Cutaneous mastocytosis

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1. WHO classification of cutaneous mastocytosis
2. Types of cutaneous mastocytosis
3. Systemic symptoms
4. The 3 big questions
5. Management of cutaneous disease

Adult mastocytosis vs children mastocytosis

TABLE I. Characteristics of typical adulthood-onset and typical childhood-onset mastocytosis

Parameter	Adulthood-onset mastocytosis	Childhood-onset mastocytosis
Most frequent category of mastocytosis	ISM	Cutaneous mastocytosis
Typical course of the disease	Chronic	Temporary
Frequency of anaphylaxis (%)	50	<10
Typical tryptase level (μg/L)	>20	<20
Typical location of *KIT* mutation	Exon 17, most frequently *KIT* D816V	Exon 8, 9, 11, or 17 or absent
Most frequent type of cutaneous lesions	Maculopapular	Maculopapular
Typical morphology of maculopapular lesions	Monomorphic	Polymorphic
Typical size of maculopapular lesions	Small	Large
Typical distribution of maculopapular lesions	Thigh, trunk	Trunk, head, extremities

Hartmann K, Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol. 2016 Jan;137(1):35-45

1. WHO classification of cutaneous mastocytosis

Classification of cutaneous mastocytosis

WHO classification of cutaneous mastocytosis (2016):

- Urticaria pigmentosa/maculopapular cutaneous mastocytosis
- Diffuse cutaneous mastocytosis
- Mastocytoma of the skin

Most cases (2/3) of cutaneous mastocytosis begin in childhood.

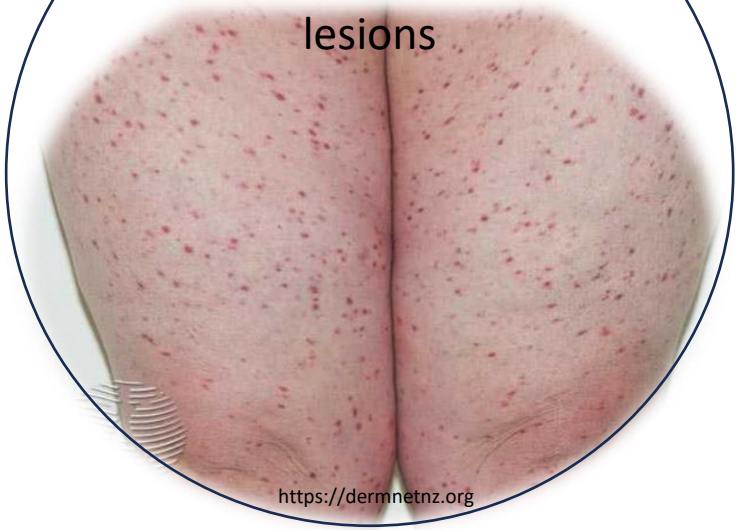
Hartmann K, Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol. 2016 Jan;137(1):35-45

2. Types of cutaneous mastocytosis

Cutaneous manifestations:

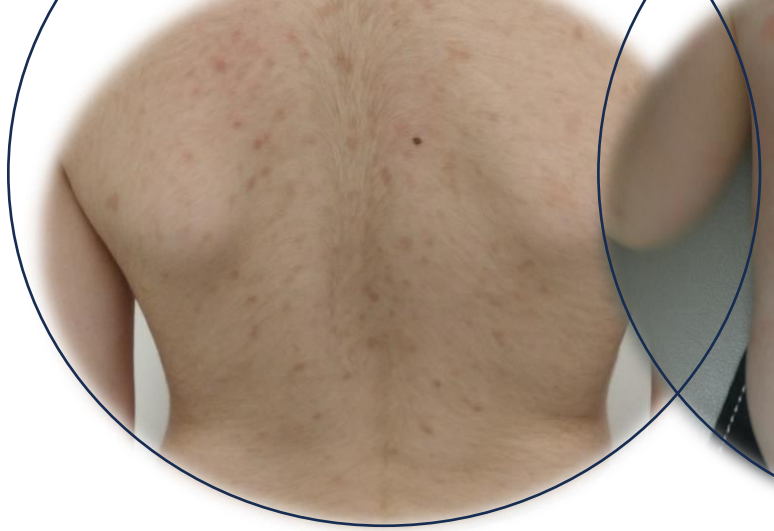
Maculopapular cutaneous mastocytosis (Urticaria pigmentosa)

