

# Microangiopathie thrombotique: Les pièges de la schizocytes

A.Lionet  
P. Chamley

SFH - Montpellier

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# Les microangiopathies thrombotiques

=AH mécanique + Thrombopénie + Coombs négatif

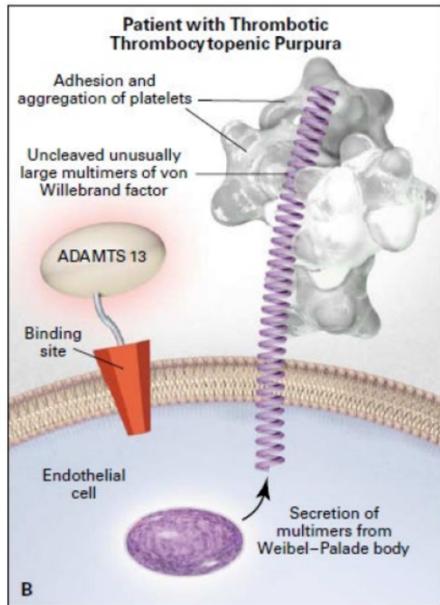


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PTT :  
pathology de l'ADAMTS-13



Moake NEJM 2002

	Clinical diagnosis*	
	TTP	HUS
Number of subjects	66	45
Clinical characteristics*		
Hemolytic anemia	100	100
Thrombocytopenia	94	60
Neurologic changes	90	15
Fever	50	21
Acute anuric renal failure	2	98
Laboratory findings*		
Mean platelet count (per $\mu$ L)	35,000	95,000
Mean creatinine (mg/dL)	1.8	4.1
Decreased protease activity	89	13
Protease inhibitor present	51	0

Veyradier, A, 2001, *Blood* 98:1765-1772.

