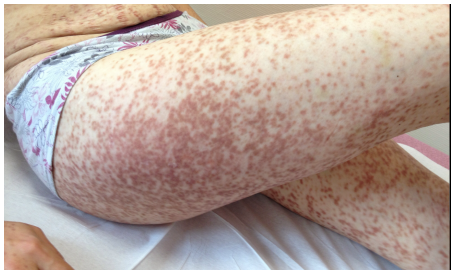
# QUEL BILAN POUR QUELLE MASTOCYTOSE ?

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FACULTE DE MEDECINE HENRI WAREMBOURG

# MASTOCYTOSES

- Prolifération clonale, néoplasique de mastocytes morphologiquement et phénotypiquement anormaux s'accumulant dans 1 ou plusieurs organes

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- Prolifération clonale, néoplasique de mastocytes morphologiquement et phénotypiquement anormaux s'accumulant dans 1 ou plusieurs organes
- Manifestations variables :
  - par leur sévérité : CM/SM/mastocytomes
  - par leurs mécanismes :
    - **infiltration tumorale : UP/HSM/cytopénies ET/OU**
    - **dégranulation : relargage des médiateurs → syndrome d'activation mastocytaire**

# 2 QUESTIONS

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# 2 situations les plus fréquentes

- Urticaire pigmentaire : mastocytose au moins cutanée
  - 1ère question : **systémique ou cutanée isolée** (<10% chez adulte)
  - puis sévérité de la mastocytose systémique
  - ➔ « indépendant » de la présence ou non d'autres signes (SAMA et anaphylaxie)

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  - puis sévérité de la mastocytose systémique
  - ➔ « indépendant » de la présence ou non d'autres signes (SAMA et anaphylaxie)

- Pas d'urticaire pigmentaire mais signes évocateurs d'une mastocytose (**syndrome d'activation mastocytaire) et/ou certaines anaphylaxies**
  - 1ère question : **est-ce une mastocytose (systémique)** ? **Y penser et en faire le dc positif**
  - puis sévérité de la mastocytose systémique

SAMA

**Table 1** Mast cell mediators and related symptoms

| | Mediator(s) | Measured in mastocytosis |
|---|---|---|
| Systemic | | |
| Vasodilation/hypotension | Histamine | + |
| | Prostaglandin D2 | + |
| Hypertension | Chymase | – |
| Fatigue/cachexia/weight loss | TNF-$\alpha$ | + |
| Fever | IL-6 | + |
| | IL-1 | – |
| Fibrosis | IL-1 | – |
| | IL-13 | – |
| | TGF-$\beta$ | – |
| Skin | | |
| Flushing | Histamine | + |
| | Prostaglandin D2 | + |
| Urticaria/angioedema | Histamine | + |
| | Prostaglandin D2 | + |
| | Leukotriene C4 | – |
| Gastrointestinal | | |
| Abdominal pain | Histamine | + |
| Peptic | | |
| Colic | | |
| Diarrhea | Histamine | + |
| Malabsorption | | |
| Bone | | |
| Bone pain | | |
| Osteoporosis/osteopenia | IL-6 | + |
| | Heparin | – |
| | Tryptase | + |
| | TGF-$\beta$ | – |
| Central nervous system | | |
| Mixed CNS syndrome | Prostaglandin D2 | + |
| | Histamine | + |