Adult: small, round, brown/red monomorphic lesions

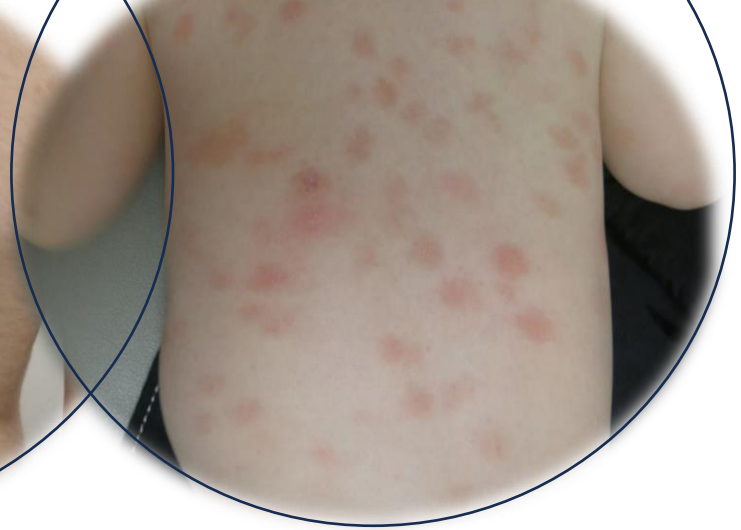


https://dermnetnz.org

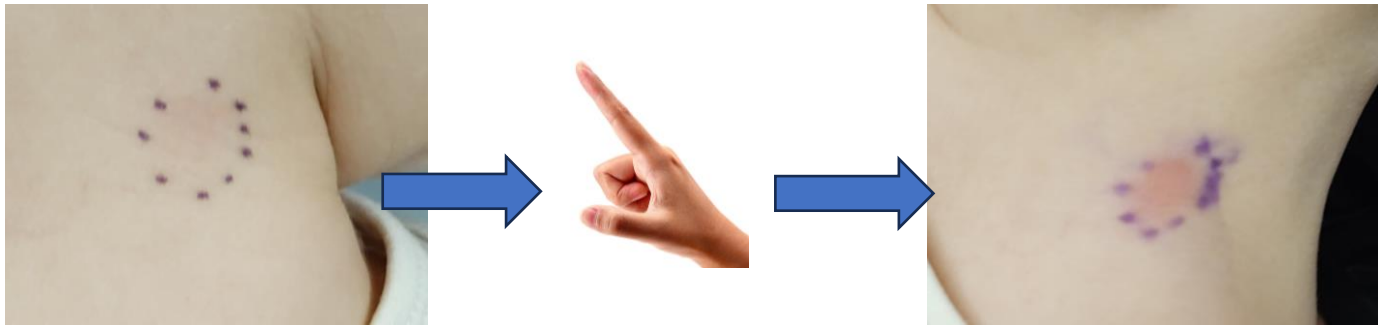
Children: monomorphic variant (like adults)



Children: polymorphic variant (more frequent)



