Complicacions de les neoplàsies mieloproliferatives còniques. Síndrome de Budd-Chairi *Cas Clínic*

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Clinical Case

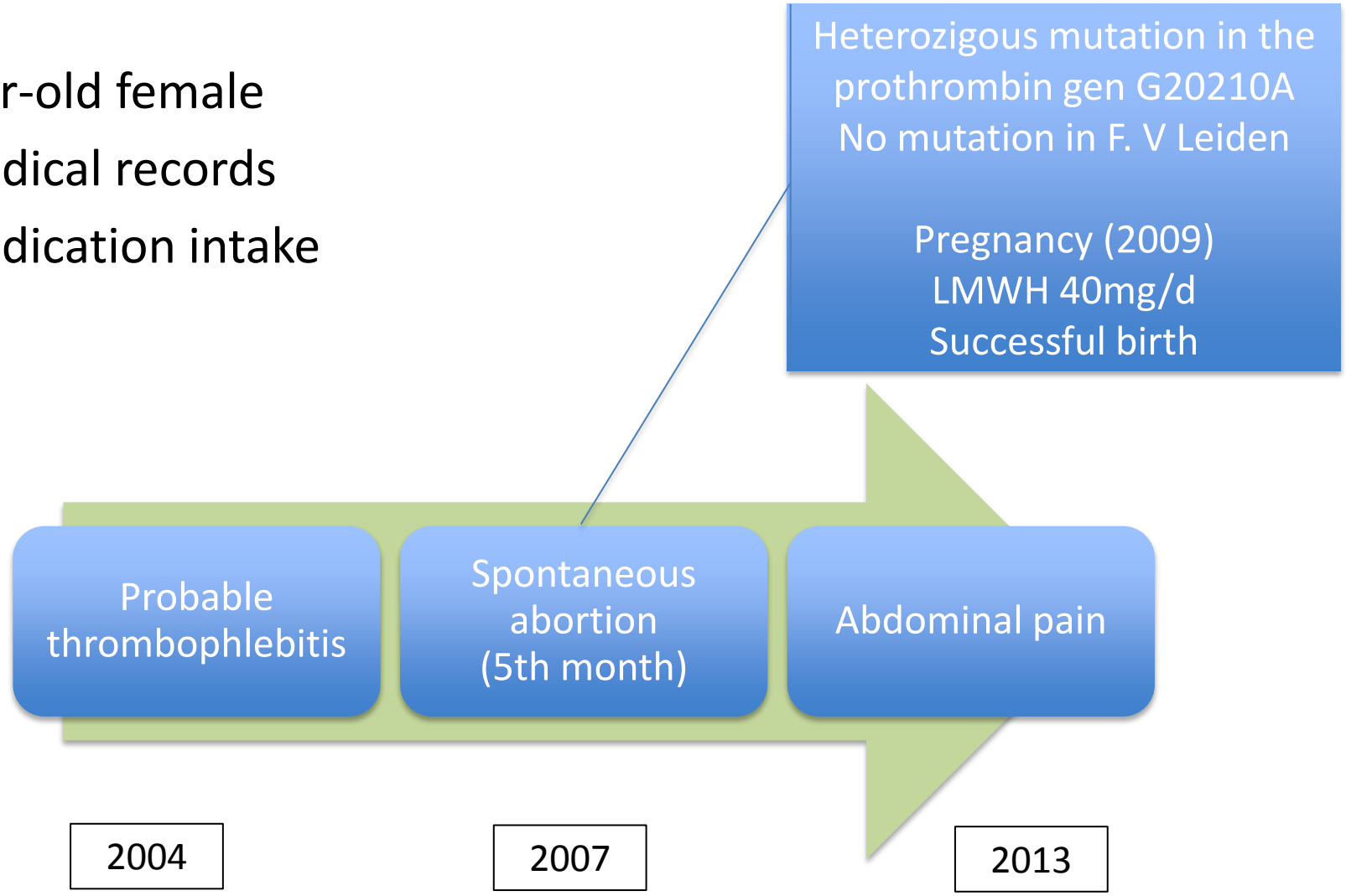
Brief discussion

Medical history

40 year-old female

No medical records

No medication intake

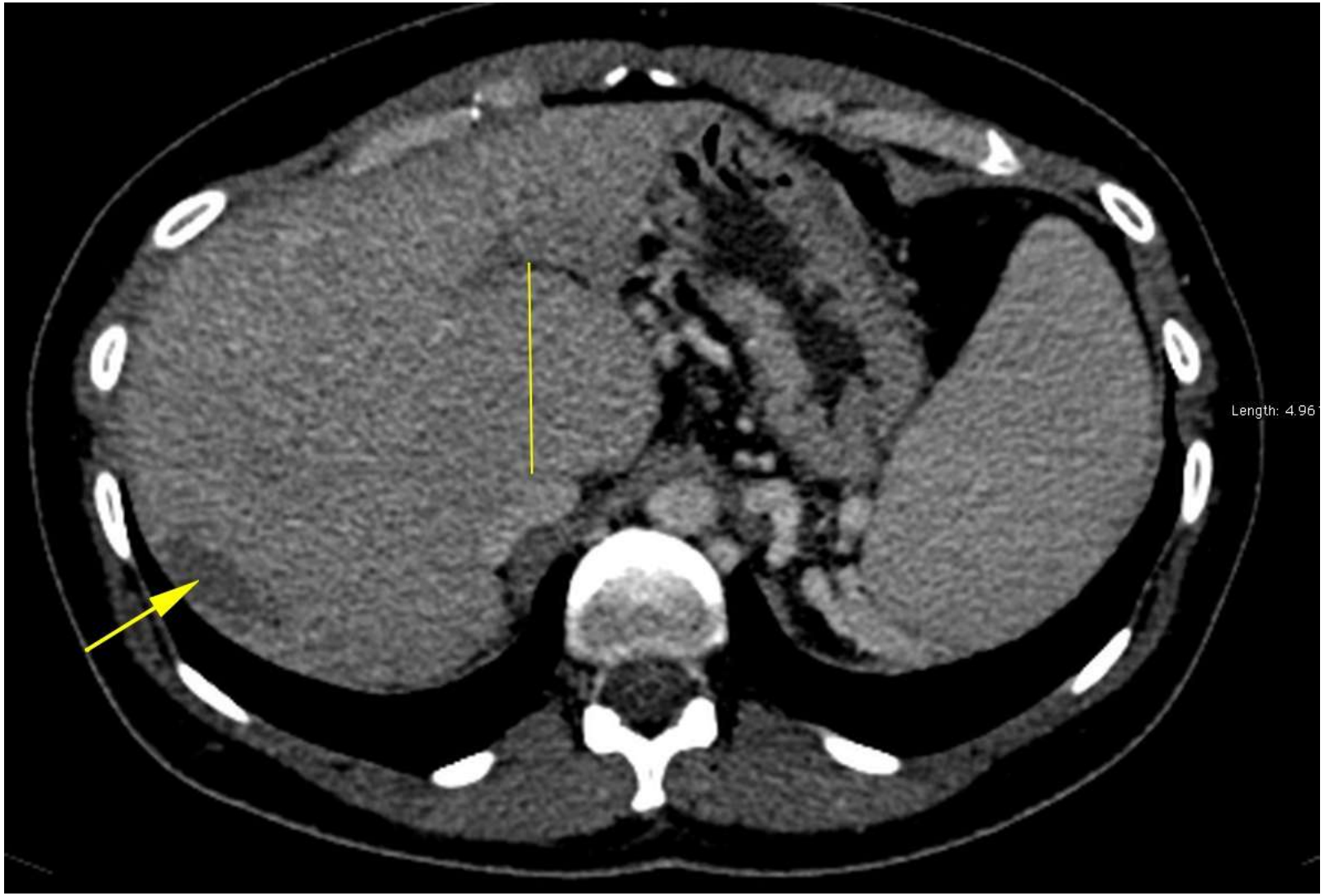


Diagnosis