Escribano et al. Ann Hematol 2002

# ANAPHYLAXIE

- 20 a 49% des patients SM

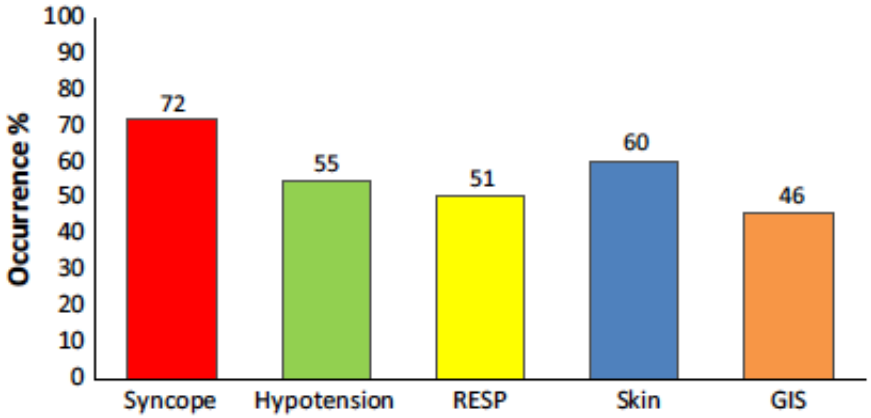


Fig. 2. Distribution of the most frequent clinical symptoms in 36 systemic mastocytosis patients with anaphylaxis. RESP, respiratory symptoms such as dyspnoea, wheeze-bronchospasm and stridor; Skin, involvement of skin/mucosal tissue such as flushing, pruritus, urticaria and swollen lips/tongue/larynx; GIS, gastrointestinal symptoms such as nausea, abdominal cramps and diarrhoea.

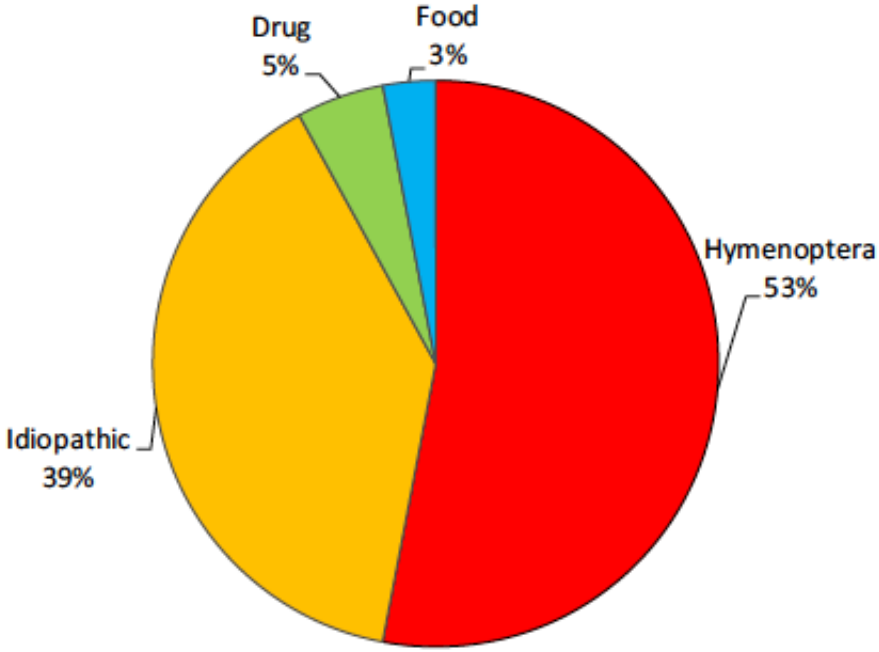


Fig. 3. Distribution of elicitors of anaphylactic reactions in 36 patients with systemic mastocytosis.

Gonzalez de Olano et al. Clin Exp Allergy 2007
Florian et al. Int Arch Allergy Immunol 2005

Gullen. Clin Exp Allergy 2014

# ANAPHYLAXIES PARTICULIERES

- anaphylaxie répétées ou sévères ou atypiques :
  - facteurs déclenchants multiples, mal identifiés
  - réactions plusieurs heures après facteur déclenchant
  - absence de cause allergique évidente : IgE négative
- anaphylaxie sévère aux hymenoptères (IgE+ ou -)

➔ si SAMA quelque soit tryptase

➔ si pas de SAMA : score REMA (tient compte de la tryptase)

Valent et al. Am J Blood Res 2013

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➔si pas de SAMA : score REMA (tient compte de la tryptase)

**➔penser à la SM même si pas de signes cutanés (UP) ni de SAMA !**

**➔ car anaphylaxie plus fréquente dans les SM sans UP !**

Valent et al. Am J Blood Res 2013

# REMA SCORE

| VARIABLE | | SCORE |
|---|---|---|
| GENDER | Male | +1 |
| | Female | -1 |
| CLINICAL SYMPTOMS | Absence of urticaria and angioedema | +1 |
| | Urticaria and/or angioedema | -2 |
| | Presyncope and/or syncope | +3 |
| TRYPTASE* | <15 ng/mL | -1 |
| | >25 ng/mL | +2 |