Darier's sign



Torrelo A et al, Eur Acad Dermatol Venereol. 2021 Oct;35(10):2079-2084.

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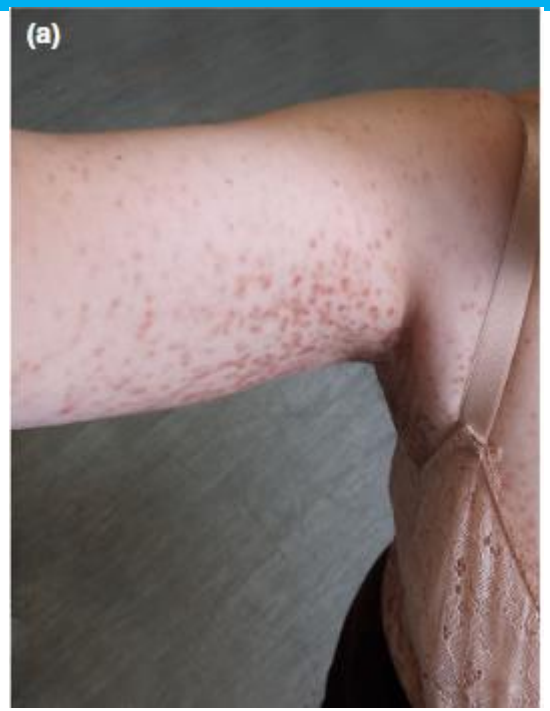
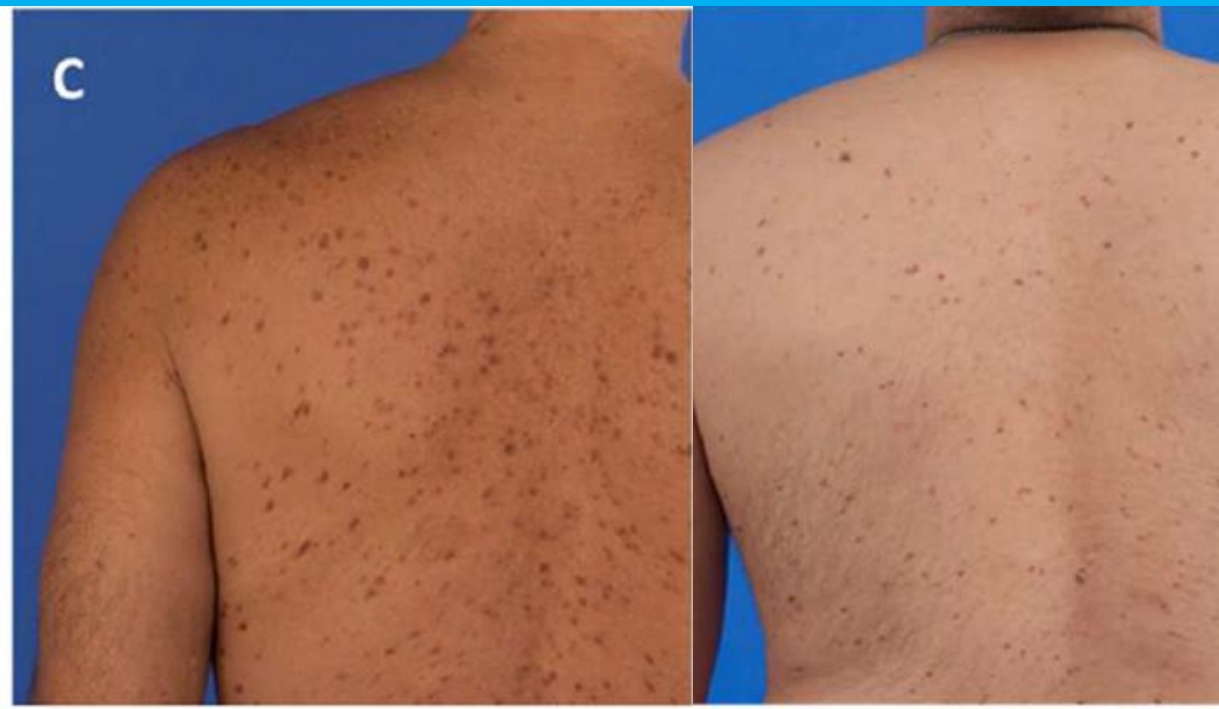
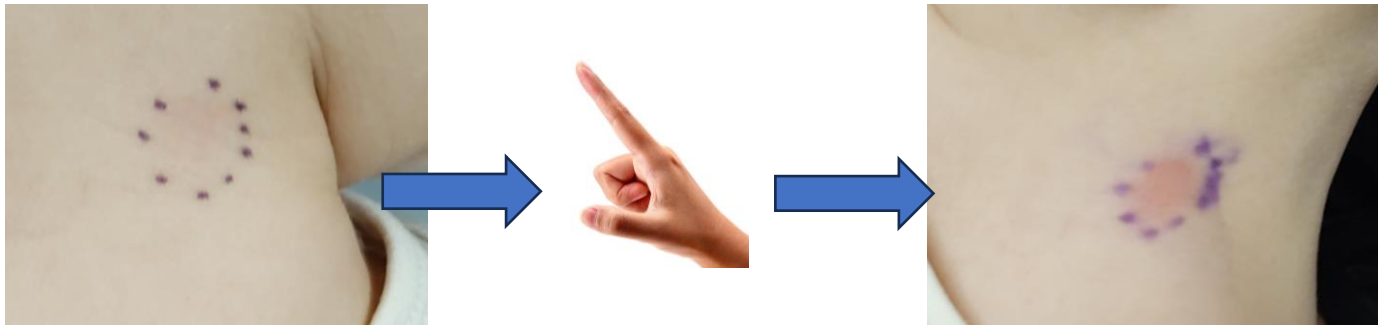


