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An unusual association of paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, and diffuse large B-cell non-Hodgkin lymphoma in a Caucasian man

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- 1998, pancytopenia syndrome has been observed: **Hb 8.7 g/dL, WBC 1.2, PLT 31. MDS**—refractory cytopenia associated to multilinear dysplasia (RCMD) (hypercellular. Perls neg); 46 XY transfusions periodically and chelating agent.
- **THERAPY: EPO+ G-CSF** a few months then stopped.
- 2006: deterioration of clinical status and an **increased need of transfusion support**. **Ham test neg.** LDH, bilirubin, reticulocytes normal
- Chrom: [**del(20q)**].

2010, severe anemia: Hb 4.5 g/dL, occasional episodes hyperchromic urines. LDH levels (700–900 U/L), low haptoglobin, elevated bilirubin level, and reticulocytosis. (PNH clone 16 %: HYPOCELLULAR MARROW)

ECULIZUMAB WAS STARTED

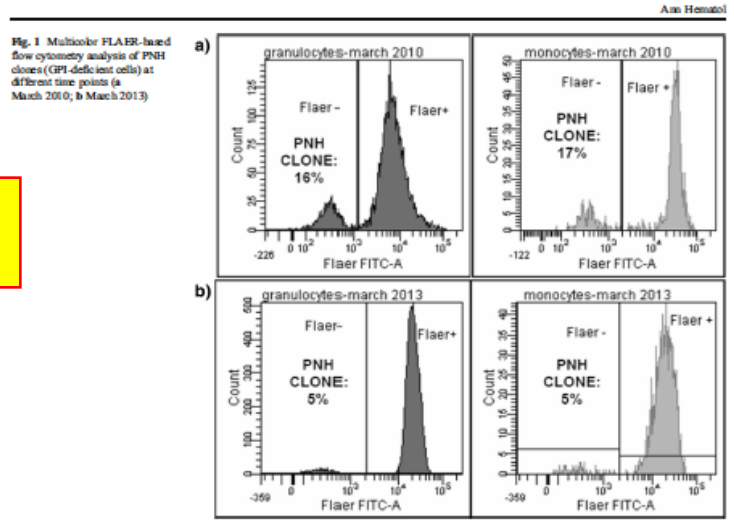


Fig. 1 Multicolor FLAER-based flow cytometry analysis of PNH clones (GPI-deficient cells) at different time points (a March 2010; b March 2013)

Table 1 Number of red blood cells transfusions performed in the different phases of the disease (1) MDS, (2) MDS + NHL, (3) MDS + NHL + PNH before eculizumab therapy, and (4) MDS + NHL + PNH after eculizumab therapy (before lymphoma relapse). The duration of each phase is also reported (months)

MDS	MDS + NHL	MDS + NHL + PNH before eculizumab	MDS + NHL + PNH after eculizumab (before lymphoma relapse)
124 months	24 months	4 months	35 months
n. 15	n. 19	n. 65	Any

- 2009 : PNH CLONE : 5%, LDH 300, BILIRUBIN NORMAL; relapse of NHL (diffuse large B-cell) in liver , spleen, bulky disease: refractory to therapy. Eculizumab was stopped.
- Patient exitus
- The presence of del(20q) could be interpreted as a confirmation of published studies that PNH is more likely to be detected in MDS patients whose disease is less likely to evolve into leukemia, and who have a better prognosis
- eculizumab was highly effective in controlling PNH, decreasing intravascular Hemolysis, improved the quality of life, reduced the risk for thrombosis, and eliminated the need for transfusions.

CASO CLINICO n. 2- EPN

P.A. F, anni 45

Anamnesi familiare: 1 sorella con TVP "idiopatica"

Anamnesi fisiologica, farmacologica, patologica remota: nulla di rilevante da segnalare

Anamnesi patologica prossima:

- **Giugno 2007: inviata in P.S. per dolore addominale più accentuato in regione periombelicale**

E.O.: dolore alla palpazione superficiale e profonda, più evidente in regione mesogastrica; fegato palpabile all' arcata costale, non splenomegalia

Esami ematochimici e strumentali in urgenza:

Hb: 10.2 g/dl con MCV=91 $\mu^{3,}$ **WBC: 3.830/mmc**

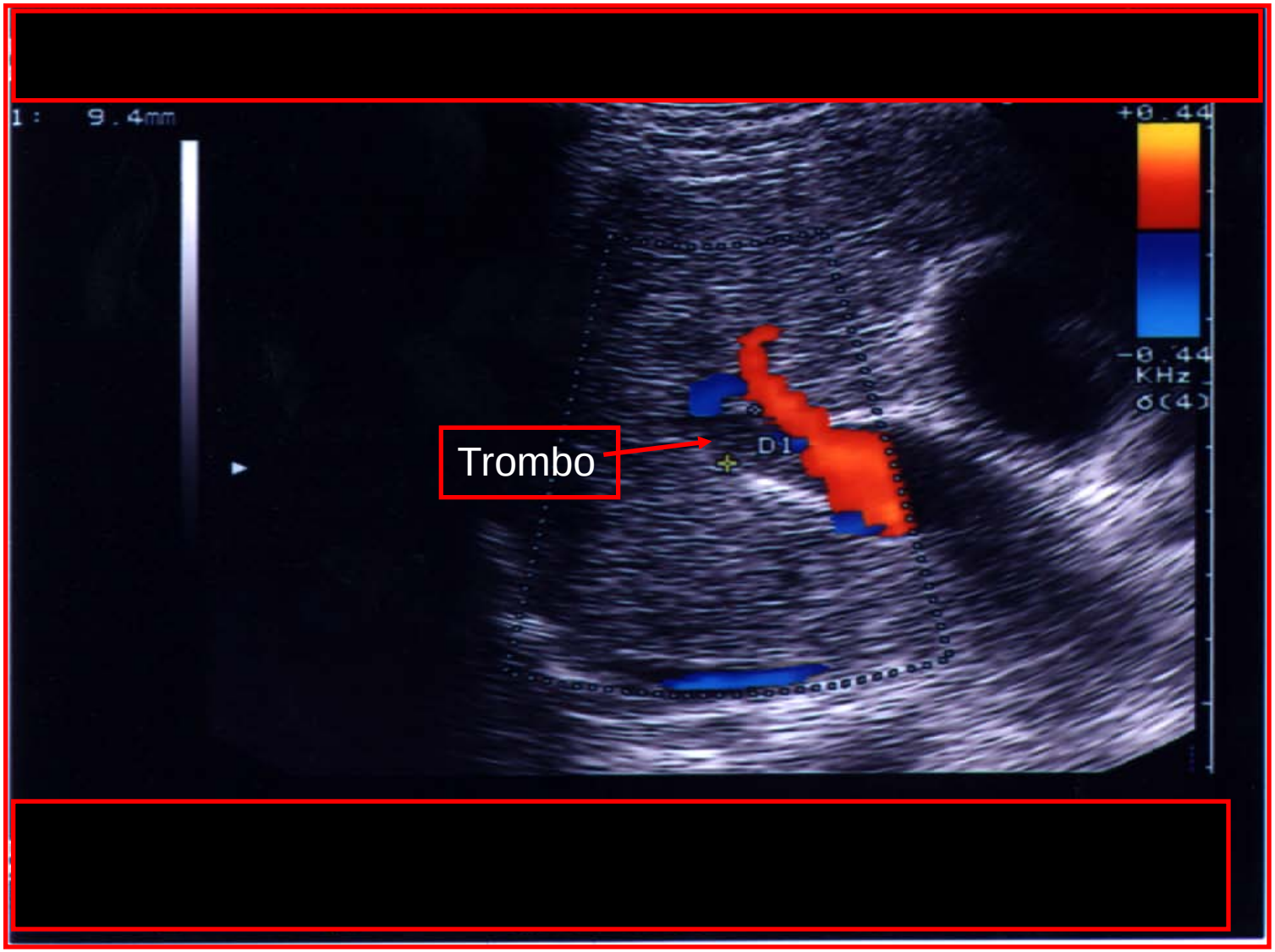
PLT: 83.000/mmc, Formula l.: N 30%, L 65%, M 5%, E 0%,