*Baseline serum tryptase

**SCORE < 2: low probability of clonal MCAD**

**SCORE ≥ 2: high probability of clonal MCAD**

Sensitivity: 0.92
Positive Predictive Value: 0.89

Specificity: 0.81
Negative Predictive Value: 0.87

**FIG 3.** Scoring model proposed as a screening tool for the presence of clonal MCs in patients presenting with anaphylaxis in the absence of skin mastocytosis before a BM study.

Alvarez-Twose et al. J Allergy Clin Immunol 2010

# VOUS SUSPECTEZ UNE MASTOCYTOSE SYSTEMIQUE

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a. poser le diagnostic positif de mastocytose systémique

b. la classer en ces différents sous-types → intérêt pronostique et thérapeutique

# 2 QUESTIONS

1. Quand faut-il suspecter une mastocytose ?
2. Comment en faire le bilan ? Rigoureux
   a. poser le diagnostic positif de mastocytose systémique : WHO
   b. la classer en ces différents sous-types ➔ intérêt pronostique et thérapeutique

**Table 2 – World Health Organization (WHO) diagnostic criteria for systemic mastocytosis (SM)[1]**

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|---|---|
| The diagnosis of SM can be made when the major criterion and one minor criterion or at least three minor criteria are present | |
| MAJOR CRITERION | |
| Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs | BOM |
| MINOR CRITERIA | |
| a. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical | BOM |
| b. Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood or other extracutaneous organ | myélo |
| c. Mast cells in bone marrow, blood or other extracutaneous organ express CD2 and/or CD25 in addition to normal mast cell markers¶ | myélo |
| d. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid) | sang |

Pardanani et al. Blood 2013

# BOM

- Inflitrat multifocal, dense, bien délimité de MC formants des agrégats avec au moins 15 MC/agrégats (**critère majeur**)
- Giemsa (peut etre negatif)/bleu de Toluidine et tryptase/CD117
- Le plus souvent : **MC en fuseau (critère mineur)** mais non obligatoire ➔ intérêt alors du marquage **CD25 +++ (critère mineur)**
- **20% des ISM n'ont pas d'agrégats : intérêt des critères secondaires ++++**
- **permet le dc des AHNMD associées (typage SM)**

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Pardanani et al. Blood 2013

# Myélogramme

- cytologie
- immunophénotypage des mastocytes
- mutation cKIT

# Cytologie

- appreciation des autres lignées (SMD/SMP)
- **qualitatif : >25% immature ou atypique**
- **quantitatif : % de mastocytes : MCL**

Valent et al. Leuk Res 2001

# Immunophénotypage des mastocytes FONDAMENTAL

- FceRI, CD117, CD38, CD2, CD25
- **CD25 (IL-2Ra)** : meilleur marqueur des mastocytes clonaux
  - Se : 90-100% (Morgado et al. Mod Pathol 2012)
- **CD2 (LFA2)** : moins fréquent que CD25 : CD25 +/- CD2 (**absence de CD2 : mastocytes plus immatures** : ASM et MCL ➔ plus sévère)
- CD30 : marqueur d'agressivité

Alvarez-Twose et al. Int Jnl Lab Hematol 2012

# Mutation cKIT sur le myélogramme

- KIT (CD117) : recepteur TK de type III
- D816V : exon 17 → critère mineur
- Sensibilité de la technique : problème essentiel +++
  - au seuil de 0.01% → 78% des ISM D816V
  - cKIT neg dans le sang : n'élimine pas la présence de la mutation

Nom d'épouse :
Née le : 25.03.1981
N°sigma :

SERVICE DE MEDECINE IN
Hopital de jour
Professeur HATRON
HOPITAL CLAUDE HURIEZ,

N°demande: 13 304C 2319
Prélevé le **24.07.2013**
Arrivée le 25.07.2013 à 08h57
;Cotation : M 1595