Di Raimondo C, et al. Australas J Dermatol. 2021



Kirshenbaum AS et al. J Allergy Clin Immunol Pract. 2019

Darier's sign



Cutaneous manifestations:

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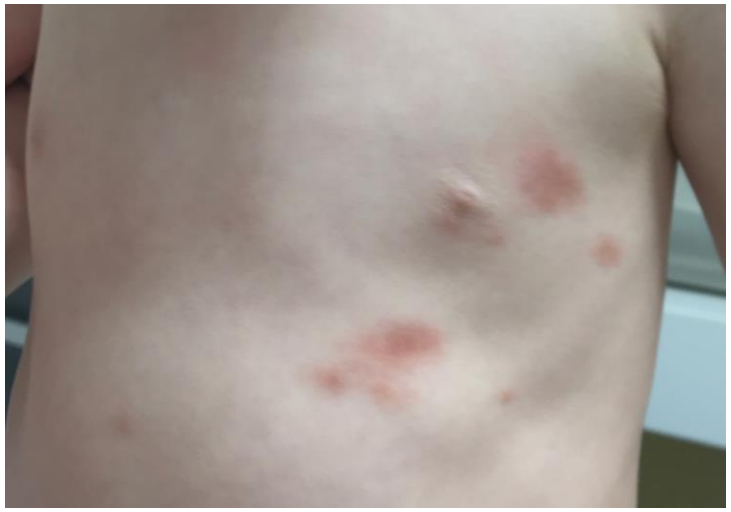
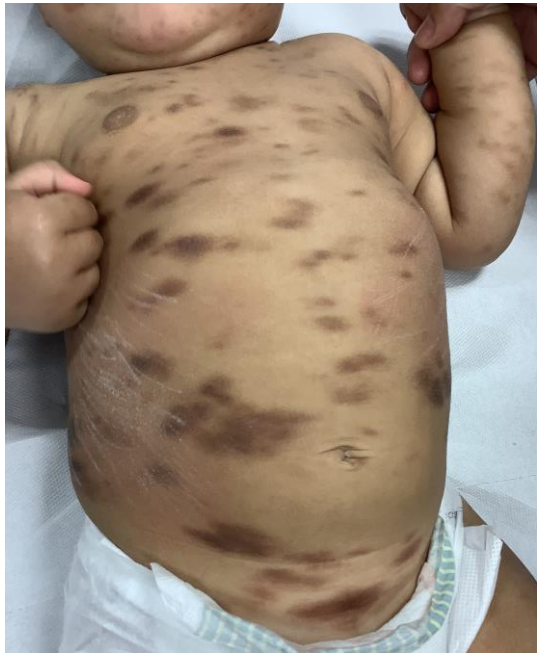
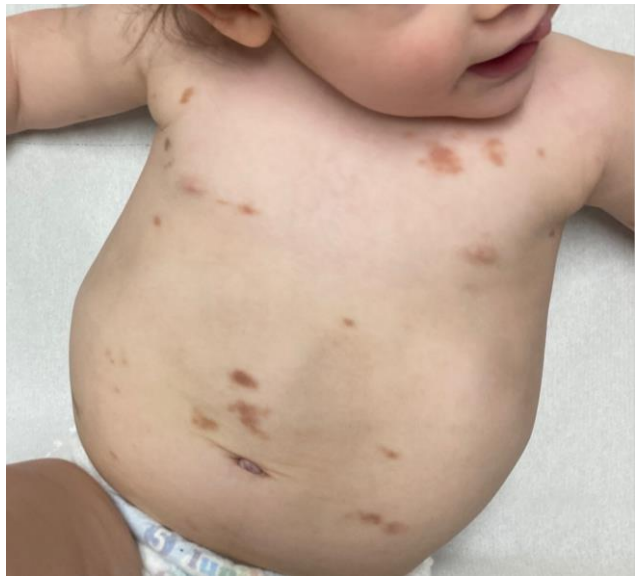
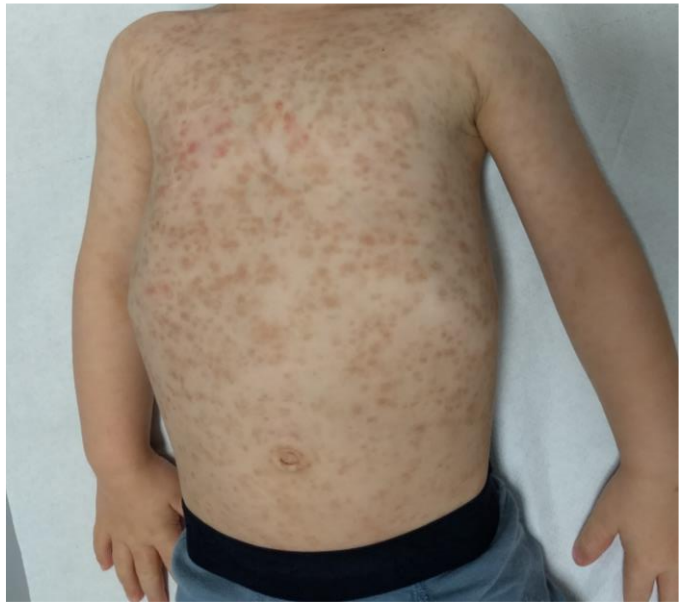
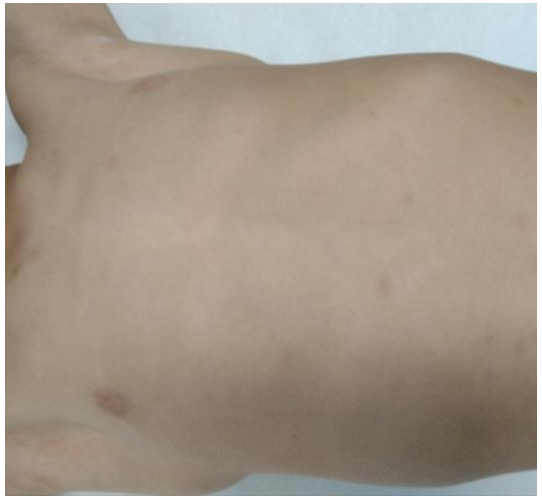




- Before the age of 2 +++
- Macular or papular lesions
- Red/brown
- Mostly trunk and limbs
- Scalp also classical







Cutaneous manifestations:
Mastocytoma

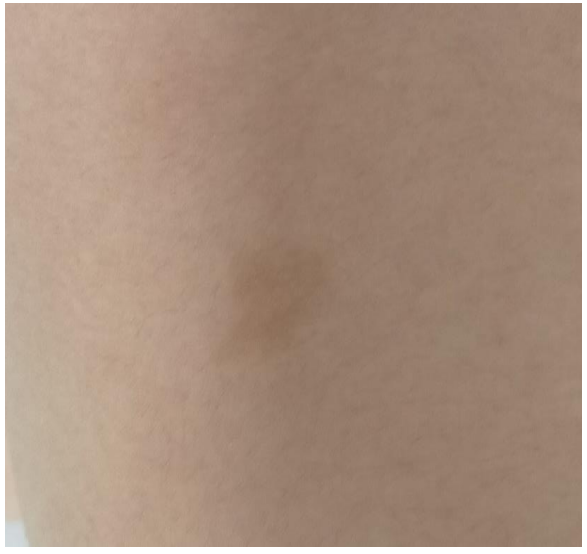
- < 3 lesions (most often 1)

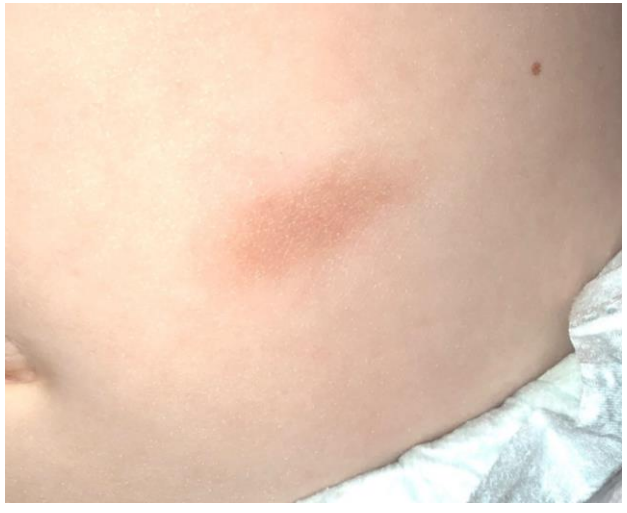
- Mostly at birth (or first months), unusual ++ in adults, very common if < 3 years