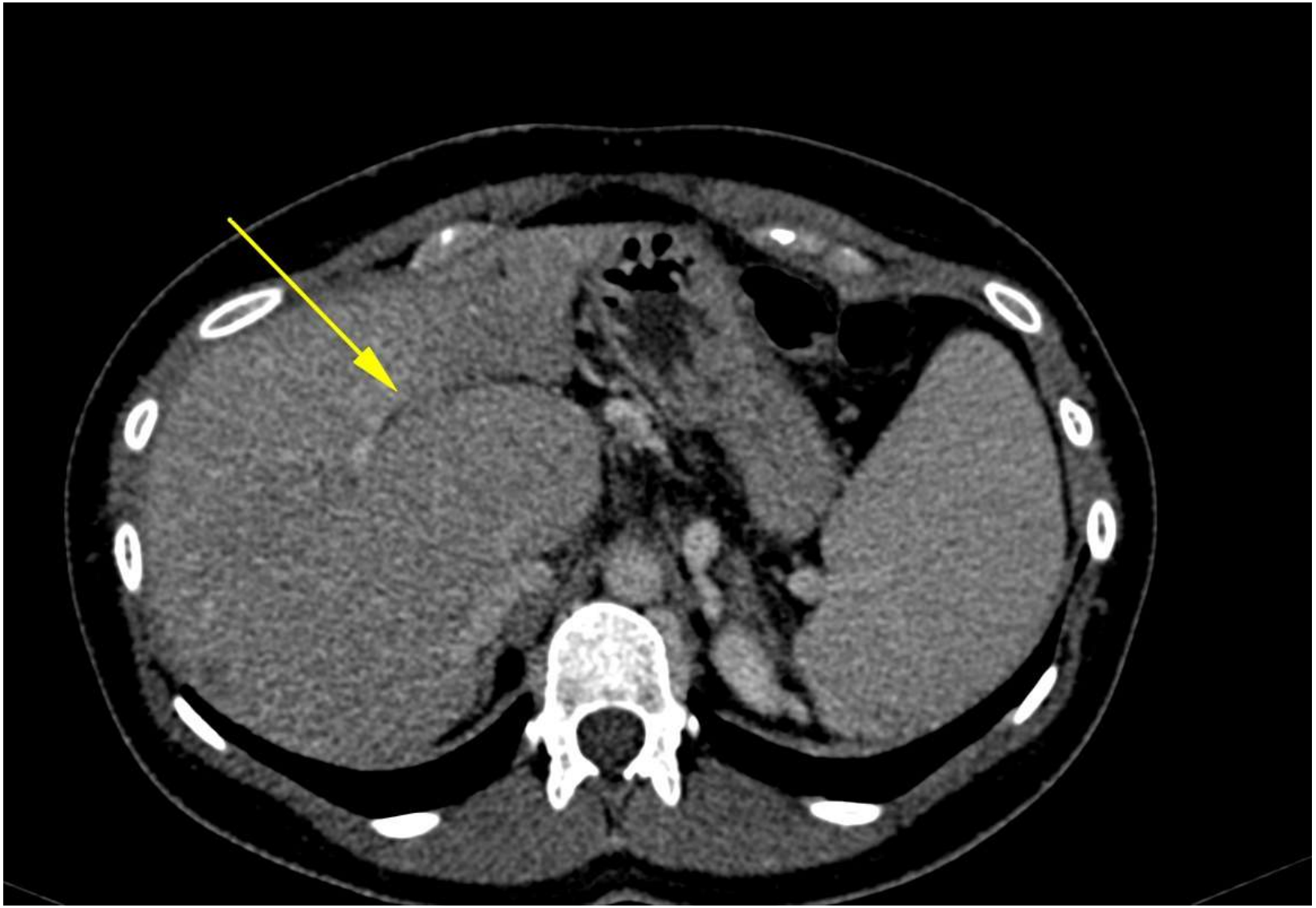
Sympthoms	• Abdominal symptoms (1 month)
Blood tests	• Blood test were “normal” • ANAs 1/320
Ultrasonography	• Hepatoesplenomegaly • Portal vein no observed