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Compte rendu **COMPLET** du 02.08.2013

Rens. Clinique : A l'attention du Pr HACHULLA
copie à UF 2227 SERVICE DE MEDECINE INTERNE

**I N S T I T U T D' H E M A T O L O G I E**
Pr J.GOUDEMAND Pr C.PREUDHOMME

**BIOLOGIE MOLECULAIRE DES HEMOPATHIES MALIGNES**
**(Poste: 44783 ou 03.20.44.47.83)**

| | | | |
|---|---|---|---|
| Date du prélèvement: | 24.07.2013 | | [ 24.07.2013 ] |
| Origine du prélèvement: | Moelle | | [ Sang ] |
| Type de prélèvement: | EDTA | | [ EDTA ] |
| N°dossier: | L1307162 | | [ L1307161 ] |
| Examen demandé: | Suivi de maladie résiduelle | | |
| Dosage de l'ADN: | 70 | ng/µl | [ 43 ] |

**Recherche des mutations de C Kit(exon17) par séquençage**

| | | |
|---|---|---|
| Mutation C Kit(exon17) | négatif | [ négatif ] |

**Recherche du transcrit FIP1L1-PDGFRa**

| | | |
|---|---|---|
| 1°tour: FIP PCR1 | Négatif | [ Négatif ] |
| 2°tour: FIP PCR2 | Négatif | [ Négatif ] |

# FICHE DE RENDU DE RESULTATS

**N°** : 1973 MO

**TECHNIQUES UTILISEES :**

☒ Analyse de l'ADN complémentaire de la région 816 du gène c-kit par séquençage direct.

☒ Analyse de l'ADN complémentaire de la région 816 du gène c-kit par technique de digestion enzymatique BsmA1 avec nested PCR/PNA.

☐ Analyse de l'ADN complémentaire des exons 8 à 13 du gène c-kit par séquençage direct.

**RESULTATS SCIENTIFIQUES :**

NM_000222.2:c.2447A>T
NP_000213.1:p.Asp816Val

**CONCLUSIONS** :

Dans la limite de nos connaissances et des techniques disponibles à ce jour et en considérant notamment qu'aucune technique n'est sensible à 100%,

☐ Nous n'avons pas détecté de mutation sur le codon 816 du gène c-kit.

☐ Nous n'avons pas détecté de mutation sur les exons XXX du gène c-kit.

☒ Nous avons détecté une mutation sur le codon 816 du gène c-kit de type D816V.

☐ Nous avons détecté une mutation sur l'exon XXX affectant le codon XXX du gène c-kit.

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Pardanani et al. Blood 2013

# Tryptase

- Augmentation non pathognomonique de SM
  - LA
  - LMC, LMMC
  - LCE
  - MDS
  - I Rénale
- Cut off de 20 ng/mL ! **Se : 90% (tryptase <20 n'écarte pas le dc)** et Spe de 98% pour le diagnostic de MS
- 4/14 patients avec des signes d'activation mastocytaire, sans UP et avec tryptase<10 microg/L ont une SM sur les données myelo/BOM (Alvarez-Twose I et al. Int Arch Allergy Immunol 2011)

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Pardanani et al. Blood 2013

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   (b) Diffuse cutaneous mastocytosis
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2. Indolent systemic mastocytosis (ISM)
   - Meets criteria for systemic mastocytosis (SM).[a] No "C" findings.[a] No evidence of associated clonal hematological non-mast cell lineage disease.

   (a) Smoldering systemic mastocytosis[b]
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   (b) Isolated bone marrow mastocytosis[b]
   - As above (ISM) with bone marrow involvement, but without skin involvement.

3. Systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD)
   - Meets criteria for SM and criteria for AHNMD as a distinct entity per the WHO classification

4. Aggressive systemic mastocytosis (ASM)
   - Meets criteria for SM. One or more "C" findings.[a] No evidence of mast cell leukemia.

   (a) Lymphadenopathic mastocytosis with eosinophilia

5. Mast cell leukemia (MCL)
   - Meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. BM aspirate smears show $\geq$20% mast cells. In typical MCL, mast cells account for $\geq$10% of peripheral blood white cells. Rare variant: aleukemic MCL.