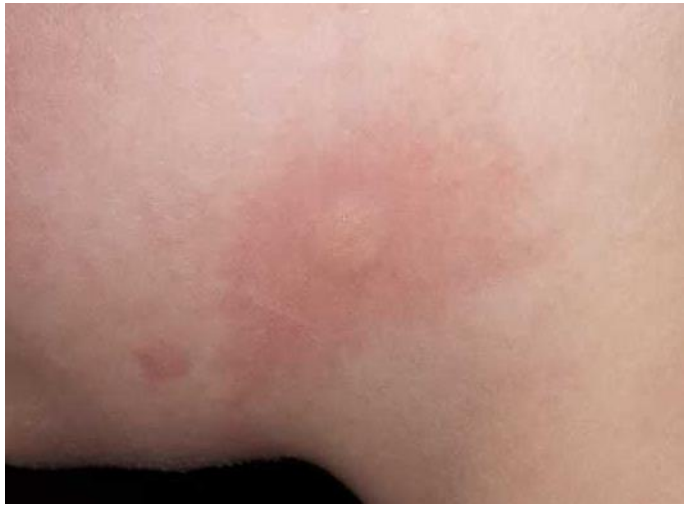
- Unique nodule, smooth, red-yellow-brown

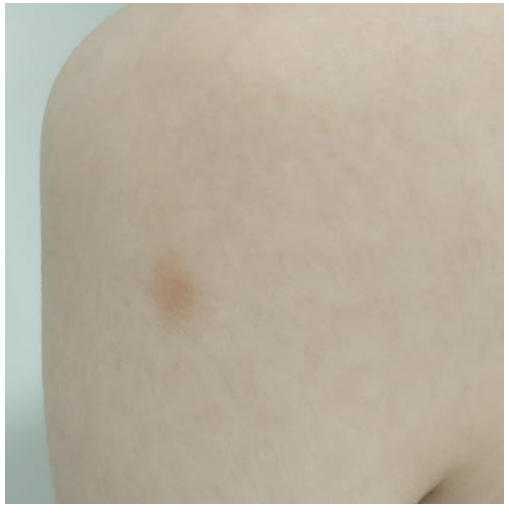
- Darier's sign

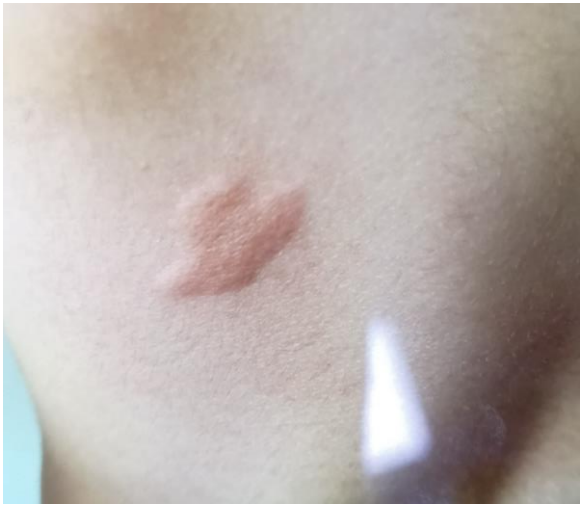
- Frequent relapsing episodes of blistering/desquamation