Diagnosis

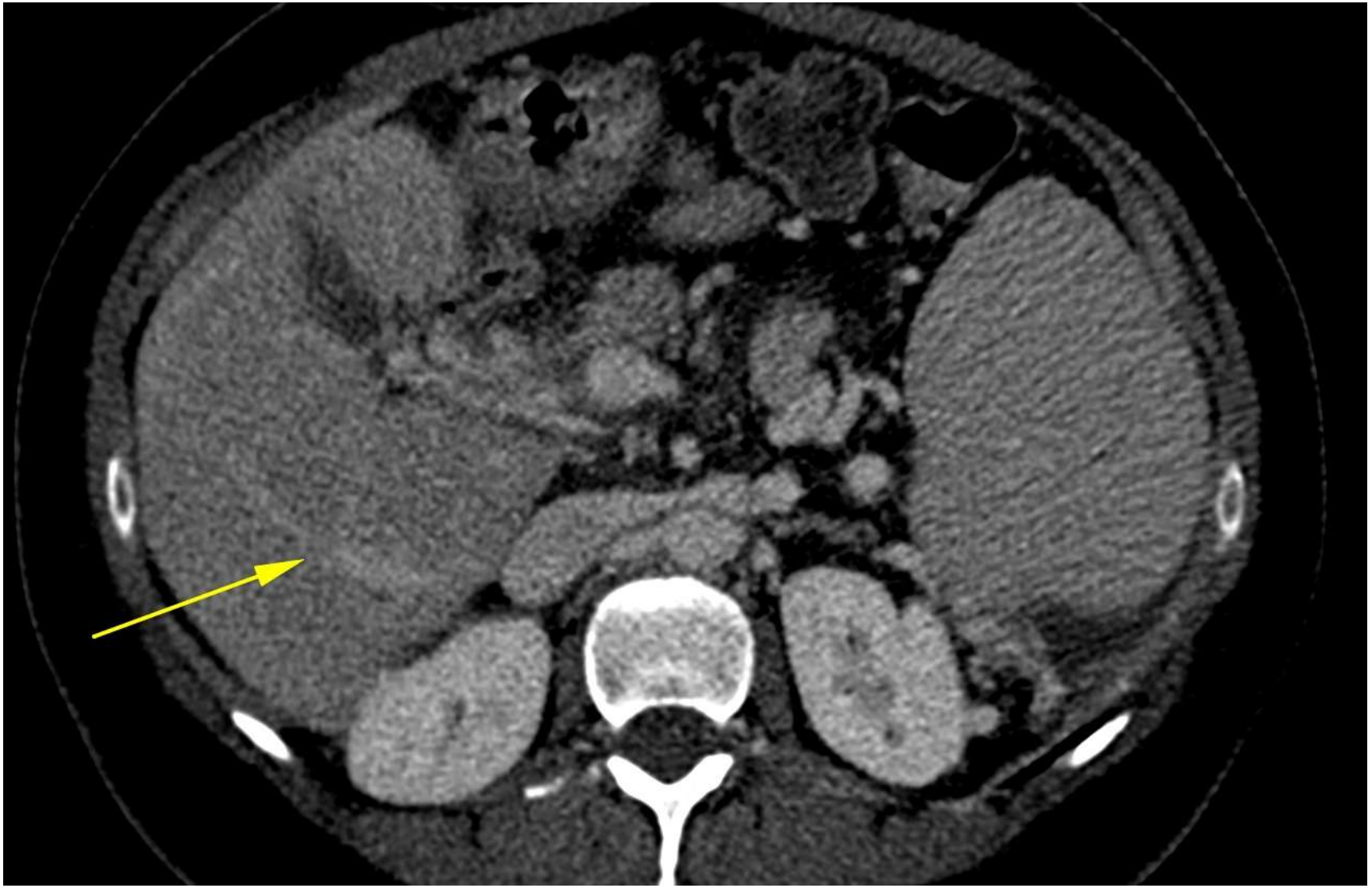
Blood Count	Hb 13.9 g/dL, HCT 41%, VCM 89 fL, WBC 3.4x10e9/L (N 2.3x10e9/L), P 131x10e9/L
Biochemical analysis	Bilirubine 1mg/dL, AST/ALT 87/94 U/L, GGT 23 U/L, LDH 238 U/L
Thrombophilia screening	MTHFR C677T mutation: non-detected, Normal levels of homocistein, APL ab. neg.
Fibrogastroscopy	Grade 3 esophageal varices



Hepatic hipodensities and cautade lobe hypertrophy.
Budd-Chiari syndrome



Left portal vein thrombosis.
Budd-Chiari syndrome



Suprahepatic veins minimally seen. Esplenomegaly.
Budd-Chiari syndrome

Treatment and follow-up

Enoxaparin 60mg/12h sc followed by acenocumarol therapy

Beta-blockers
Acenocumarol control in local basic health facility (unstable INR)

JAK-2 V617F mutation(44%)
Bcr-Abl negative

Hematology Dptm.