6. Mast cell sarcoma (MCS)
   - Unifocal mast cell tumor. No evidence of SM. Destructive growth pattern. High-grade cytology.

7. Extracutaneous mastocytoma
   - Unifocal mast cell tumor. No evidence of SM. No skin lesions. Nondestructive growth pattern. Low-grade cytology.

[a] See Table II for diagnostic criteria for systemic mastocytosis and definition of "B" and "C" findings.
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Pardanani et al. Blood 2001

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tumeurs mastocytaires

Pardanani et al. Blood 2001

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GRAVITE/AGGRESSIVITE

Pardanani et al. Blood 2001

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EXCELLENT PRONOSTIC

GRAVITE/AGGRESSIVITE

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GRAVITE/AGGRESSIVITE

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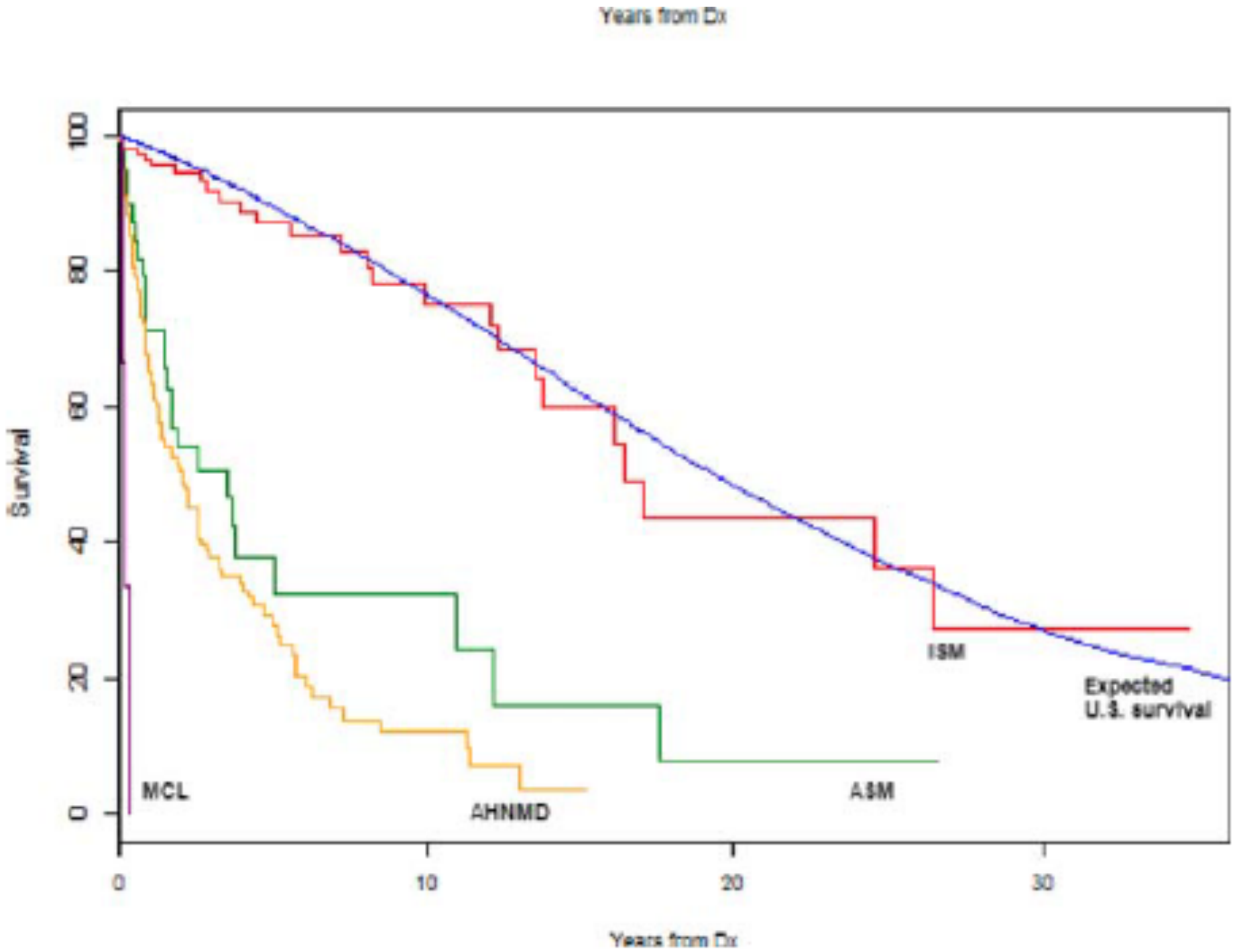
Pardanani et al. Blood 2001