SHU :  
plus polymorphe

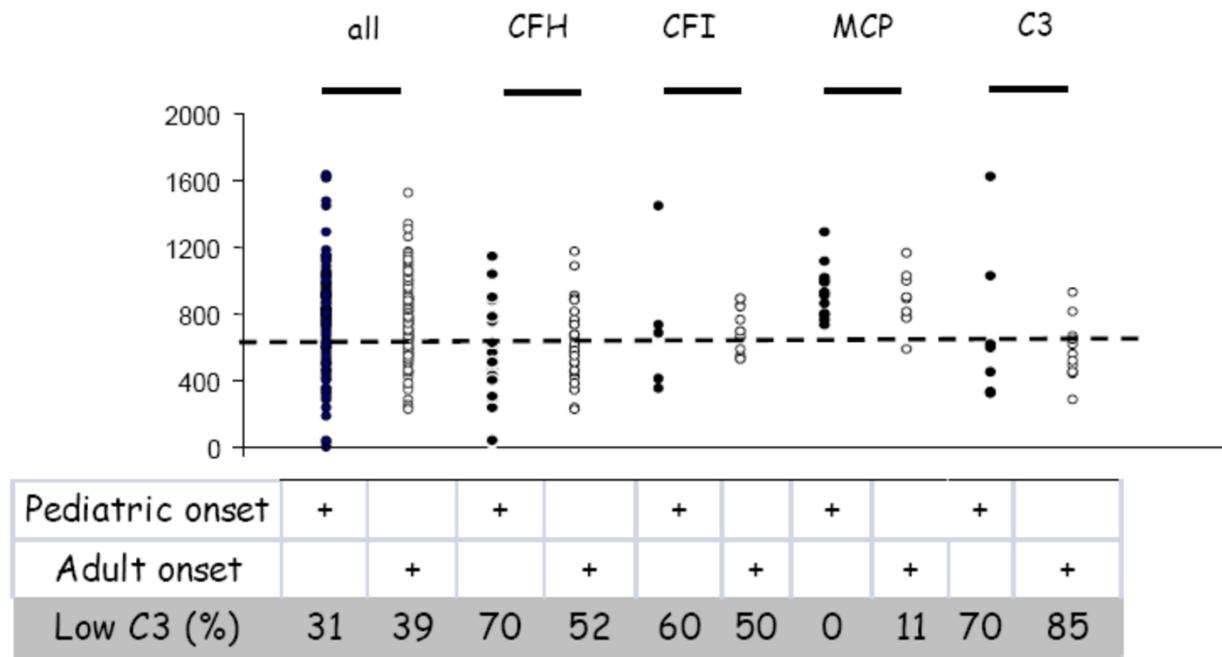
SHU typique  
A STX

SHU atypique  
avec anomalie de la VAC

SHU atypique  
sans anomalie de la  
VAC

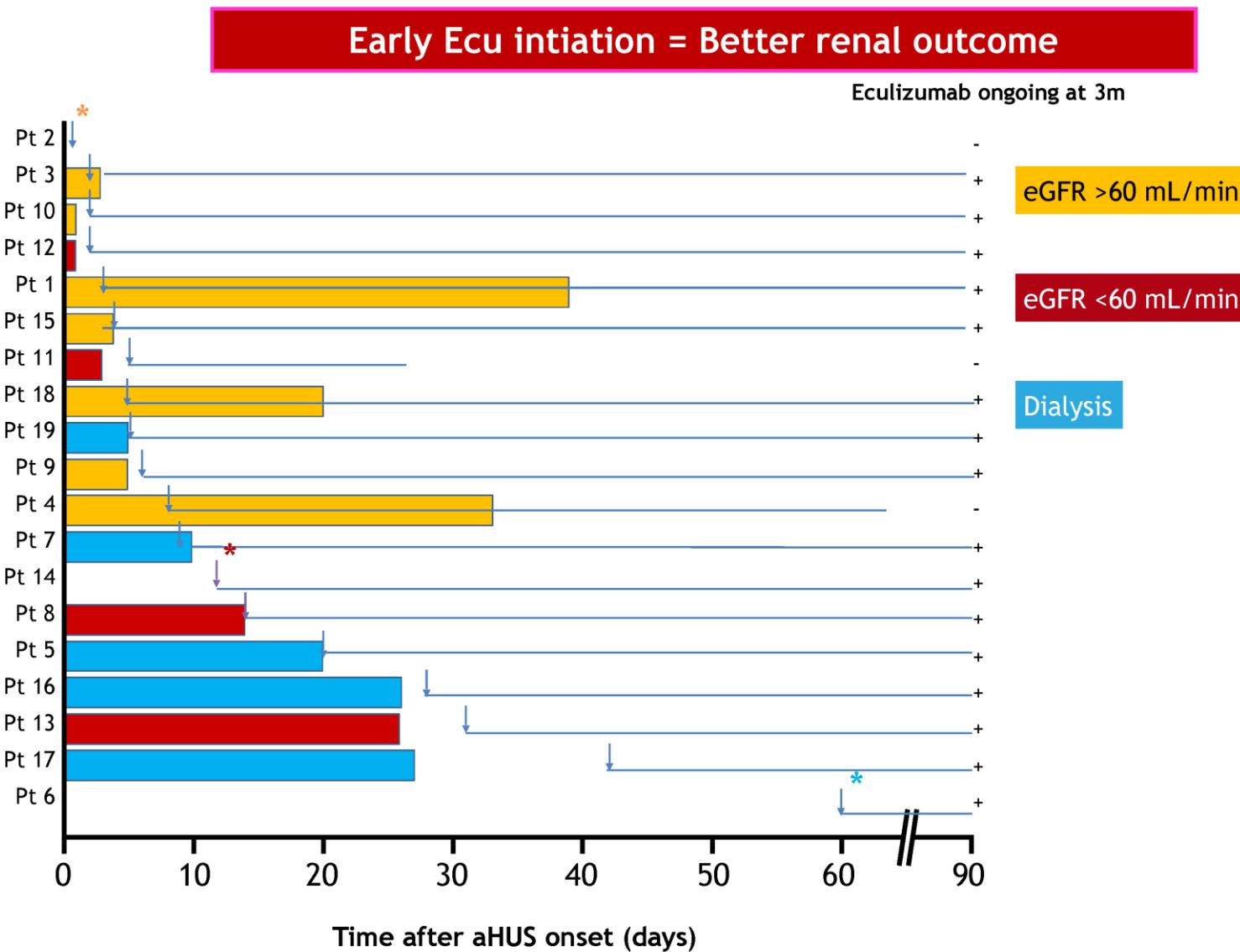
# Anomalies du complément et SHUa

## Complement assays



Normal complement levels do not exclude aHUS diagnosis

# Insights from use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases



# PTT

## Urgence thérapeutique

Longer delay in initiating plasma exchanges, presence of stupor or coma, and higher creatinine levels at the beginning of plasma exchanges were independent predictors of treatment failure.

Perrera, Ann Hematology, 1995

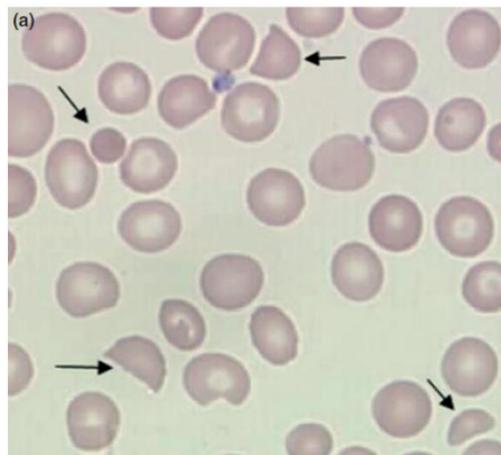
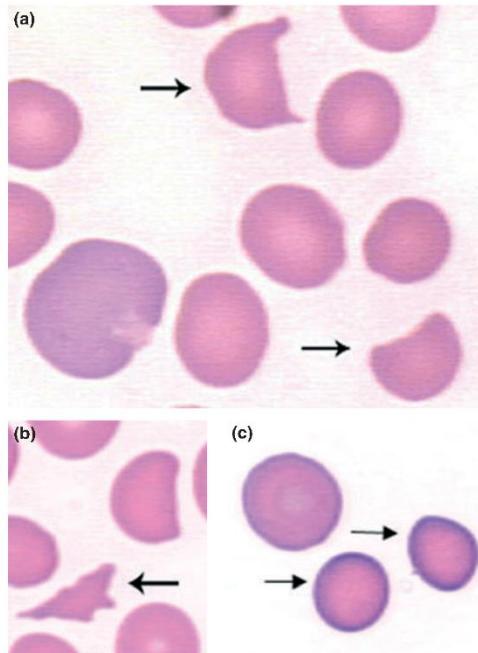
3 In view of the high risk of preventable, early deaths in TTP, treatment with PEX should be initiated as soon as possible, preferably within 4–8 h, regardless of the time of day at presentation, if a patient presents with a MAHA and thrombocytopenia in the absence of any other identifiable clinical cause (1B).

Scully, BJH, 2012

Schizocytes



# Qu'est ce qu'un schizocyte ?



Keratocytes (cornes)  
Microspherocyte  
Chapeau de gendarme (helmet)

- Les hématies crénelées, spiculées sont à rejeter.
- Les termes hématie mordue, hématie de taille diminuée et déformée de manière importante, et hématie en virgule ou en bâtonnet sont discutables.

# Standardisation de l'évaluation des schizocytes

Table 1. International Council for Standardization in Haematology recommendations for schistocyte counting

1. Schistocytes should be evaluated on peripheral blood smears using an optical microscope at medium magnification and estimated as a percentage after counting at least 1000 red blood cells
2. A schistocyte count should be requested and carried out when a diagnosis of thrombotic microangiopathies caused by red cell mechanical damage is suspected, usually in patients with thrombocytopenia
3. Schistocytes should be identified by specific positive morphological criteria. Schistocytes are always smaller than intact red cells and can have the shape of fragments with sharp angles and straight borders, small crescents, helmet cells, keratocytes, or microspherocytes\*
4. A schistocyte count should be considered clinically meaningful if schistocytes represent the main morphological red blood cells abnormality in the smear (other than signs of erythropoietic regeneration)
5. A robust morphological indication for the diagnosis of thrombotic microangiopathic anemia in adults should be recognized when the percentage of schistocytes is above 1%
6. Fragmented red cell enumeration by automated blood cell counters should be considered a useful complement to microscopic evaluation, as it provides rapid results with a high predictive value of negative samples. A microscope check is needed for positive and macrocytic samples†

\*Microspherocytes only in the presence of other mentioned RBC shapes.

†Macrocytic samples are at risk of underestimation or absence of flag ('false-negative' test).

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# Tous cela n'est pas qu'un concept...

## Erreur N°1

Erreur d'analyse.

Dysmorphies érythrocytaires

## Erreur N°2

Erreur d'interprétation,

La shizocytose ne fait pas la MAT

# Dysmorphie érythrocytaire

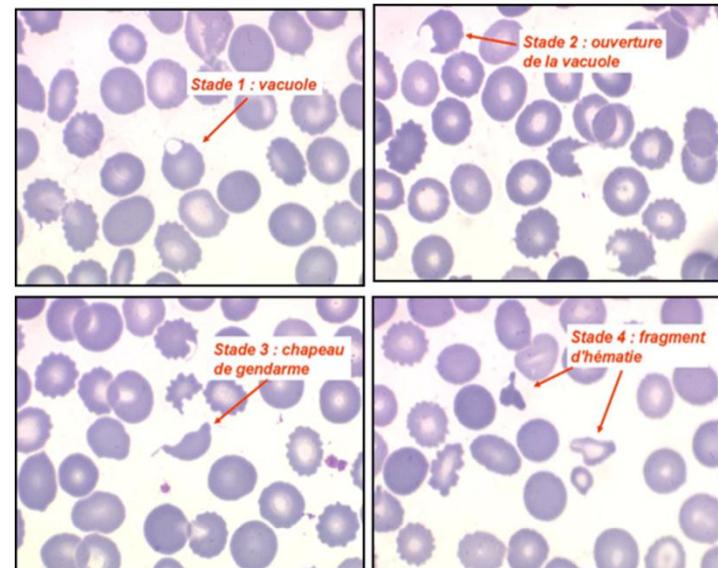
Sans (ou peu) de schizocyte, autres atteintes des lignés possibles