Red cell volume	• Hb 13.8 g/Dl (HCT 42%) • Red cell mass at 131% above the predicted value (51Cr-autologous red cells)
JAK2	• V617F mutation (44%)
BMB	• Light hypercellularity for age. Trilineage growth. Grade I reticulinc fibrosis
EPO	• 3.8 mUI/ml (4.3-29)

Hematological diagnosis

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria:

Major criteria

1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
2. Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

Polycythemia Vera

CBC (03/2014): Hb 12.7 g/dL, HCT 39.2%, VCM 95 fL, WBC 3.2x10e9/L (N 1.8x10e9/L), P 88x10e9/L

CBC (05/2010): Hb 15.2 g/dL, HCT 45.5% , VCM 86 fL, WBC 5.6x10e9/L (N 3.8x10e9/L), P 293x10e9/L, iron deficiency

Splacnic vein thrombosis

SVT includes Budd-Chairi syndrome (VCS) and portal vein thrombosis (PVT)

BCS: Thrombosis of hepatic veins or suprahepatic inferior vena cava
PVT: More frequently related with local factos (cirrhosis, malignancy) and highly associated with primary BCS

Prothrombotic Disorders	PVT, %[a]	BCS, %[b]	DVT, %[c]
Myeloproliferative diseases[d]	14–35	28–47	NA
Antiphospholipid syndrome	5–23	5–21	4–21
Factor V Leiden mutation	3–14	14–31	15–20
Factor II gene mutation	3–22	4–6	4–8
Protein C deficiency	0–9	0–13	3–6
Protein S deficiency	2–30	0–6	2
Antithrombin deficiency	0–4.5	0–4	0.5–7.5
C677T MTHFR gene mutations[e]	0–11	13–52	Variable
Hyperhomocysteinemia	NA	0–37	10–25
Elevated factor VIII	NA	NA	15–25
Pregnancy	0–4	0–15	[f]
Oral contraceptive use	0–48	7–55	[f]
None	16–22	6–23	50

Bittencourt PL Clin Liver Dis. 2009 Feb;13(1):127-44.

Splacnic vein thrombosis

MPNs are the most frequent cause of nonmalignant, non-cirrhotic BCS (30-50%) and PVT (15-30%).

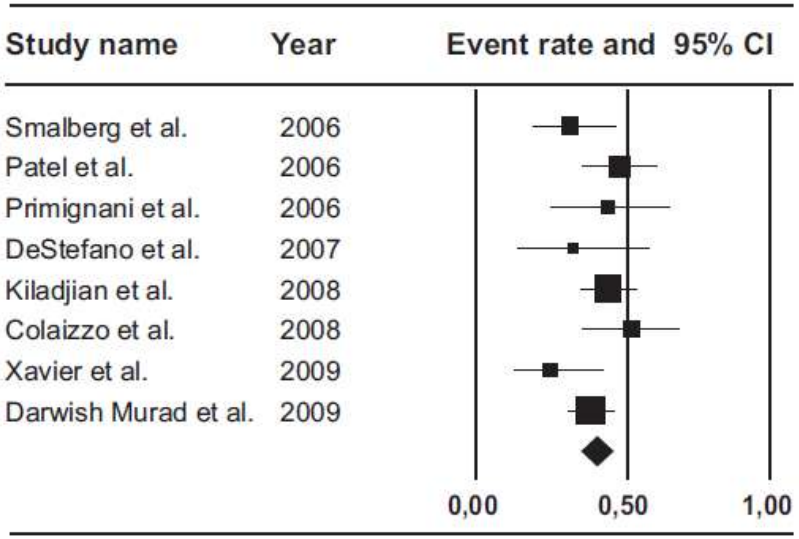
Usual diagnostic criteria might not be met (splenomegaly, iron deficiency).