Pardanani et al. Blood 2013

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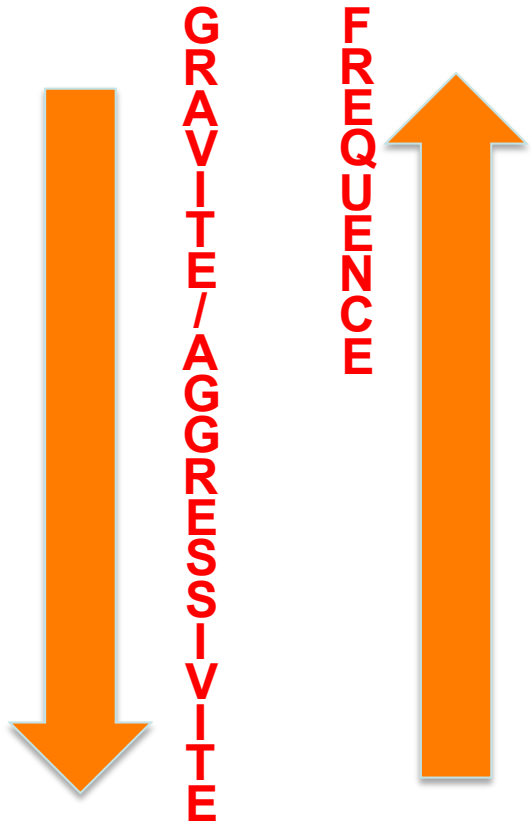


Pardanani et al. Blood 2001

**"B" findings**

1. BM biopsy showing >30% infiltration by MC (focal, dense aggregates) and/or serum total tryptase level >200 ng $mL^{-1}$
2. Signs of dysplasia or myeloproliferation, in non-MC lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts.
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.

**"C" findings**

1. Bone marrow dysfunction manifested by one or more cytopenia(s) (ANC $<1.0 \times 10^9$/L, Hgb <10 g $dL^{-1}$, or platelets $<100 \times 10^9$/L), but no obvious nonmast cell hematopoietic malignancy.
2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension.
3. Skeletal involvement with large osteolytic lesions and/or pathological fractures.
4. Palpable splenomegaly with hypersplenism.
5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