Indici di funzionalità epatica e renale: nella norma

PT, aPTT, fibrinogeno: nei limiti di norma; **D-dimero: elevato**

Rx torace: negativo: **RICOVERO IN REP MEDICINA**

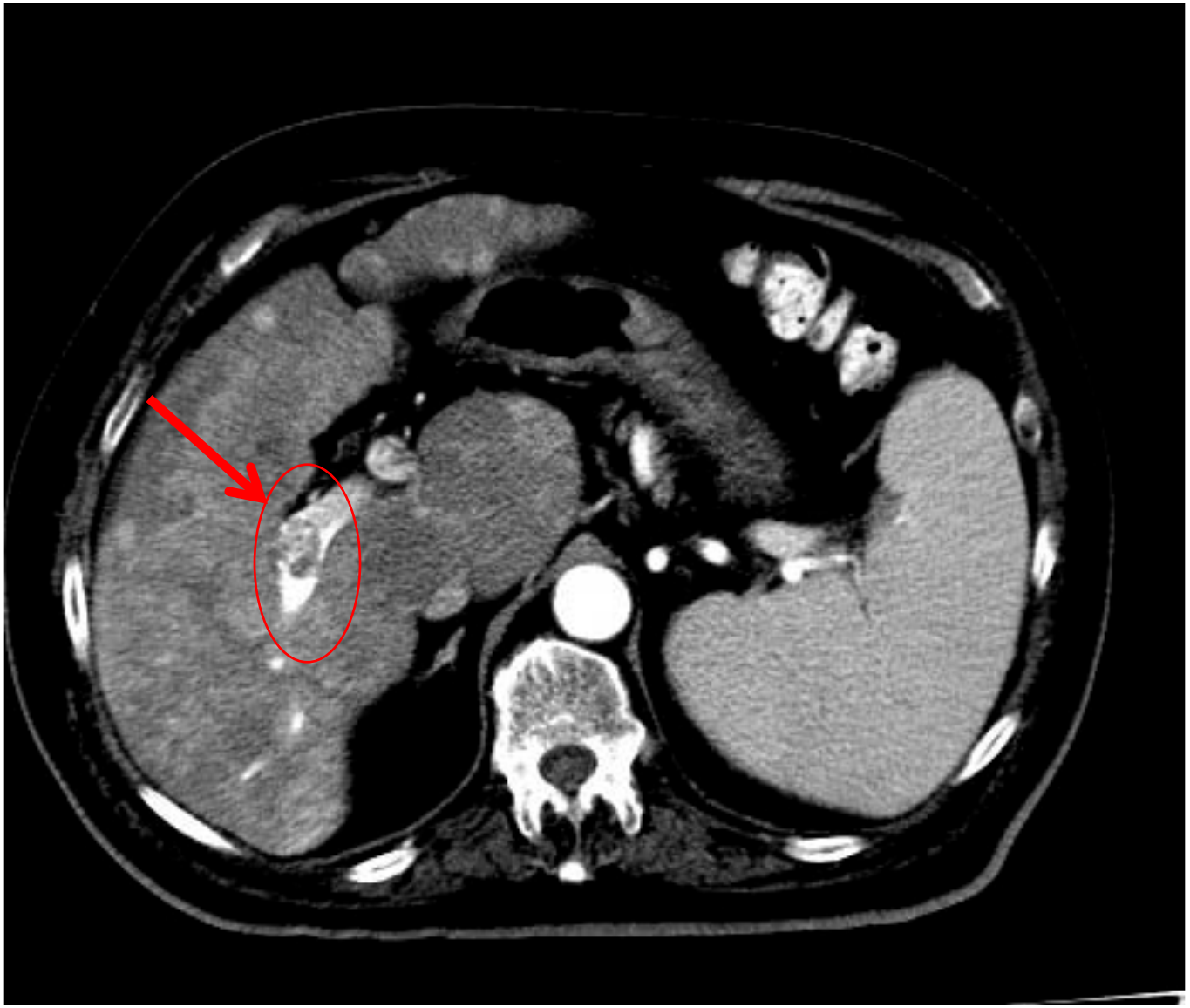
Ecografia addome con color-doppler:
trombosi ramo portale destro



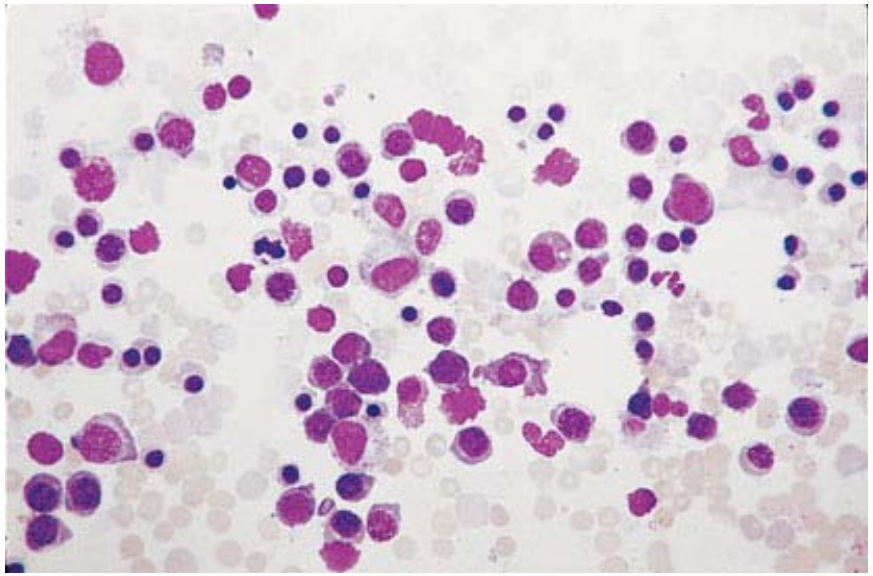
Esami ematochimici e strumentali <u>in degenza</u>:

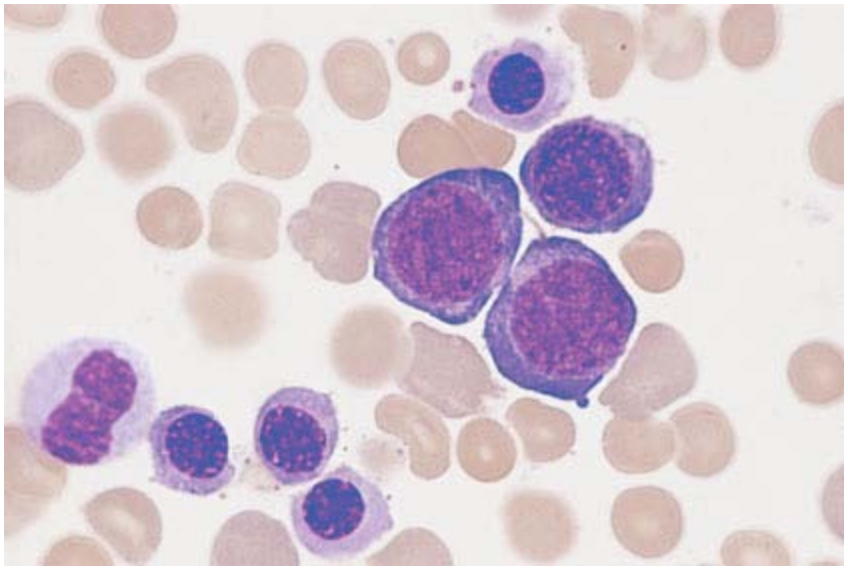
VES: 41 mm/h
Reticolociti: 27‰
Ferritina: 11 ng/ml
Eritropoietina sierica: 49 UI
LDH: 679 U/L (v.n. ≤ 245 U/L)
Test di Coombs diretto ed indiretto: negativi
Aptoglobina: < 30 mg/ml
Bilirubina totale ed indiretta: nei limiti della norma
C3: consumato
C4: nella norma
ANA, ENA, dsDNA, ASMA, APCA, AMA: assenti

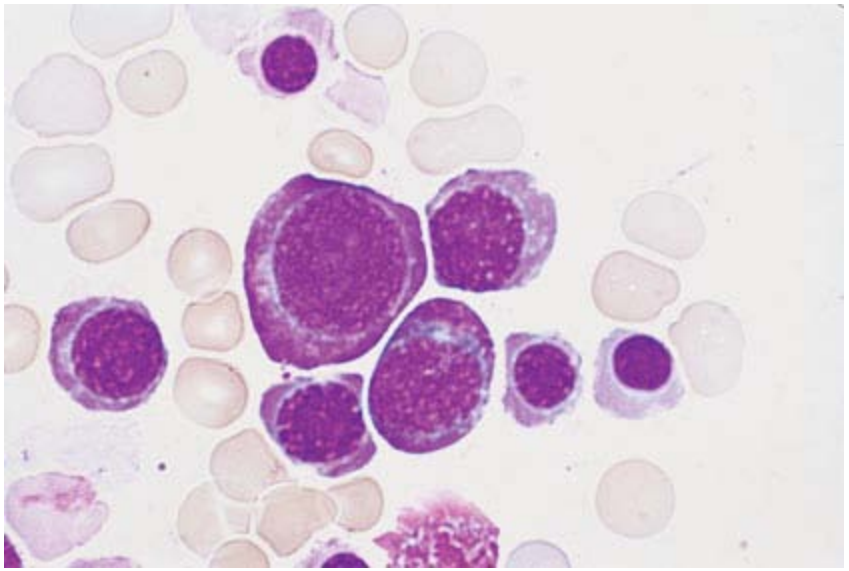
TC addome in fase arteriosa: **trombosi ramo portale destro**