ETIOLOGY	
Malignancies	Thrombophilia
Liver chirrosis	Other hypercoagulability states
Myeloproliferative neoplasms	Behçet syndrome
Oral contraceptives	Others

Splacnic vein thrombosis and MPNs

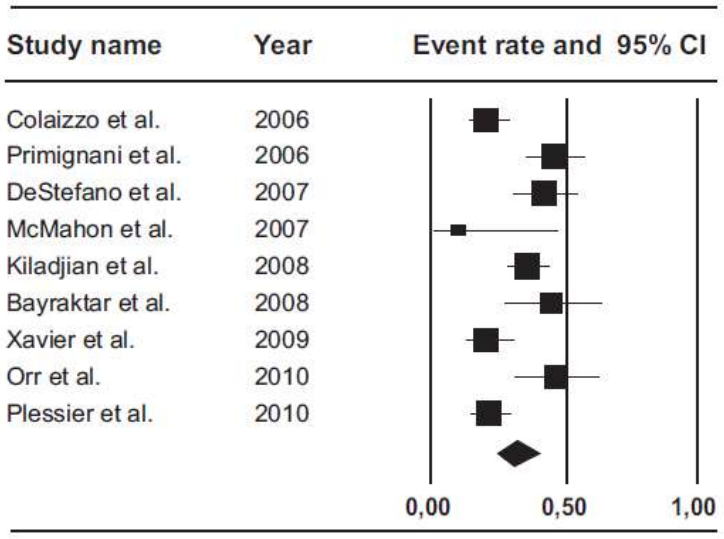
Meta-analysis of 32 studies (from 713 screened) including 1062 BCS and 855 PVT.