## Grandes dysérythropoïèses :

- Sepsis
- Carences en vit B12
- SAM et Nécrose médullaire

## Anémies Hémolytiques :

- Médicamenteuse (ACADIONE),
- Immune
- Infectieuses
- Corpusculaire : Beta-thalassemie majeur et déficit en G6PD (associé à des “bite-cell” = phagocytose d'une partie des GR par les macrophage de la rate)
- Hépatopathies sévères (syndrome de Zieve)
- Grands brûlés (parfois les hyperthermies majeures)

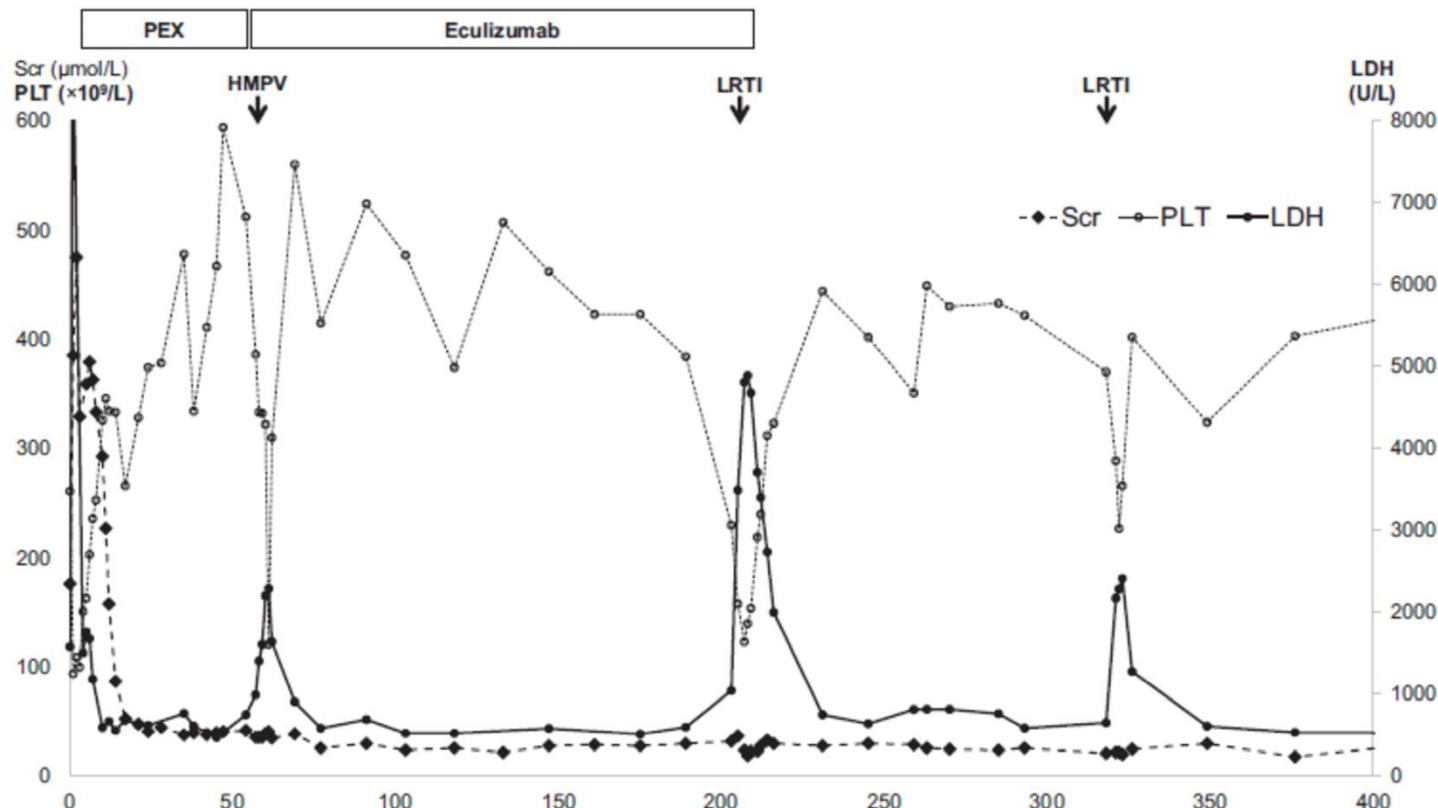


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# Glucose-6-Phosphate Dehydrogenase Deficiency Mimicking Atypical Hemolytic Uremic Syndrome



Patrick R. Walsh, Sally Johnson, Vicky Brocklebank, Jacobo Salvatore, Martin Christian, and David Kavanagh



**Figure 1.** Clinical course. Serum creatinine (Scr), lactate dehydrogenase (LDH), and platelet (PLT) count values plotted over the first 400 days following the initial presentation. Clinical interventions with plasma exchange (PEX) and eculizumab are shown above. Arrows demonstrate infectious triggers (human metapneumovirus [HMPV], lower respiratory tract infection [LRTI]). Conversion factor for Scr in  $\mu\text{mol/L}$  to mg/dL, +88.4.

# Mme D

45 ans. Syndrome anxio-depressif. Troubles neurologiques aigus. IOT=>réanimation

	25/07/2016
LEUCOCYTES	11.40
HEMOGLOBIN	8.4
VGM	104.7
NUMPLAQUE	21
CPK	94 - H
TROPONINE	73
TCA MALADE	31
UREE	195 - H
CREATININE	46
LDH	12607 - H
TGO	2715 - H
TGP	2609 - H
PAL	94
BILITOTALE	72 - H
GGT	
FERRITINE	>10000
FOLATES SÉRUM	3.1
VITAMINE B1	>1.0
HAPTOGLOB	<0.07 - L

FV15%

Schizocytes 1 à 2%

Poikilocytose  
Polychromasie  
Anisocytose

# Mme D

45 ans. Syndrome anxiо-depressif. Troubles neurologiques aigues. IOT=>réanimation

	25/07/2016	26/07/2016	27/07/2016	28/07/2016	29/07/2016	30/07/2016	31/07/2016	01/08/2016
LEUOCYTES	11.40	6.69	6.46	9.00	10.03	12.90	14.51	13.14
HEMOGLOBIN	8.4	8.4	8.4	7.6	7.7	7.3	9.6	8.9
VGM	104.7	VGM no	VGM no	103.1	102.7	105.1	96.9	91.4
NUMPLAQUE	21	42	34	32	42	67	115	166
CPK	94-H	63-H	48-H	45-H	42-H	48-H		32-H
TROPONINE	73	38	23	24				38
TCA MALADE	31	32	31	31	29	29	30	36
UREE	195-H	0.84-H	0.57-H	0.29	0.36	0.79-H	0.59-H	0.87-H
CREATININE	46	26	20	15	17	41	37	53
LDH	12607-H					1419-H		
TGO	2715-H	795-H	538-H	203-H	100-H	58-H		31-H
TGP	2609-H	1514-H	1347-H	798-H	509-H	330-H		142-H
PAL	94	73	72	73	92	107-H		118-H
BILITOTALE	72-H	118-H	122-H	113-H	99-H	84-H		57-H
GGT		36-H	37-H	36-H				69-H
FERRITINE	>10000							
FOLATES SÉRUM	3.1							
VITAMINE B1	>1.0							
HAPTOGLOB	<0.07-L					<0.07-L		

