild left shift

Bone Marrow Biopsy

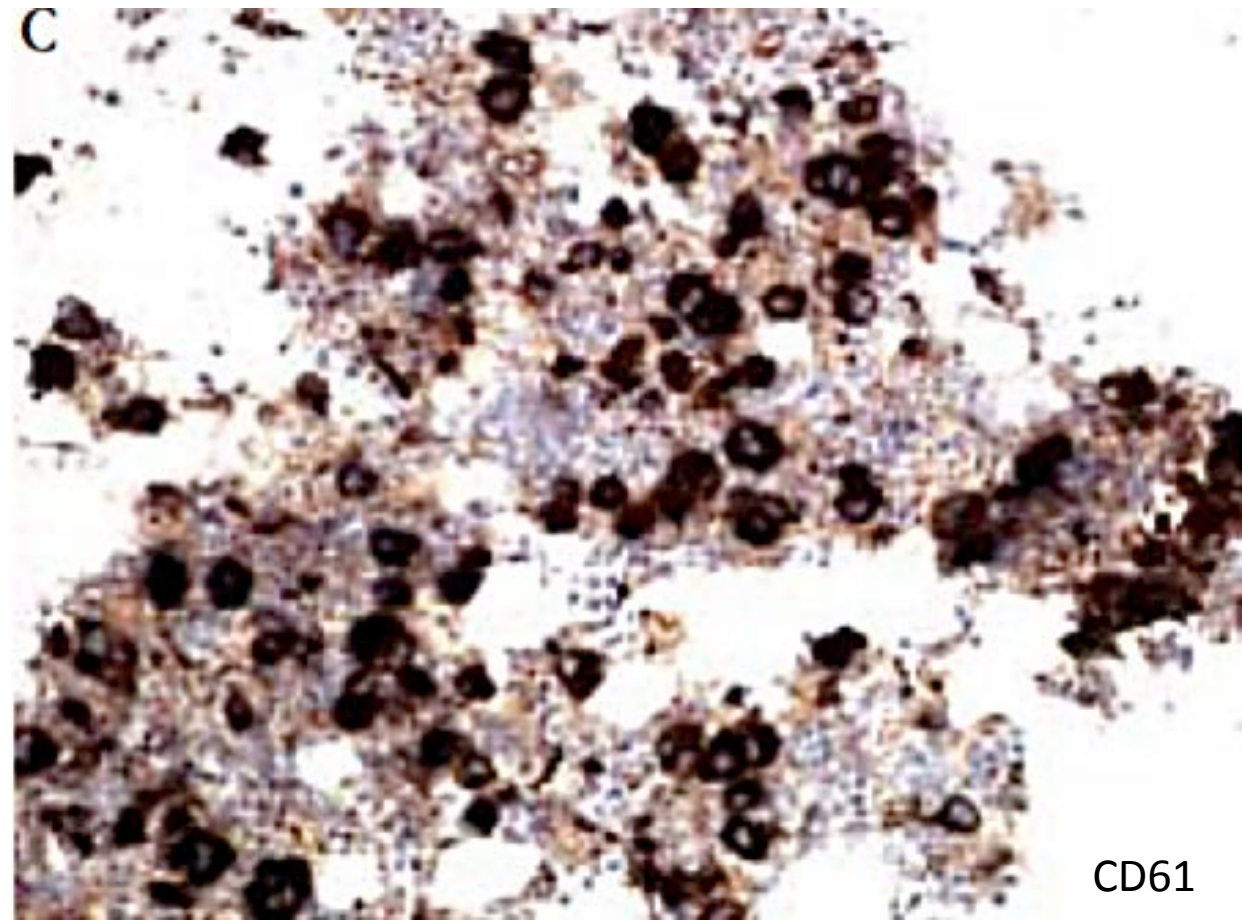
90% cellular
Erythroid hypoplasia
Increased atypical megs
35% ring sideroblasts
<5% blasts
2-3/4 fibrosis