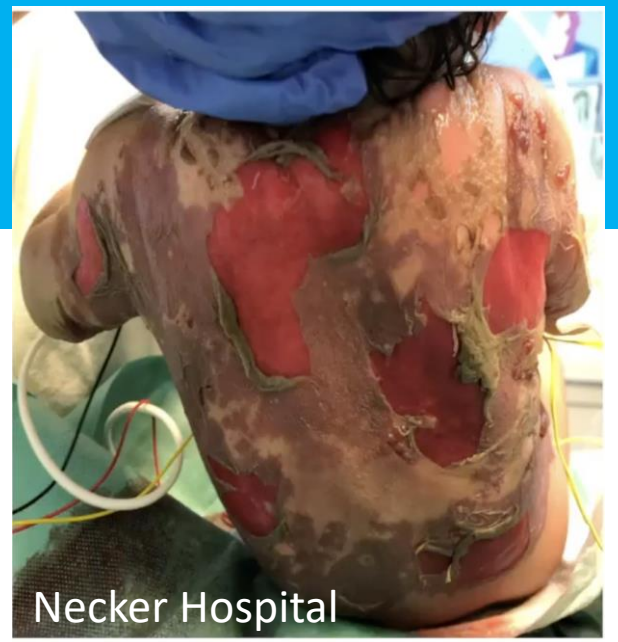








Cutaneous manifestations:
Diffuse cutaneous mastocytosis



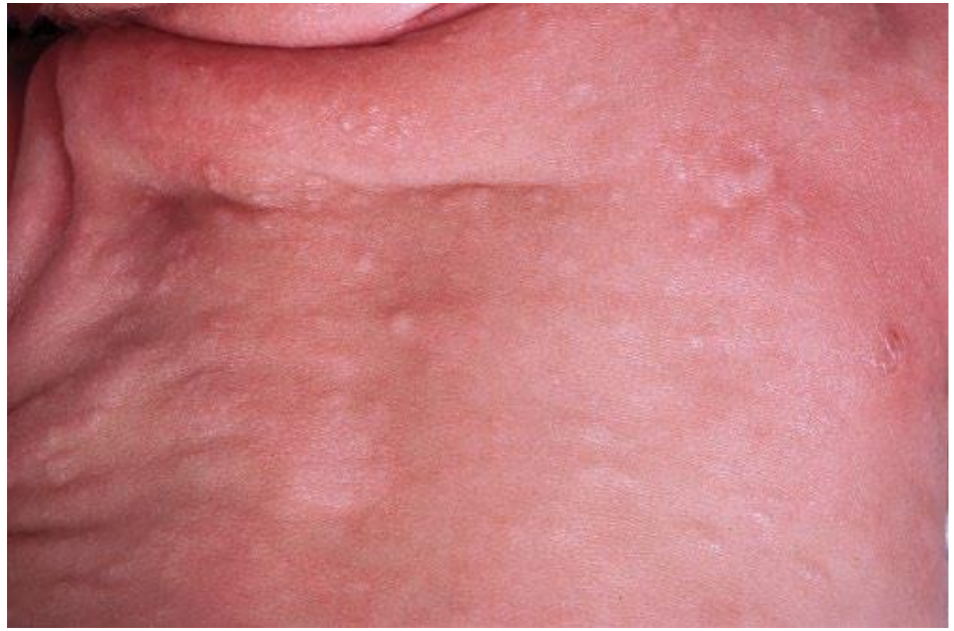
- Rare

- Neonatal period

- Generalized erythema (erythrodermic), pachyderma (peau d'orange), blistering (generalized or minimal)

- Systemic involvement +/-, anaphylaxy ++

- Tryptase increased



Harper's Textbook of Pediatric Dermatology

Differential diagnosis

Mastocytoma

- Juvenile xanthogranuloma
- Spitz naevus
- naevocellular naevus
- Histiocytoma

Maculopapular mastocytosis

- Juvenile xanthogranuloma
- Histiocytosis
- Multiple lentigines
- CAL macules

Bullous forms

- incontinentia pigmenti
- SSSS
- Epidermolysis bullosa
- Bullous pemphigoid

3. Systemic symptoms

Mast Cell Activation – Systemic Symptoms

Cutaneous mastocytosis can also give systemic symptoms, caused by MC (mast cell mediator) relase: pruritus, flushing , abdominal pain, vomitting, diarrhea, bone pain, headache, neuropsychiatric symptoms (ADHD, autism, …)

=> possible with any form of CM

=> pruritus/flush: associated with skin extend

Risk of anaphylaxy:

- children: <10%,
- adults: 50%
  - 2 factors very closely linked to risk:
    - extent of skin lesions
    - serum tryptase level (if >15: more frequent hospitalisation, if >30: ICU management).

Brockow K et al, Allergy. 2008 Feb;63(2):226-32.

4. The three big questions

Cutaneous mastocytosis

As dermatologist, 3 mains questions

- Is there an associated systemic mastocytosis?
- Can we expect a resolution (at puberty/adult age)?
- Is there a risk for anafylaxy?

Systemic mastocytosis?
Inital work-up in **adults**

- Virtualy always systemic, may be aggressive, persistent
- Skin biopsy
- Blood tests: COFO, bilan hépatique, LDH, ionogramme, tryptase (1x/year)
- If highly elevated tryptase: c-KIT mutation in peripheral blood
- Abdominal ultrasound

- BM biopsy
- Bone involvement frequent.

Systemic mastocytosis?
Inital work-up in **children**

Rarely systemic, usually regresses, rarely aggressive

- Skin biopsy if the diagnosis is doubtful
- Blood tests: COFO, bilan hépatique, LDh, ionogramme, tryptase (1x/year)
- if highly elevated tryptase: c-KIT mutation in peripheral blood
- Abdominal ultrasound (1x/year)

- BM biopsy only in a few patients: extensive skin involvement, high tryptase levels, severe systemic symptoms

- Bone involvement very rare in children.

Carter MC, Clayton ST, Komarow HD, Brittain EH, Scott LM, Cantave D, Gaskins DM, Maric I, Metcalfe DD. Assessment of clinical findings, tryptase levels, and bone marrow histopathology in the management of pediatric mastocytosis. J Allergy Clin Immunol. 2015 Dec;136(6):1673-1679.e3. doi: 10.1016/j.jaci.2015.04.024. Epub 2015 Jun 1. PMID: 26044856; PMCID: PMC4984538.

Systemic mastocytosis?
In children

10% of children with UP, begins after the age of 5 years.