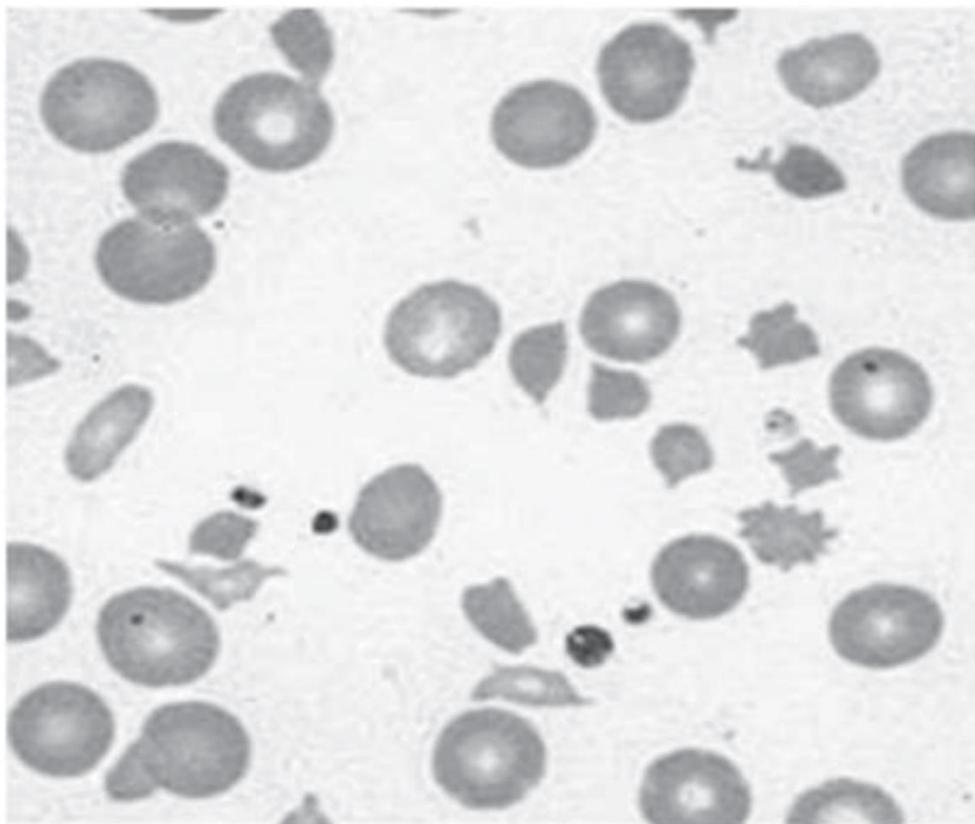
FV15%

FV80%

Schizocytes 1 à 2%

Poikilocytose  
Polychromasie  
Anisocytose

ADAMTS 13 normale  
Pas d'anomalie du Complément



Senatore, Am J GastroEnt, 2016

# Madame B

Madame B 70 ans:

- Hypertension artérielle ;
- Adénocarcinome colique avec extension hépatique, opéré il y a 2 ans et pris en charge par chimiothérapie notamment par FOLFOX.

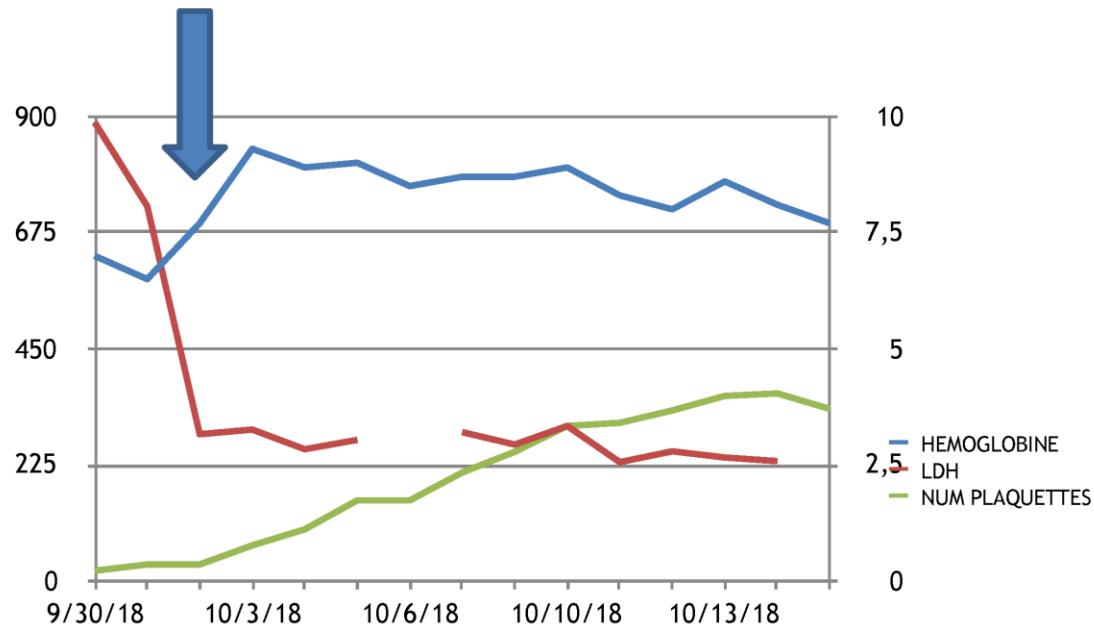
=>Récemment mise en évidence d'une poursuite évolutive hépatique péritonéale et pulmonaire avec un statut KRAS sauvage pour laquelle la patiente a déjà reçu 3 cures de chimiothérapie par FOLFOX VECTIBIX.