BM :iperplasia eritroide, diseritropoiesi, megacario-mielopoiesi ridotte







Trombosi in sede atipica: iter diagnostico

Trombosi eredo-familiari

ATIII
Proteina C
Proteina S
PCA-R
FV Leiden
Protombina mutata
Iperomocisteinemia

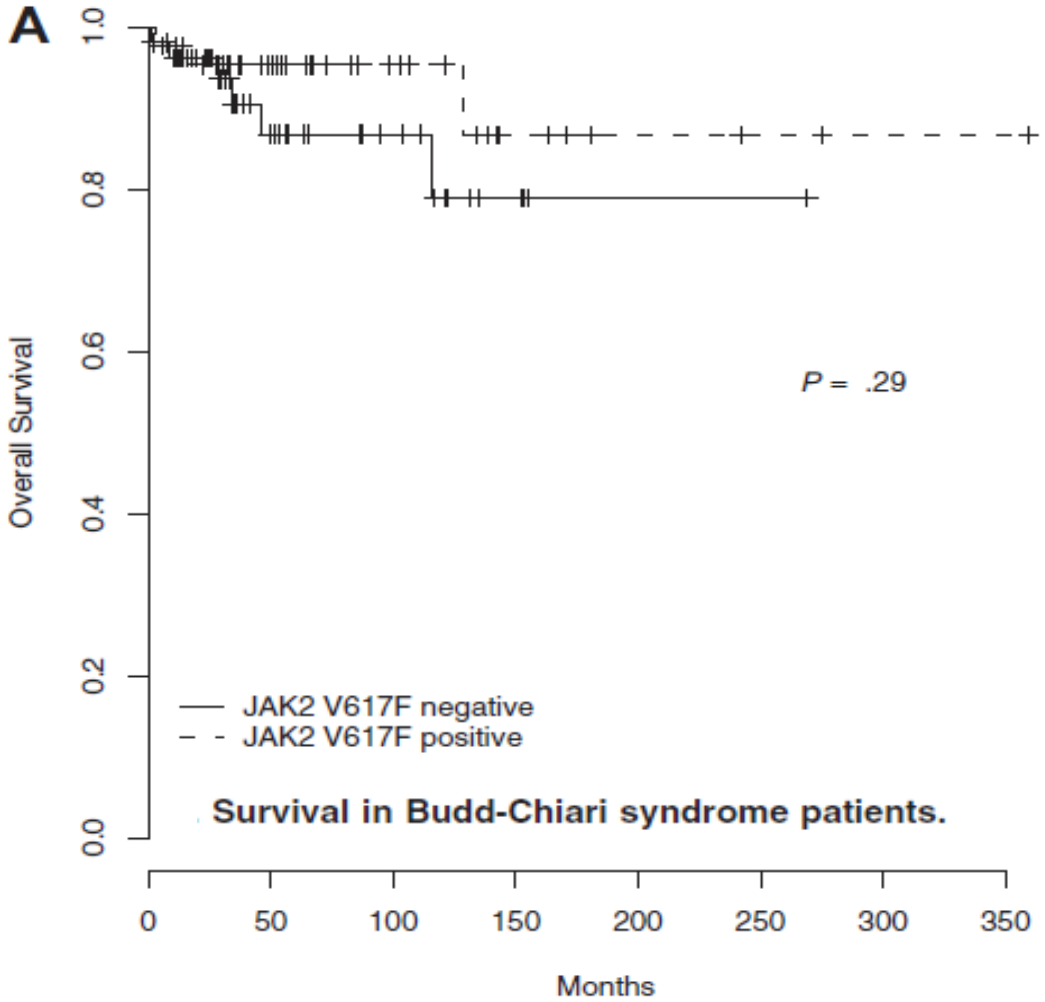
Più rare:
↑ lipoproteina (a)
Ridotta fibrinolisi
(↑ di PAI-1 o ↓ di tPA)

Stati trombofilici acquisiti

Diabete mellito
Sindrome da APA (atc anti-fosfolipidi)
Neoplasie (pancreas, stomaco, polmone)
Neoplasie mieloproliferative Phneg
Sindrome nefrosica
MPD Jak2+
Protesi valvolari
Morbo di Crohn
Sindrome di Behcet
Trombocitopenia da eparina
EPN