Genetics

Del(5q31) [30]
(-): *JAK2*, *BCR-ABL1*,
ETV6-PDGFRB

Proposed Diagnosis
RARS-T with superimposed 5q-syndrome

Hydroxyurea + Lenalidomide



Szpurka et al, Blood, 2006	70 yo Splenomegaly 0.5 IPSS score	Hgb 10.2 g/dL Plt 691 k/ μ L MCV 106 ANC 2.3 k/ μ L AMC 0.4 k/ μ L	<ul style="list-style-type: none"> • 20% cellularity • 2% BM blasts • Megs unremarkable • 51% ring sideroblasts • No reticulin fibrosis 	(+) <i>JAK2</i> V617F (+) Del(5q)	RARS-T
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Patnaik et al, Am J Hematol, 2016	12/82 (15%) patients with RARS-T had abnormal karyotype	One with Del(5q31)	Cytogenetic abnormality associated with worse overall survival	Lenalidomide	RARS-T
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Woll et al, Cancer Cell, 2014	83 yo M Low IPSS score	WBC 22 k/ μ L Hgb 8.7 g/dL Plt 877 k/ μ L ANC 16 k/ μ L	<ul style="list-style-type: none"> • <5% BM blasts • No ring sideroblasts 	(+) <i>SF3B1</i> (VAF 18-37%) (+) <i>JAK2</i> V617F (VAF 18-33%) (+) Del(5) (q21q34) [25]	Transfusion- independent with lenalidomide	MDS/ MPN
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	Patient 1	Patient 2
Date of Diagnosis	11/15/2010	12/22/2011
Age/Sex	62M	71M
Original Diagnosis	MDS/MPN	MPN
CBC	WBC nl, Hgb 10.1, Plt 783	WBC 9.0, Hgb 12.1, Plt 1,400
BM Findings*	<ul style="list-style-type: none"> • >95% cellular • Increased left-shifted myeloid precursors • Meg hyperplasia and dysplasia <ul style="list-style-type: none"> • Reported ring sideroblasts • 2-3+ reticulin fibrosis 	<ul style="list-style-type: none"> • >90% cellular • Mild granulocytic dysplasia <ul style="list-style-type: none"> • Meg hyperplasia and dysplasia • 5% ring sideroblasts (suboptimal) • 2+ reticulin fibrosis
Molecular Alterations	<ul style="list-style-type: none"> • Normal karyotype • FISH: del(5q) (10%), del(17p13) (10%) <ul style="list-style-type: none"> • <i>MPL</i> W515L 	<ul style="list-style-type: none"> • 46,XY,del(5)(q22q35)[17]/46,idem,del(20)(q11.2)[3] • FISH: del(5q31) (92%), del(20q) (15%) • <i>SF3B1</i> K666N (VAF 42%) • <i>MPL</i> W515L (VAF 45%) • <i>IDH1</i> R132C (VAF 9%)

*Bone marrow findings based on follow-up biopsies reviewed at MSKCC

	Patient 1	Patient 2
Complications	TIA, DVT, HSM Transfusion dependent	Retinal vein occlusion, SM Transfusion dependent
Symptoms	Bone pain, fever, night sweats, fatigue, early satiety, weight loss	Fatigue
Therapies	1. Lenalidomide and hydroxyurea 2. Hydroxyurea only and darbepoetin prn 3. Ruxolitinib	Hydroxyurea Lenalidomide trial Darbepoetin added
Outcome	Progressive anemia and leukocytosis DOD	Progressive anemia Progressed to AML-MRC DOD
Time to Death	63 mo	64 mo

Patient Y.K. Follow-Up

- Received pRBC transfusions
 - Anemia (Hgb 8.2 g/dL), fatigue and atrial fibrillation
- Restarted on low dose lenalidomide
- Alive at 18 months

Conclusions

- Biology unclear
 - Belong in one defined category?
 - Overlap disease?
 - Two concurrent processes?
- Order of genetic alterations?
 - Relatively high VAF of *SF3B1* and *JAK2/MPL* mutations and percentage of cells with del(5q) by FISH
- MDS with isolated del(5q)?
 - Mixed response to lenalidomide
 - Possible increased thrombotic risk
 - Possible worse outcomes

Conclusions

- Myeloid neoplasms with features overlapping between MDS/MPN-RS-T and MDS with isolated del(5q) are rare and poorly understood
- Classification and treatment planning may be difficult
- Descriptive diagnosis

Expert Panel Proposed Diagnosis

Myeloid neoplasm with features of both myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis and myelodysplastic syndrome with isolated del(5q)