In children, no clear predictive signs of systemic involvement, but risk increased if:

- High serum tryptase (If high tryptase persists into adolescence, and skin lesions too => BMB)
- Organomegaly
- C-KIT mutation (peripheral)
- Severe symptoms of mast cell activation

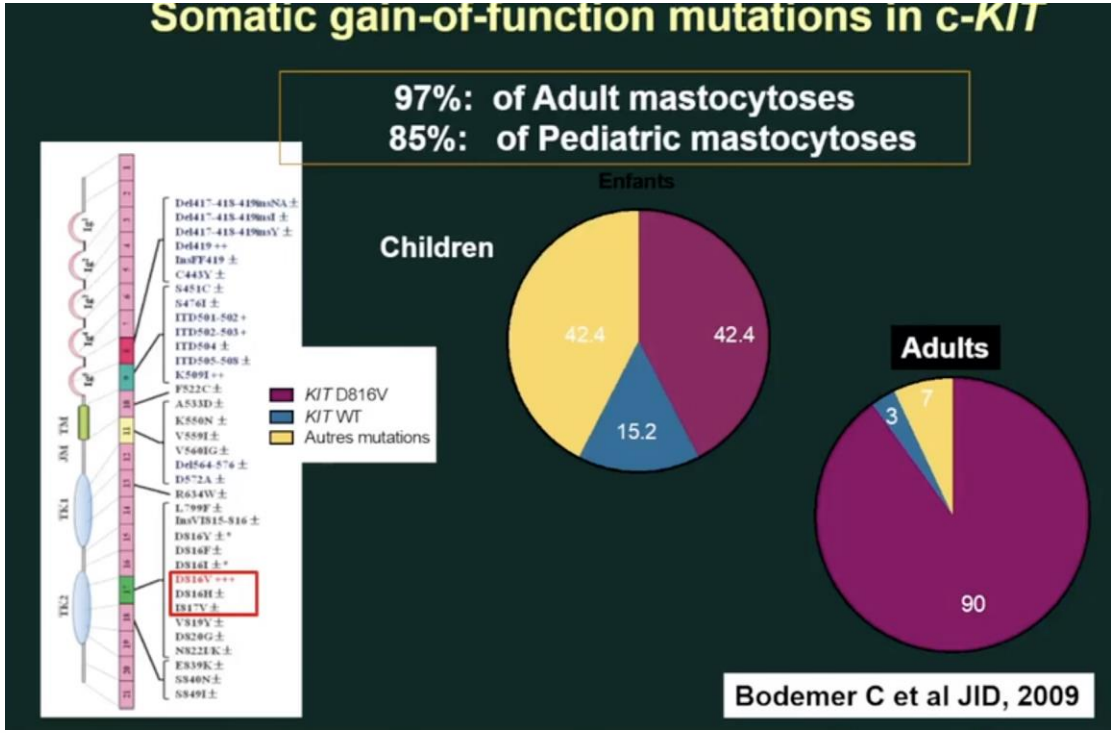
In the rare cases of aggressive SM, it is clinicaly apparent at disease onset (organomegaly with impaired organ function, pancytopenia, …)

Carter MC, Clayton ST, Komarow HD, Brittain EH, Scott LM, Cantave D, Gaskins DM, Maric I, Metcalfe DD. Assessment of clinical findings, tryptase levels, and bone marrow histopathology in the management of pediatric mastocytosis. J Allergy Clin Immunol. 2015 Dec;136(6):1673-1679.e3. doi: 10.1016/j.jaci.2015.04.024. Epub 2015 Jun 1. PMID: 26044856; PMCID: PMC4984538.

Polivka L et al, J Allergy Clin Immunol Pract. 2021 Apr;9(4):1695-1704.e5.

Prognosis of cutaneous mastocytosis

Childhood mastocytosis	Adult mastocytosis
Early or late onset	May start in childhood
Usually regresses	Indolent or progressive
Rarely systemic	Virtually always systemic
Typical forms (solitary, DCM)	Non existing
Rarely aggressive / malignant	May be aggressive /malignant
Variable skin manifestations	Skin lesions less variable