B- ANNIE	30/09/20 18
LEUCOCYTES	7,15
HEMOGLOBINE	7
VGM	92,7
POLY NEUTRO ABS	5,8
LYMPHO ABS	0,2
NUM PLAQUETTES	21
reticulocytes %	3
CRP	60
TROPONINE T (TnThs)	15
CPK	14
CREATININE	74
LDH	888
HAPTOGLOBINE	<0,08
DIURESE 24H	0,5
PROTEINES URINE/L	0,34

Hyposegmentation du noyau des granulocytes (CHX)  
Anisochromie  
Poïkilocytose  
Corps d'Howell-Jolly  
Anisocytose

# Madame B

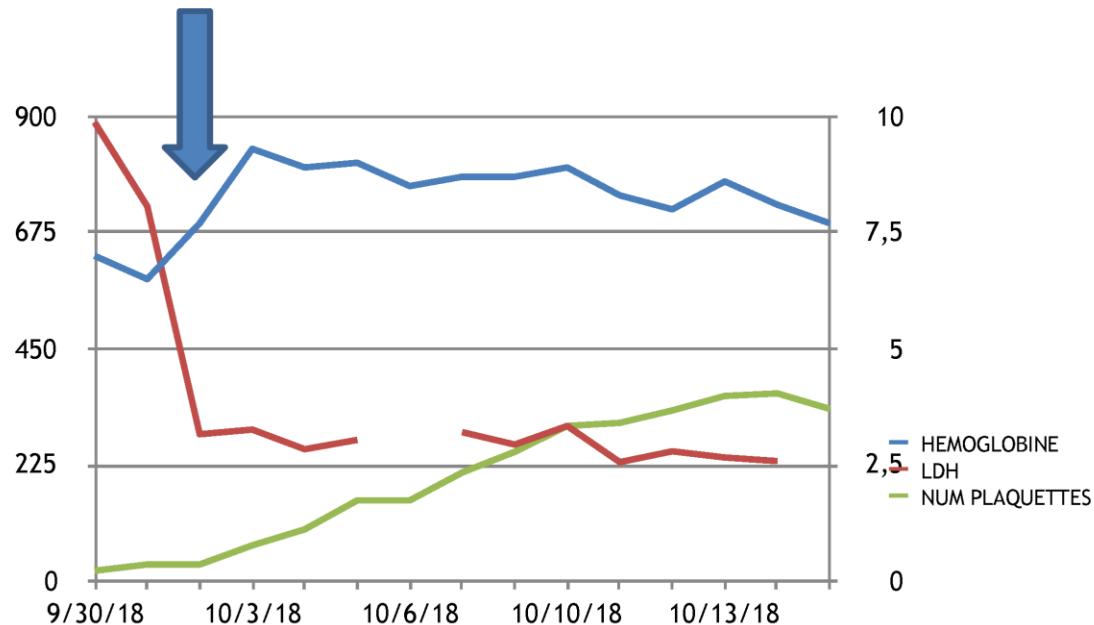
Échange plasmatique 100% PFC



schizo +

# Madame B

Échange plasmatique 100% PFC

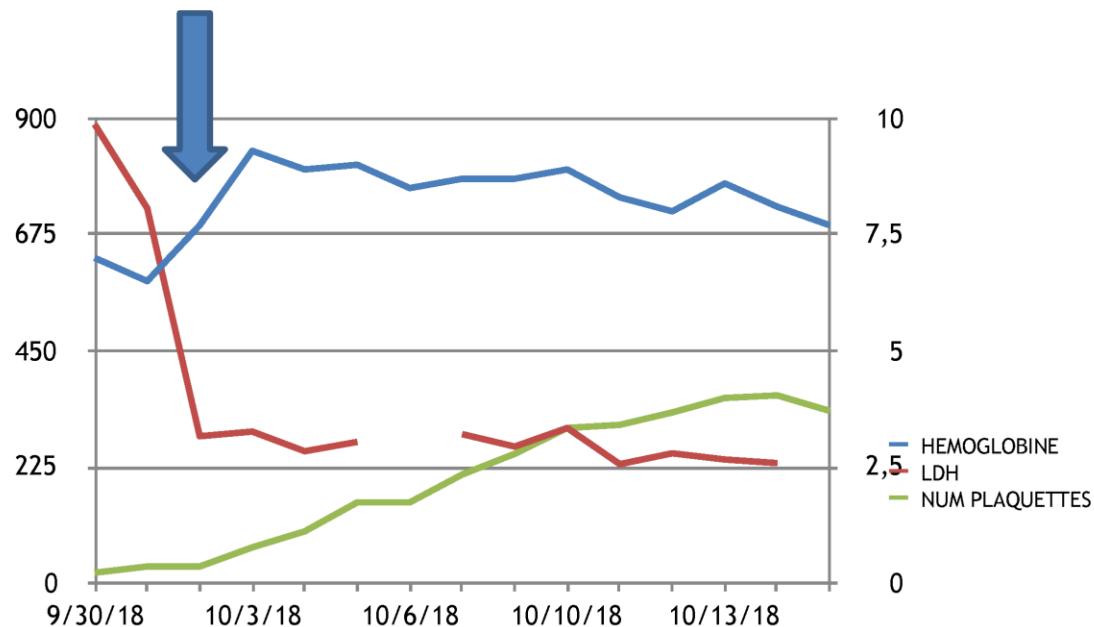


schizo +

Test direct à l'antiglobuline positif de type mixte (IgG + complément)  
Ac anti Plaquettaire en cours