The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases

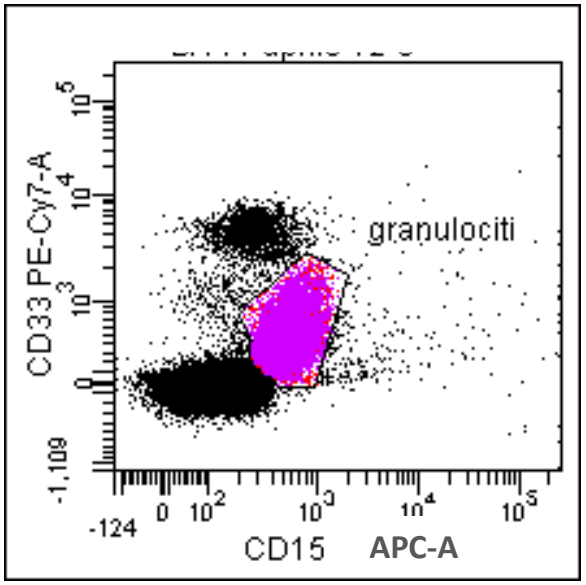
Jean-Jacques Kiladjian, Francisco Cervantes, Franck W. G. Leebeek, Christophe Marzac, Bruno Cassinat, Sylvie Chevret, Dominique Cazals-Hatem, Aurélie Plessier, Juan-Carlos Garcia-Pagan, Sarwa Darwish Murad, Sebastian Raffa, Harry L. A. Janssen, Claude Gardin, Sophie Cereja, Carole Tonetti, Stéphane Giraudier, Bertrand Condat, Nicole Casadevall, Pierre Fenaux and Dominique C. Valla

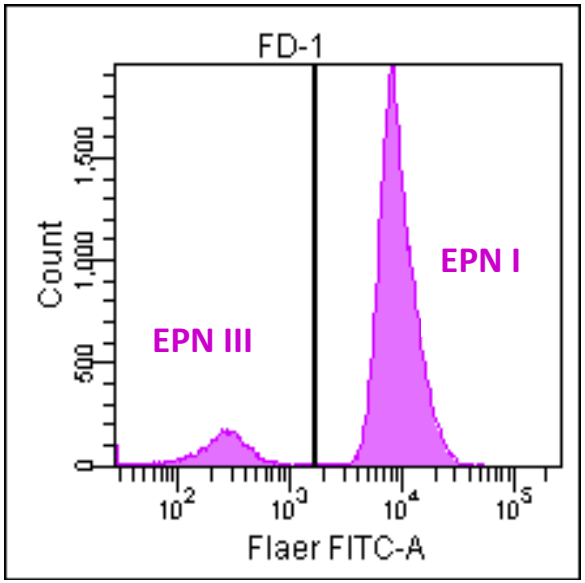


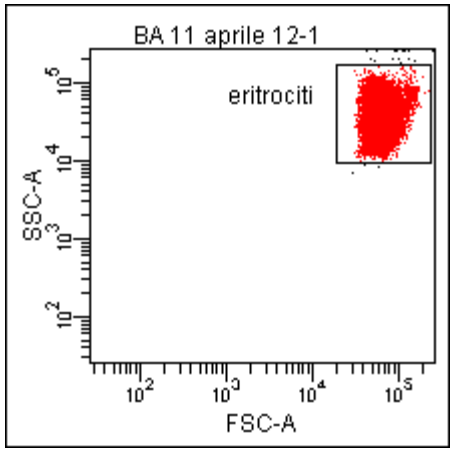
Jak 2 +:
34% PVT
45% BCS

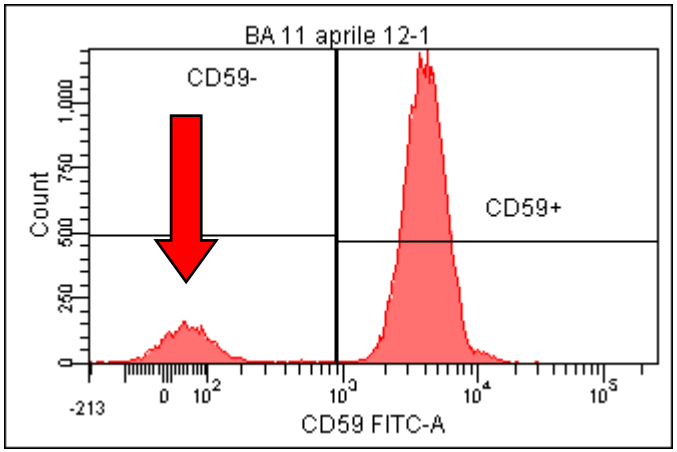
BLOOD, 15 MAY 2008 • VOLUME 111, NUMBER 10

Analisi multiparametrica citometrica (sp): **FLAER** sui granulociti e **CD59** su globuli rossi