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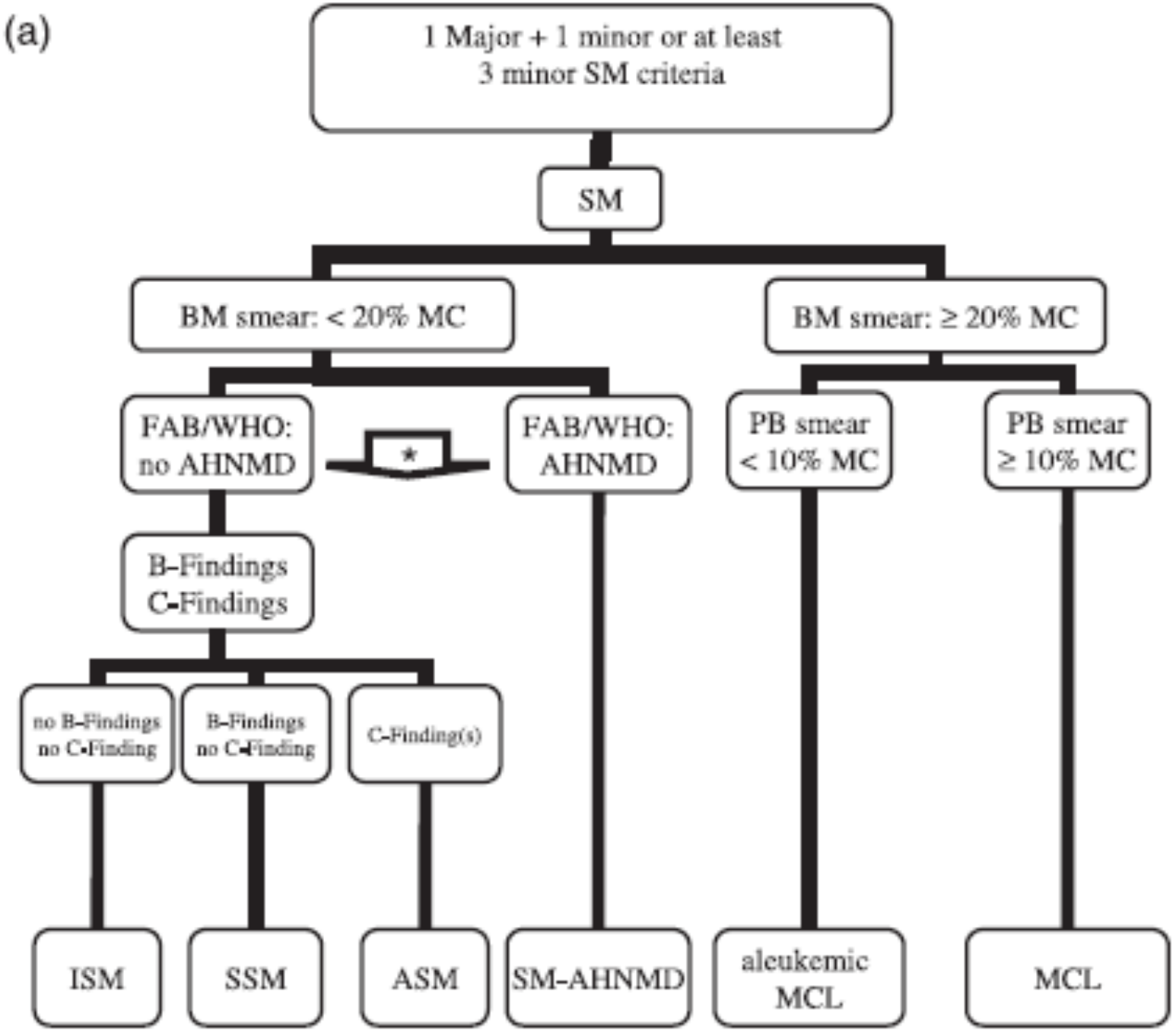
**bilan initial : radiographie osseuse et osteodensitométrie; TDM TAP (+ analyse fenetre osseuse); NFS, TP/bilan hépatique et malabsorption (albumine/préalbumine)**

Pardanani et al. Blood 2001




**Valent et al. Eur J Clin Invest 2007**

# CONCLUSION

- Evoquer une SM peut être simple (UP/ degranulation) ou pas (anaphylaxie inexpliquée à bilan allergologique négatif et isolée sans UP ni dégranulation)
- Diagnostic : bon dialogue clinicobiologique à organiser
- Si on pense à une SM : il faut suivre les critères WHO et ne pas s'arreter à une tryptase normale
- Intérêt pronostique/thérapeutique/édcucatif
- CEREMAST (Necker/Pr Hermine) et AFIRMM : aide +++ (RCP/prélèvement)

# Atopie, anaphylaxie et mastocytose

- Prévalence atopie/mastocytose similaire population générale (31 à 36%)

  Brockow JAAD 2003, Muller Allergy 1990

- Gonzalez de Olano et al:
  - 31,2% rhinites, 7,3% asthmes et 24,5% conjonctivites allergiques
  - 5,5% de réactions aux AINS chez mastocytoses/ 1,4 à 3,4% population générale (11,1% anaphylaxies et 14,2% urticaires)
  - 5,5% de réactions aux β-lactamines chez mastocytoses/ 2 à 4% population générale (5,5% anaphylaxies et 19% urticaires)

  Gonzalez de Olano Clinical Exp Allergy 2007