# Madame B

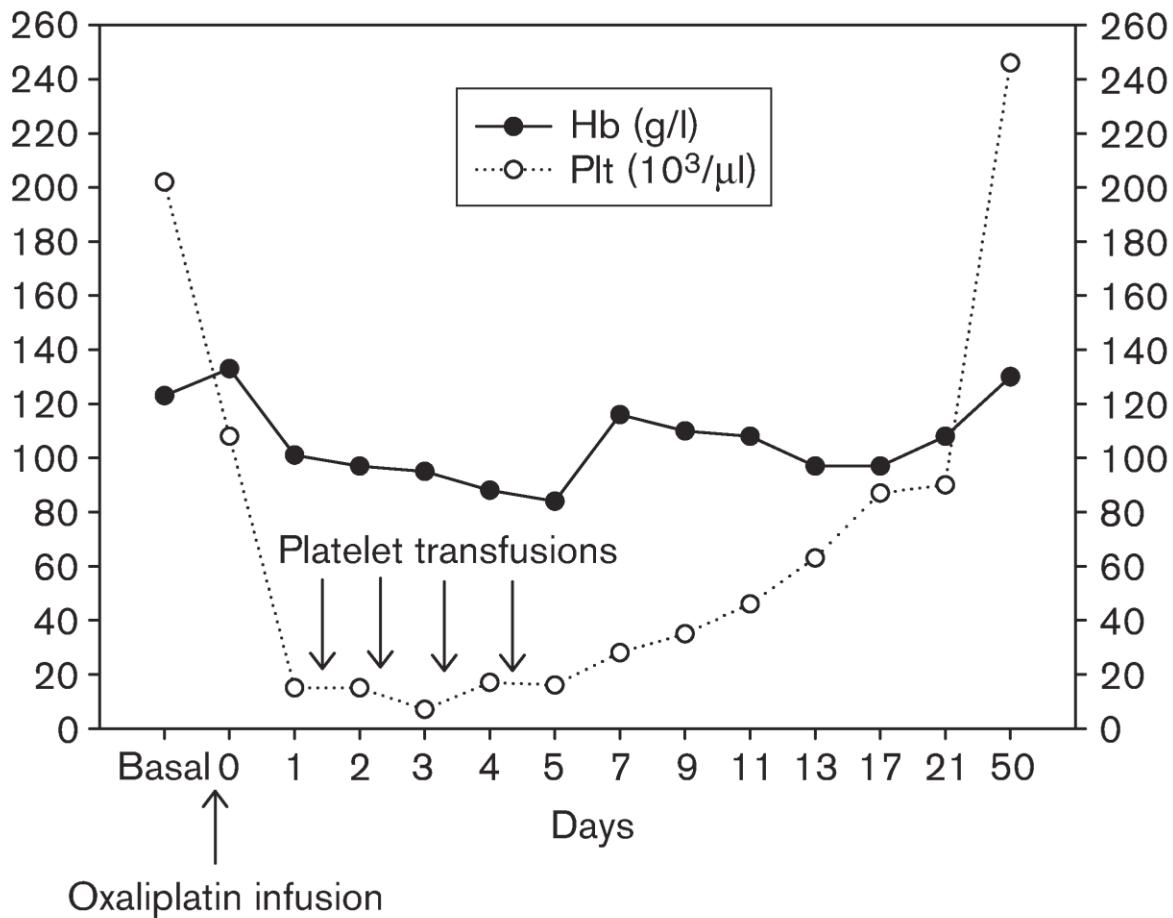
Échange plasmatique 100% PFC



schizo +

Test direct à l'antiglobuline positif de type mixte (IgG + complément)  
Ac anti Plaquettaire en cours

PBR : néphrite aigue immunoallergique

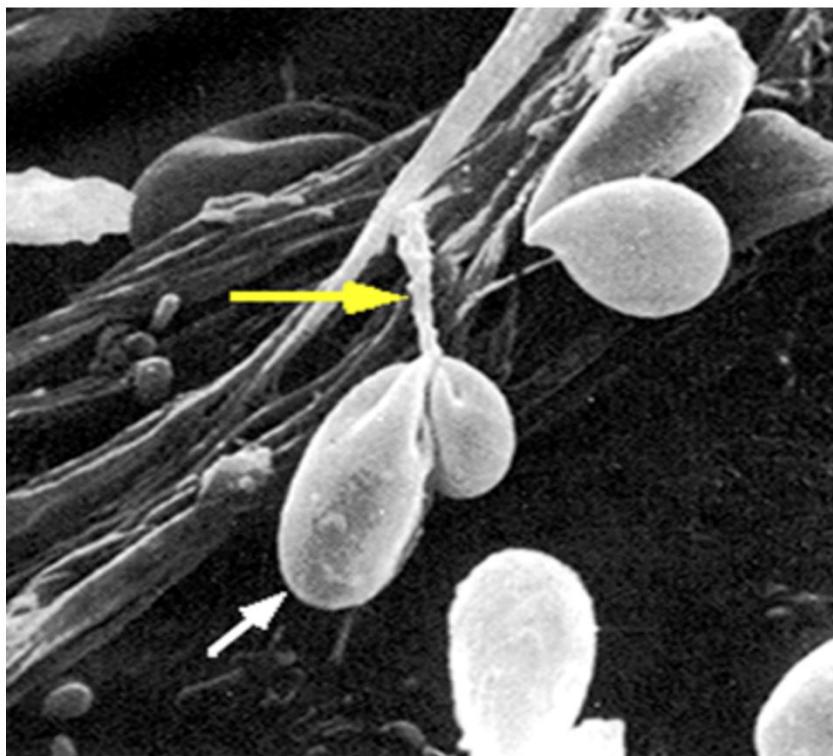


## Oxaliplatin-induced immune hemolytic anemia: a case report and review of the literature

Francesc Cobo<sup>a</sup>, Guillem De Celis<sup>b</sup>, Arturo Pereira<sup>c</sup>, Xavier Latorre<sup>b</sup>, Jaume Pujadas<sup>a</sup> and Santiago Albiol<sup>a</sup>

*l'hirondelle ne fait pas le printemps....*

*.....la shizocytose ne fait pas la MAT*



PTT/HUS

Obstacles mécaniques

Desinsertion valves

Un circuit de dialyse ou d'EP

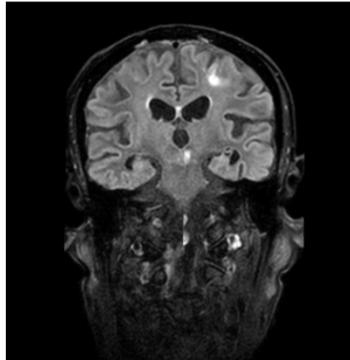
CIVD

CIVL : Hémangiomes caverneux

Myélofibrose

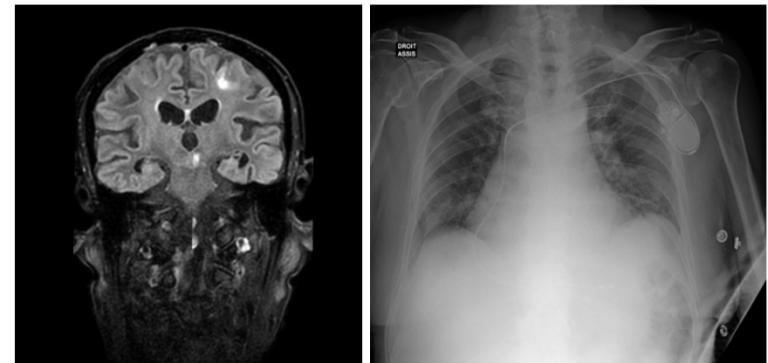
# Mr P

72 ans. TAVI, maladie oreillette.  
Cancer de prostate ? Tassement T11-RaO-DNID-AOMI.  
Arrêt AVK/relais calciparine.  
Troubles neurologiques aigus PL, Zovirax  
Elévation troponine, USIC = KT => coma => réa



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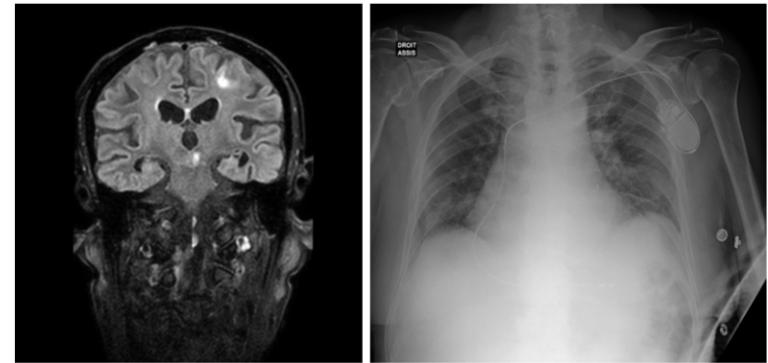


	29/09/2016
LEUCOCYTES	14.15
HEMOGLOBINE	10.5
VGM	1028
NUM PLAQUETTES	48
CPK	
TROPONINET	
UREE	106-H
CREATININE	46
SODIUM	130
POTASSIUM	4.9
ACIDE URIQUE	35
PROTEINES	55-L
LDH	733-H
TGO	55-H
TGP	32
PAL	63
BILITOTALE	0
HAPTOGLOBINE	0.18-L