Caso 3

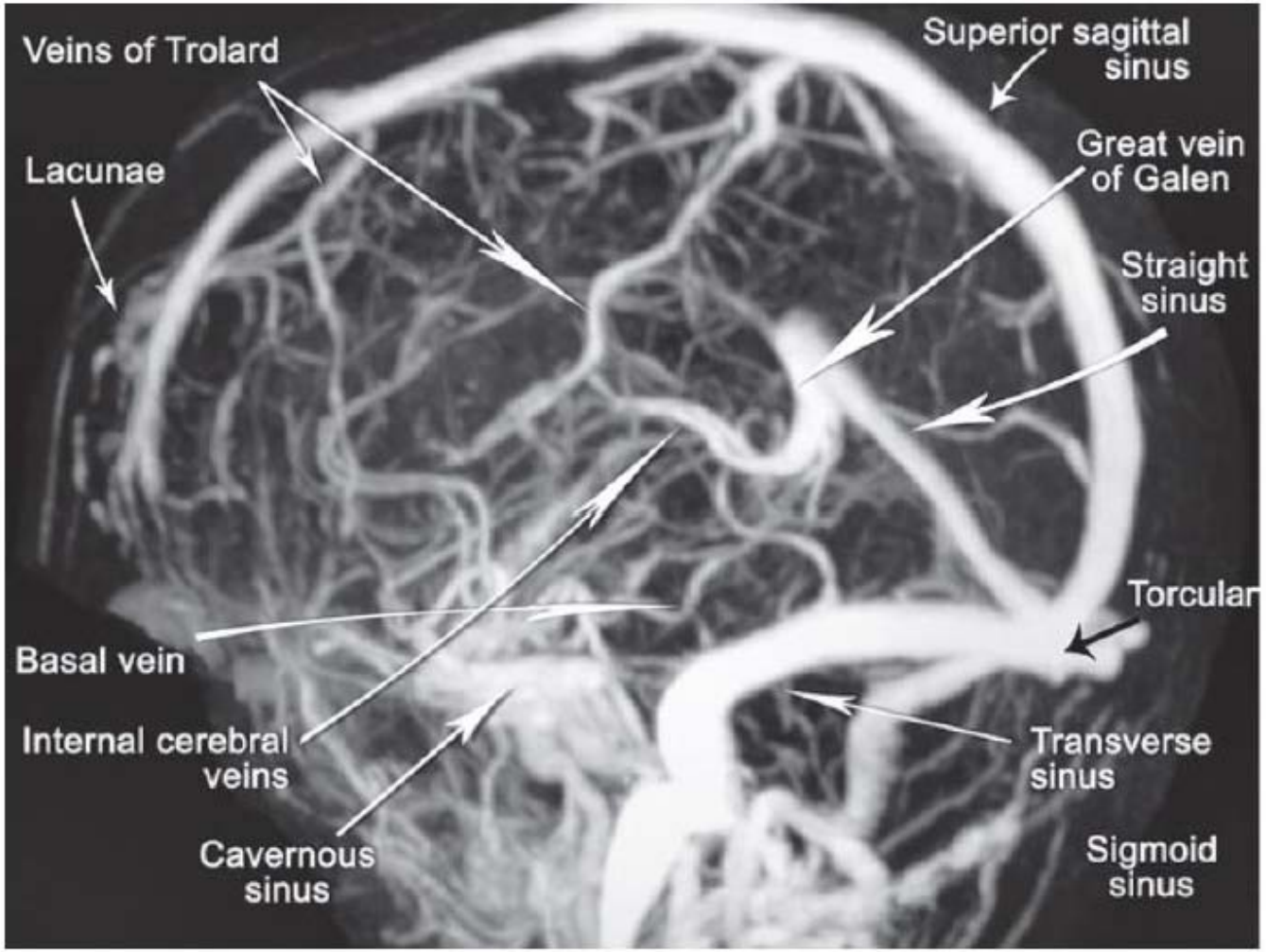
- **Anni 69**. **Esordio Marzo 2018** con **dolore addominale:** esami: leucopenia (WBC 2.2), piastrinopenia (88), anemia (Hb 9.5) ,

  insuff epatica: ipertransaminasemia. ittero, epatomegalia, splenomegalia, ascite, ipertensione portale, Insuff renale grado lieve.
- **Ricovero: S di Budd Chiari** (trombosi 3 vene sovraepatiche).
- Citometria: clone EPN 80% in Gr neutrofili e monociti, 30% in GR.