BCS



80% JAK-2 mutated MPNs
53% PV, 25% ET, 17% u-MPNs

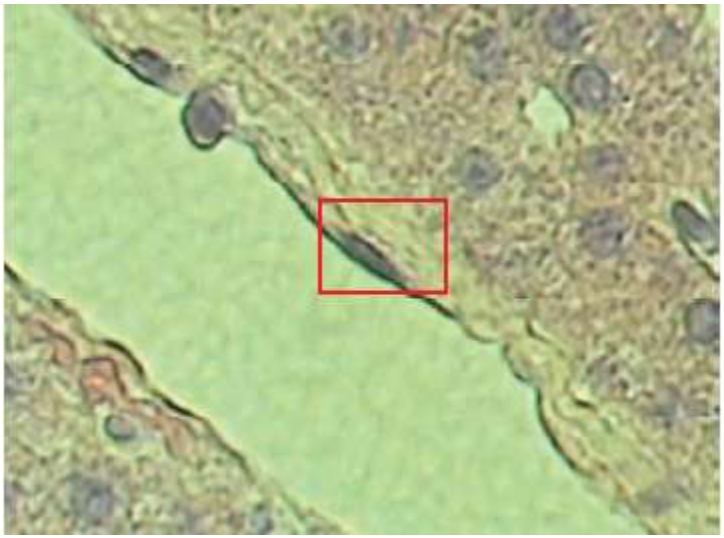
PVT

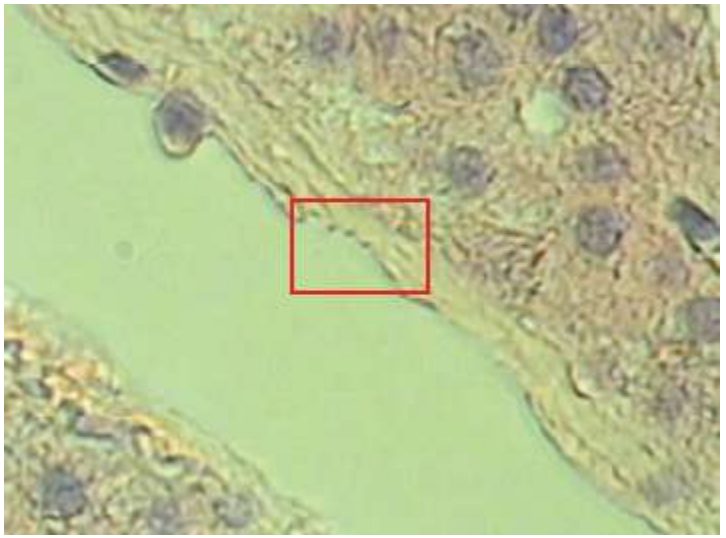


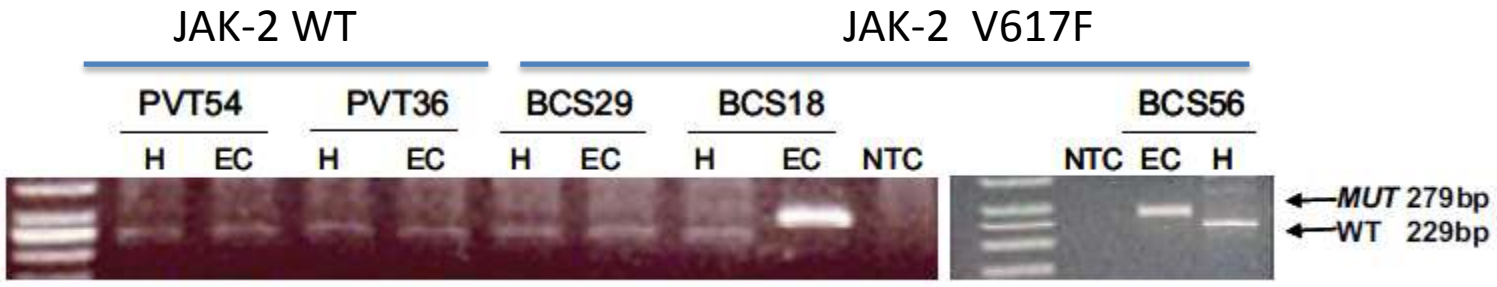
87% JAK-2 mutated MPNs
28% PV, 26% ET, 18% u-MPNs

Smalberg JH et al. Blood. 2012.120(25):4921-8

JAK-2 mutations in endotelial cells

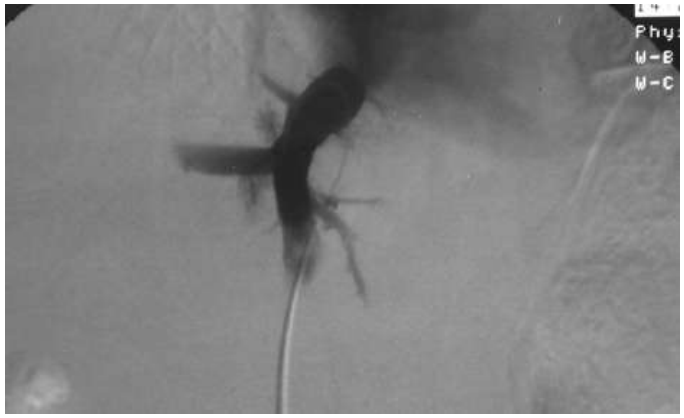


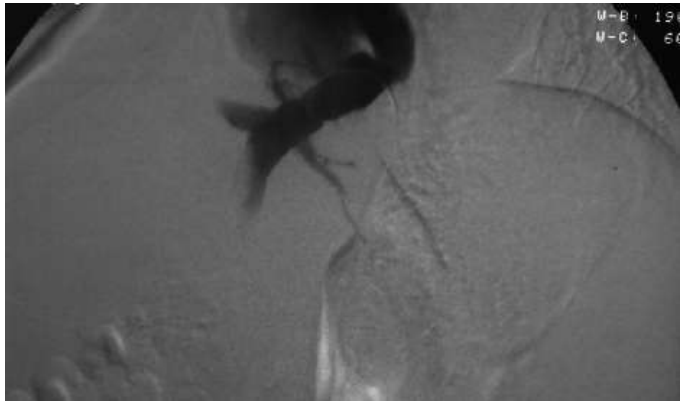




Sozer S et al. Blood. 2009;113:5246-9

Treatment





Treatment (step strategy)
1. Anticoagulation and symptomatic therapy
2. Angioplasty (short-length)
3. TIPS
4. Liver transplantation

Uskudar O et al. World J Gastroenterol. 2008;14:2858-62

Response criteria for BCS

Complete response	No ascites
	Normal Na and creatinine with no or low-dose diuretics (spironolactone 75 mg or furosemide 40 mg/die)
	Factor V increase > 40% of the normal range
	Bilirubin decrease < 15 μmol/L
	No portal hypertension bleeding
	No spontaneous bacterial peritonitis
	Body mass index > 20 kg/m^2
Ongoing response	Ascites detectable but responsive to low-dose diuretics
	Normal Na and creatinine
	Factor V increase (if initially low)
	Bilirubin decrease
Treatment failure	When criteria for complete or ongoing response were lacking

Mancuso A et al. World J Hepatol. 2011;3(10):262-4.

Take-home messages

- MPNs should always be considered in patients with BCS even if other plausible causes are present
- Definitive diagnosis of MPNs might be challenging in patients with previous BCS.
- Thrombosis progression should be carefully monitored in patients with MPNs and BCS

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Moltes gràcies