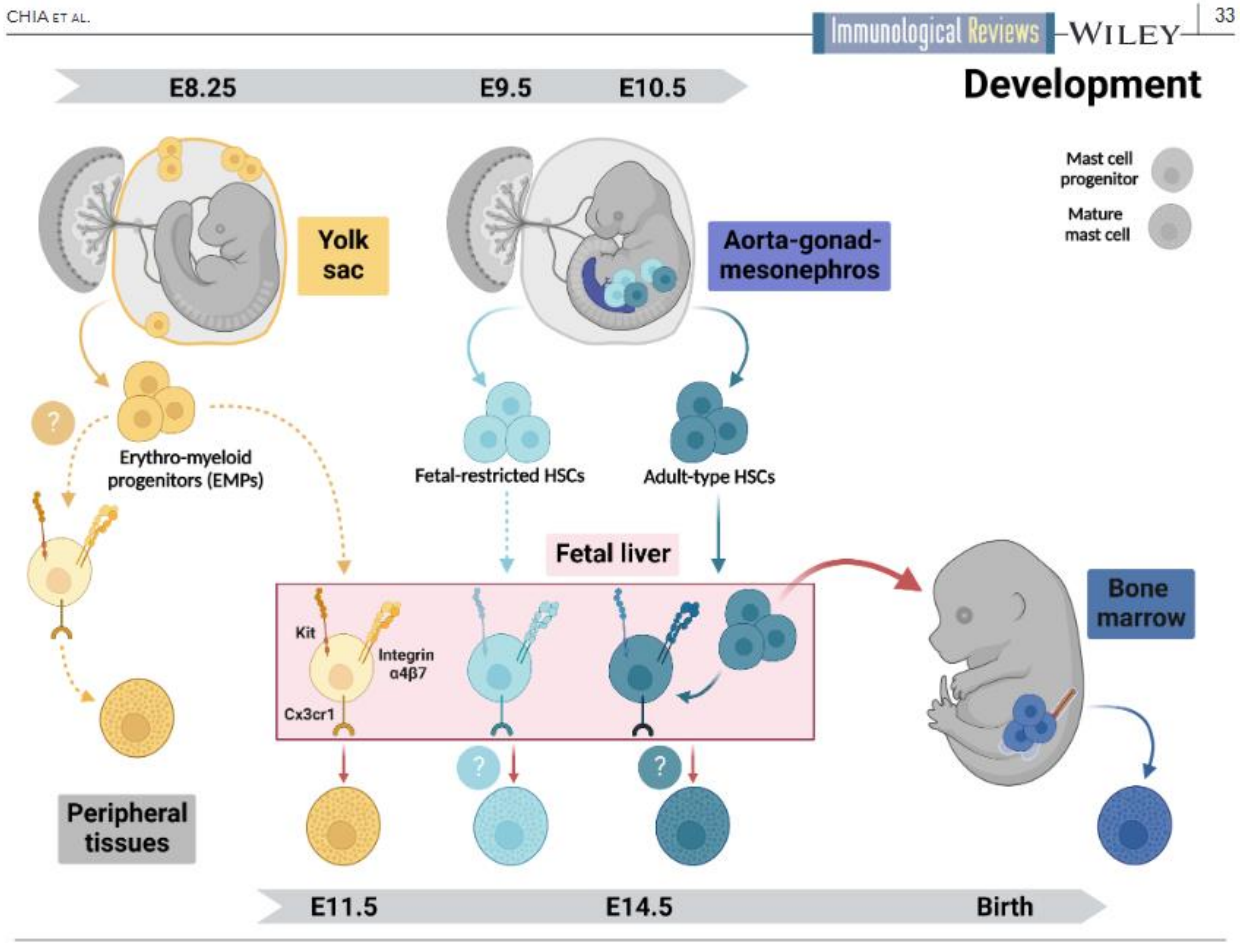
Credits to C. Bodemer, Munich, 2022

Same disease or two (or more) different diseases

Credits to A. Torrelo, Madrid, 2021

Bodemer C et al, J Invest Dermatol. 2010 Mar;130(3):804-15.
Polivka L et al, J Allergy Clin Immunol Pract. 2021 Apr;9(4):1695-1704.e5.

Prognosis of cutaneous mastocytosis



Chia SL, Kapoor S, Carvalho C, Bajénoff M, Gentek R. Mast cell ontogeny: From fetal development to life-long health and disease. Immunol Rev. 2023 May;315(1):31-53.

Cutaneous mastocytosis in children:
Prognosis of cutaneous lesions

- Mastocytoma: spontanous regression of the symptoms

- Maculopapular mastocytosis

    - 50%: resolution of lesions and symptoms by adolescence

- Bullous disease: disappears by the age 1-3 years

Prognostic factors for progression of CM	Prognostic factors for regression of CM
- Any MCAS at baseline - Aggravation or stabilization of MCAS - WT KIT	- KIT D816V - Congenital lesions - large lesions

>< adult form

Polivka L et al, J Allergy Clin Immunol Pract. 2021 Apr;9(4):1695-1704.e5.

Risk of anaphylactic reaction

IgE-mediated allergy or nonspecific activation of mast cells.

Cumulative incidence of anaphylaxis: 49% in adults and 9% in children

Risk factors for anaphylaxis

-age > 18 years

-high baseline tryptase values (>15 ug/L). If >30: association with ICU management.

-children with extensive skin involvement

-Hymenoptera stings

No guidelines or consensus for management of the risk of anaphylaxis in patients with cutaneous mastocytosis.

Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Aberer W, Birnbaum J, Bodzenta-Lukaszyk A, Bonifazi F, Bucher C, Campi P, Darsow U, Egger C, Haeberli G, Hawranek T, Körner M, Kucharewicz I, Küchenhoff H, Lang R, Quercia O, Reider N, Severino M, Sticherling M, Sturm GJ, Wüthrich B. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol. 2009 Nov;124(5):1047-54.

Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008; 63:226–32.

5. Management of cutaneous disease

Management of cutaneous mastocytosis

For mediator-related symptoms (pruritus, flushing, urticarial lesions)

- Topical steroids
- H1-antihistamines +/- H2-antihistamines (mainly for other symptoms: heartburn, diarrhoea, food reaction)
- Leukotriene inhibition, PUVA (adolescents and adults), omalizumab

- If diffuse cutaneous mastocytosis or history of anaphylaxy: **Epipen**

- Severe MCAS: AntiH1 + antiH2 + Montelukast + Omalizumab

- Diffuse blistering, systemic forms: steroids 0,5-1 mg/kg/d – imatinib

Avoid factors leading to MCA (physical factors, drugs (aspirine, codeine, morphine, NSAIDS), diet only if clinically justified.

Anaesthesia: deviation from routine anesthesia is not necessarily warranted (Carter et al), **but meticulous preparation.** The risk perists for the **entire life**