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	29/09/2016	30/09/2016	01/10/2016
LEUCOCYTES	14.15	1207	14.04
HEMOGLOBINE	10.5	10.0	9.9
VGM	102.8	105.4	104.3
NUM PLAQUETTES	48	47	80
CRP		183-H	
TROPONINET			
UREE	1.06 -H	0.84 -H	0.61 -H
CREATININE	46	31	20
SODIUM	135	138	141
POTASSIUM	4.9	3.7	3.8
ACIDE URIQUE	35		
PROTEINES	55-L	50-L	55-L
LDH	733-H	838-H	574-H
TGO	55-H		
TGP	32		
PAL	63		
BILITOTALE	9		
HAPTOGLOBINE	0.18-L	0.20-L	0.37



ADAMTS13, et complément normaux

Schizocytes 1 à 2%,

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BILITOTALE	9		
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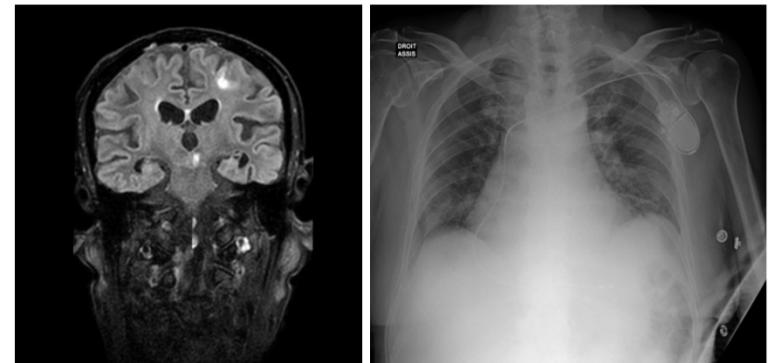
ADAMTS13, et complément normaux

Schizocytes 1 à 2%,

ETO : volumineux  
Thrombus dans l'auricule  
gauche

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72 ans. TAVI, maladie oreillette.  
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Agravation neurologique le 03/10/2016  
Encéphalopathie aux betalactamines ?

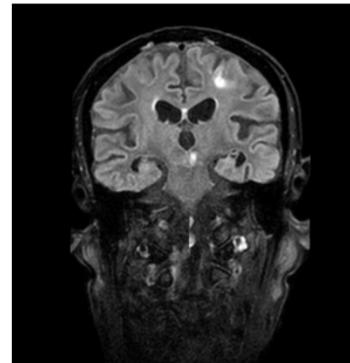


	02/10/2016	03/10/2016
LEUCOCYTES	13.99	17.74
HEMOGLOBIN	9.5	9.3
VGM	104.5	105.0
NUMPLAQUE	70	79
CPK		97 - H
TROPONINE T (TnThs)		
UREE	0.59 - H	0.66 - H
CREATININE	18	19
SODIUM	142	141
POTASSIUM	3.5	3.5
ACIDEURIQUE		
PROTEINES	51 - L	52 - L
CALCIUM	86	87
LDH		659 - H
TGO		
TGP		
PAL		
BILUTOTALE		
HAPTOGLOB	0.42	0.26 - L

Schizocytes 1 à 2%,

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Cancer de prostate ? Tassement T11-RaO-DNID-AOMI.  
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	02/10/2016	03/10/2016	04/10/2016
LEUCOCYTES	13.99	17.74	20.89
HEMOGLOBIN	9.5	9.3	9.1
VGM	104.5	105.0	104.7
NUMPLAQUE	70	79	67
CPK		97 - H	
TROPONINE T (TnThs)			
UREE	0.59 - H	0.66 - H	0.91 - H
CREATININE	18	19	25
SODIUM	142	141	140
POTASSIUM	3.5	3.5	4.0
ACIDE URIQUE			
PROTEINES	51 - L	52 - L	48 - L
CALCIUM	86	87	82 - L
LDH		659 - H	725 - H
TGO			
TGP			
PAL			
BILITOTALE			
HAPTOGLOB	0.42	0.26 - L	0.12 - L

Schizocytes 1 à 2%,

Schizocytes 6 à 10%



# Mr P

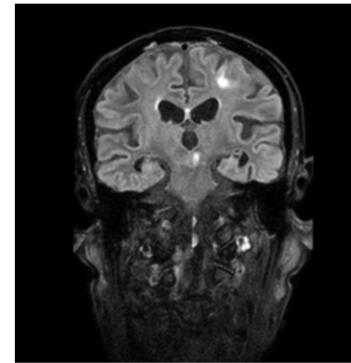
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TROPONINE T (TnThs)			
UREE	0.59 - H	0.66 - H	0.91 - H
CREATININE	18	19	25
SODIUM	142	141	140
POTASSIUM	3.5	3.5	4.0
ACIDE URIQUE			
PROTEINES	51 - L	52 - L	48 - L
CALCIUM	86	87	82 - L
LDH		659 - H	725 - H
TGO			
TGP			
PAL			
BILITOTALE			
HAPTOGLOBINE	0.42	0.26 - L	0.12 - L

Schizocytes 1 à 2%,



Schizocytes 6 à 10%



	04/10/2016	05/10/2016	06/10/2016
LEUCOCYTES	20.89	23.46	20.32
HEMOGLOBINE	9.1	8.8	9.0
VGM	104.7	103.7	105.5
NUM PLAQUETTES	67	82	126
CRP		34 - H	19 - H
UREE	0.91 - H	0.69 - H	0.72 - H
CREATININE	25	21	21
LDH	725 - H	621 - H	555 - H
HAPTOGLOBINE	0.12 - L	0.24 - L	0.26 - L

ETO de contrôle : thrombus de l'auricule absent  
 + dé-insertion avec fuite importante du TAVI

# Allogreffe de moelle

## Evaluation of schistocyte monitoring after haematopoietic stem cell transplantation

J.-F. LESESVE\*, F. ALLA<sup>†</sup>, F. DUGUÉ<sup>‡</sup>, S. SALIGNAC\*, L<sup>§</sup> CLÉMENT<sup>‡</sup>, T. LECOMPT<sup>\*</sup>, P. BORDIGONI<sup>‡</sup>

125 greffes moelle 50 jours :

- 80% schizocytes en moyen à 0,7%
- 1 à 4% : GVHa, GVHc, MVO du foie, hépatite cholestatique, hémorragie vesicale, infection pulmonaire.
- >5% MAT

# Attention a l'analyse séquentielle

## Mm S-R

55 ans

Asthénie, consultation cardiologue, urgence

S R	19/09/201 8
LEUCOCYTES	6,09
HEMOGLOBINE	12.5
reticulocytes	
NUM PLAQUETTES	38
CREATININE	6
LDH	470
HAPTOGLOBINE	<0,08
PROTEINES URINE/ L	
Schizocytes	neg

# Mm S-R

55 ans

Asthénie, consultation cardiologue, urgence

S R	19/09/201 8	21/09/201 8
LEUCOCYTES	6,09	7.03
HEMOGLOBINE	12.5	11.2
reticulocytes		4,9%
NUM PLAQUETTES	38	30
CREATININE	6	6
LDH	470	459
HAPTOGLOBINE	<0,08	<0.08
PROTEINES URINE/ L		0.25
Schizocytes	neg	2 à 3%