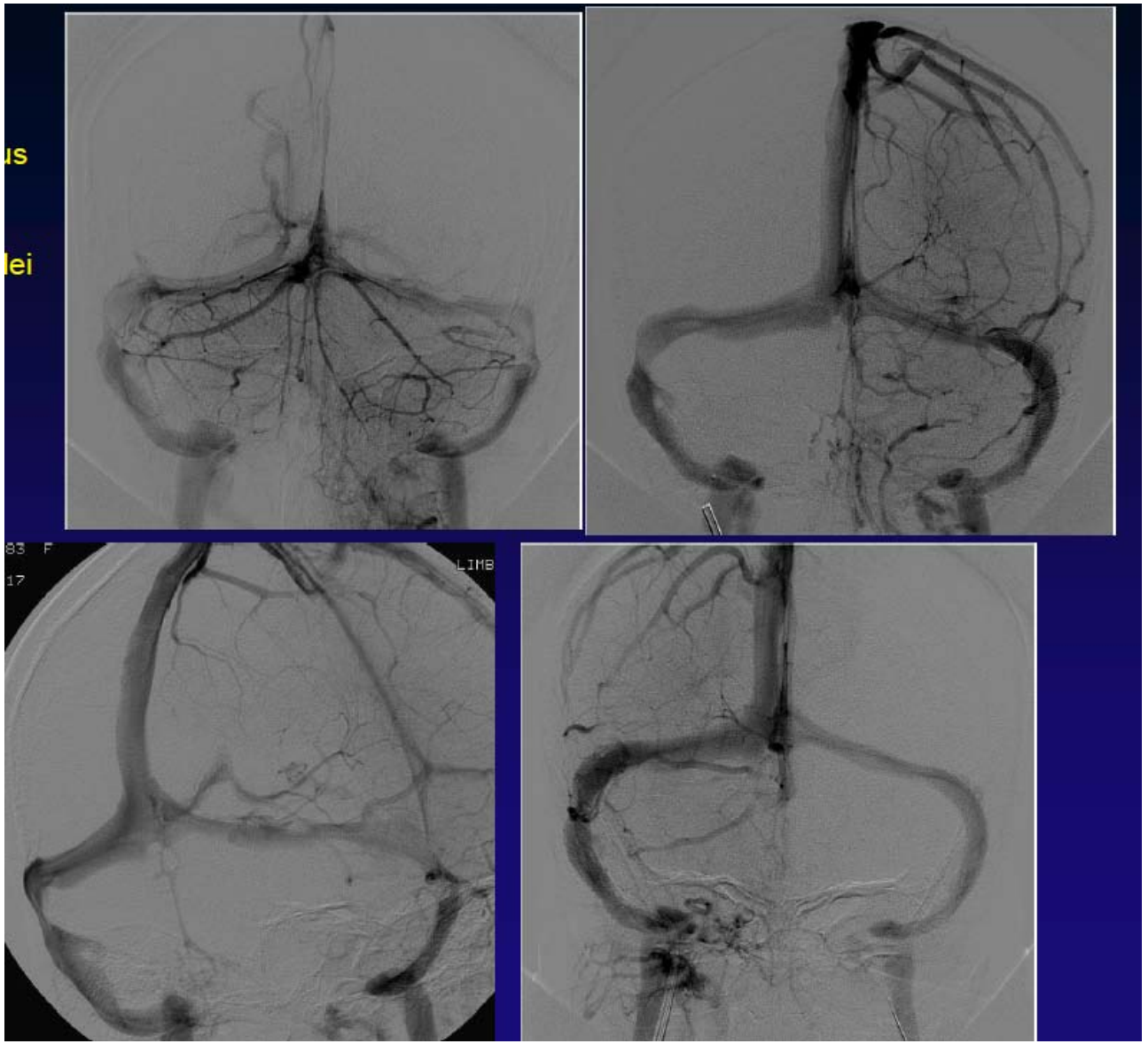
Caso 4

- Storia negli ultimi **24 mesi di oltre 10 episodi trombotici** (vene dei seni cerebrali, splancnici multipli, TVP, TIA, s.coronarica)
- Screening trombofilico negativo
- **Consulenza ematologica** Marzo 2016: clone **EPN 85%,**
- **Aprile 2016: inizio terapia con eculizumab**
- Nessun evento trombotico dal 2016 ad oggi

VENE CEREBRALI



Stenting bilaterale seni trasversi e sigmoidei



Caso 5

- Esordio aplasia severa e clone EPN 5-45 % in 9 mesi : ATG CyA : no risposta ; ATG cavallo-CyA
- No risposta_ Cy A e boli endxan e VCR no risposta ; eculizumab : no risposta sulla serie rossa
- 2 anni dopo: clone 90%, AA non severa: N 700/ul, Pst 40.000/mmc, Hb 8 g/dl: ottima risposta ematologica.