# Mm S-R

55 ans

Asthénie, consultation cardiologue, urgence

S R	19/09/201 8	21/09/201 8	22/09/201 8	23/09/201 8
LEUCOCYTES	6,09	7.03	8.00	6.12
HEMOGLOBINE	12.5	11.2	12.1	10.0
reticulocytes		4,9%		
NUM PLAQUETTES	38	30	25	44
CREATININE	6	6	7	6
LDH	470	459	507	217
HAPTOGLOBINE	<0,08	<0.08		0.38
PROTEINES URINE/ L		0.25	0.46	0.28
Schizocytes	neg	2 à 3%	2 à 3%	2 à 3%

Activité ADAMTS-13 <1%  
Ac anti Adamts-13 60 ui

**TABLE I. Presence of Residual Schistocytosis Versus Early Relapse Rate\***

	Presence of residual schistocytosis	Absence of residual schistocytosis	Total
Relapse	5	9	14
No relapse	11	20	31
Total	16	29	45

\*Comparison of the number of patients with or without residual schistocytosis at the time of cessation of plasma exchange. Overall, residual schistocytosis was present in 35.6% of patients but was not a predictor for relapse ( $P = 1.00$ ).

# Mr L-Jc

- Homme 70 ans, oppression thoracique

Adamts-13<1%  
Ac 13 ui/l

	09/11/201 4
HEMOGLOBINE	8,4
NUM PLAQUETTES	9
CREATININE	11
LDH	1414
HAPTOGLOBINE	<0.008
reticulocytes	13%
coombs	neg
tropo	200 ui
schizocyte	
Cs	

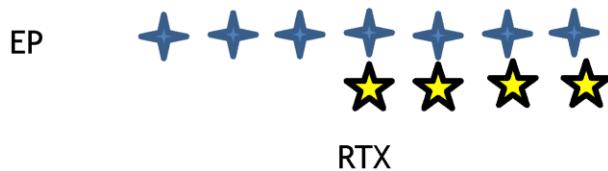
EP      -

# Mr L-Jc

- Homme 70 ans, oppression thoracique

Adamts-13<1%  
Ac 13 ui/l

	09/11/201 4	13/11/201 4	17/11/201 4
HEMOGLOBINE	8,4	8,5	8,6
NUM PLAQUETTES	9	13	14
CREATININE	11	8	8
LDH	1414	1200	1100
HAPTOGLOBINE	<0.008		0,09
reticulocytes	13%		8%
coombs	neg		
tropo	200 ui		
schizocyte		3%	
Cs			



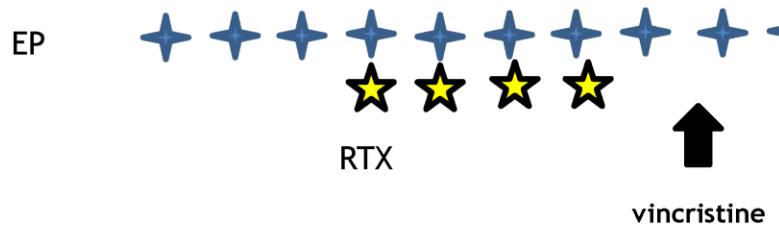
PTT acquis avec atteinte cardiaque

# Mr L-Jc

- Homme 70 ans, oppression thoracique

Adamts-13<1%  
Ac 13 ui/l

	09/11/201 4	13/11/201 4	17/11/201 4	20/11/201 4
HEMOGLOBINE	8,4	8,5	8,6	9
NUM PLAQUETTES	9	13	14	26
CREATININE	11	8	8	
LDH	1414	1200	1100	224
HAPTOGLOBINE	<0.008		0,09	0,42
reticulocytes	13%		8%	6%
coombs	neg			
tropo	200 ui			
schizocyte		3%		3 à 6%
Cs				



PTT acquis avec atteinte cardiaque

# Mr L-Jc

- Homme 70 ans, oppression thoracique

Adamts-13<1%  
Ac 13 ui/l

	09/11/201 4	13/11/201 4	17/11/201 4	20/11/201 4	04/12/201 4	14/12/201 4
HEMOGLOBINE	8,4	8,5	8,6	9	8,2	8
NUM PLAQUETTES	9	13	14	26	16	35
CREATININE	11	8	8			
LDH	1414	1200	1100	224	225	350
HAPTOGLOBINE	<0.008		0,09	0,42		
reticulocytes	13%		8%	6%	3%	3%
coombs	neg					
tropo	200 ui					
schizocyte		3%		3 à 6%	1 à 2%	1 à 2%
Cs						



PTT acquis avec atteinte cardiaque

Mr L-Jc

- Homme 70 ans, oppression thoracique

**Adamts-13<1%**  
**Ac 13 ui/l**

Activité 63%  
Ac Adams-13 3 ui

PCR CMV = 6 log

The figure consists of two parts: a table of laboratory results and a timeline diagram below it.

**Table of Laboratory Results:**

	09/11/2011 4	13/11/2011 4	17/11/2011 4	20/11/2011 4	04/12/2011 4	14/12/2011 4	20/12/2011 5	29/12/2011 5
HEMOGLOBINE	8,4	8,5	8,6	9	8,2	8	7,6	9
NUM PLAQUETTES	9	13	14	26	16	35	46	136
CREATININE	11	8	8					
LDH	1414	1200	1100	224	225	350	400	
HAPTOGLOBINE	<0.008		0,09	0,42			1,2	1,25
reticulocytes	13%		8%	6%	3%	3%	3%	3%
coombs	neg							
tropo	200 ui							
schizocyte		3%		3 à 6%	1 à 2%	1 à 2%	1 à 2%	1 à 2%
Cs								

**Timeline Diagram:**

The timeline shows the progression of treatments from November 9 to December 29. Blue stars represent EP treatments, yellow stars represent RTX treatments, and a yellow triangle represents vincristine. A blue arrow points right along the timeline. A black double-headed arrow highlights the period from December 14 to December 29, which includes the vincristine treatment and the splenectomy procedure. A box labeled "rovalcyte" is positioned at the end of the timeline.

## PTT acquis avec atteinte cardiaque

# En conclusion

- Les pièges de la schizocytes sont :
  - Les erreurs d'analyse : Autres dysmorphies érythrocytaires
  - Les erreurs d'interprétation : assimilé *de facto* le schizocyte à de la MAT.
- Importance de la qualité de l'analyse cytologique.
- L'ensemble des diagnostics différentiels évoqués ne doit pas induire de confusion qui ne se pose pas en pratique. **L'attention doit rester focalisé sur le SHU-PTT aux conséquences graves.**
- Attention aux situations limites et à la tentation des thérapies innovantes.
- Importance du contexte clinique. Ne pas oublier b12, medullogramme, CIVD, Coombs.
- Savoir remettre en cause un diagnostic.

Merci pour votre attention