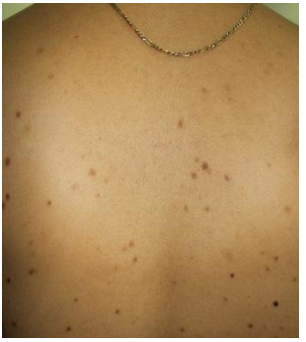
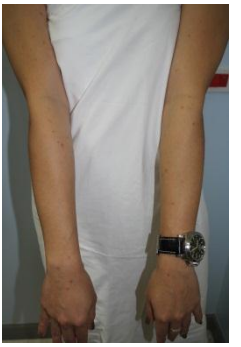
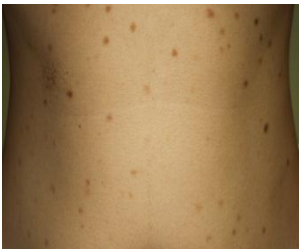
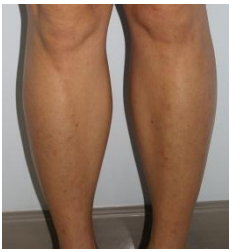
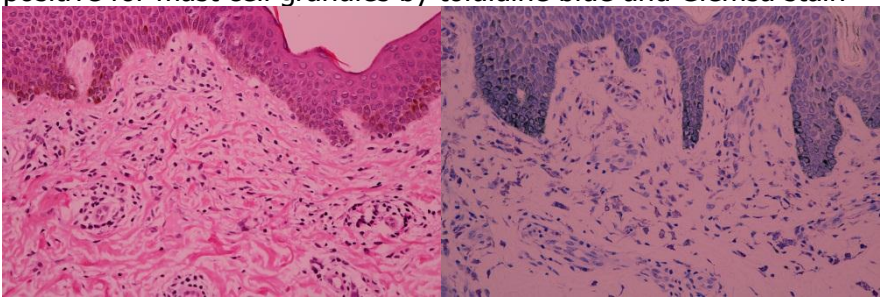
Case 22
A 30-year-old Thai woman from Bangkok.
Chief complaint: Red and brown spots on face, trunk and extremities for 5 years.

Present illness: The patient has developed asymptomatic multiple red and brown spots on face, trunk and all extremities for 5 years. Initially, the lesions were raised red small rashes and subsequently collapsed into brown rashes. The rashes were aggravated by heat. There were no systemic symptoms such as nausea/ vomiting, diarrhea, skeletal pain, chest pain, headache and fainting.
Past history: She has underlying allergic rhinitis but is not taking any medications. No smoking or drinking alcohol. No previously serious illness. No family history of any skin problems.

Physical examinations
Vital signs: BP 117/84 mmHg P 92 bpm RR 20 /min T 37 °C
HEENT: Not pale, no jaundice
Lymph nodes: Not palpable
Heart and lungs: Clear
Abdomen: Soft, not tender, no hepatosplenomegaly
Skin examination: Generalized multiple discrete ill-defined erythematous papules and brownish macules on face, neck, trunk and all extremities. Darier's sign is positive.
Histopathology (S13-14628)
Superficial dilated blood vessels with sparse perivascular lymphocytic infiltrate of lymphocytes, eosinophils and scattered round or oval cell with central nuclei and abundant cytoplasm with positive for mast cell granules by toluidine blue and Giemsa stain



Investigations: CBC is normal. Total Serum Tryptase: 13 ng/ml
Diagnosis: Urticaria pigmentosa
Managements:

- Advice avoidance of aggravating factors
- Antihistamine: Levocetirizine(5) 1 tab PO o.d.
  Ranitidine(150) 1 tab PO b.i.d.
- Topical steroids: 0.05% Clobetasol cream
  apply lesions b.i.d.

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Discussion

Urticaria pigmentosa is the most common form of cutaneous mastocytosis, a myeloproliferative neoplasm characterized by abnormal proliferation and accumulation of mast cell within various organs, most commonly in the skin. Urticaria pigmentosa more commonly appears during children than adults.

The World Health organization (WHO) classification of mastocytosis include:[1]

1. Cutaneous mastocytosis(CM)
2. Systemic mastocytosis(SM) include four major subtypes
    a. Indolent systemic mastocytosis(ISM)
    b. Systemic mastocytosis with an associated non-mast cell clonal hematological disease(SM-AHNMD)
    c. Aggressive systemic mastocytosis(ASM)
    d. Mast cell leukemia(MCL)
    e. Mast cell sarcoma(MCS
3. Extracutaneous mastocytoma(ECM)

Systemic mastocytosis occurs more frequent in adults than children and ISM is the most common form of SM.

Most ISM and CM have mild symptoms which are due to the release of mast cell mediators. The symptoms and signs may range from pruritus and flushing to abdominal pain, palpitation and syncope and can be exacerbated by heat, local trauma, exercise, or certain drugs.

In extracutaneous manifestations of systemic mastocytosis, gastrointestinal symptoms are the most common such as peptic ulcer[2], malabsorption with diarrhea which is limited to advanced disease. Hepatic and splenic involvement, lymph node enlargement[3], abnormal hematologic findings[1] and musculoskeletal pain[4] are suggest systemic mastocytisis especially ASM or SM-AHNMD. Neuropsychiatric abnormalities also have been reported.[5]

Variants of Cutaneous mastocytosis include:

1. Urticaria pigmentosa (UP)

2. Mastocytoma of skin
3. Diffuse cutaneous mastocytosis (DCM)
4. Paucicellular mastocytosis [also termed telangiectasia macularis eruptive perstan (TMEP)]

The majority of UP in adult cases are caused by somatic point mutation of the codon 816 proto- oncogene c-kit, a transmembrane protein bounding to mast cell growth factor (MCGF), signals mast cell to divide, resulting in abnormally continued mast cell proliferation.[6] An activating mutation in codon 560 also has been presented in some adult patients with mastocytosis but less common.[7] However, some patients have no detectable c-kit mutation.[8]

UP is characterized by oval or round red-brown macule, papules or plaque ranging in number from few to many. However the morphology of UP lesions differs significantly between children and adults. (Table1.)

Table 1. The comparison of clinical manifestation of CM between children and adult

Onset / Manifest.	Children	Adult
Onset	birth/infancy	young adult
Lesion	-tan-brown color -papules, less macules -size 1.0-2.5 cm(larger)	-red-brown color -macules+papules with hyperpigmentation and fine telagiectasia -size <0.5 (smaller)
Distribution	-trunk -often spare face, scalp, palm, sole	-trunk and prox. extremities -less frequent face, palm, sole, distal extremities
Darier' sign	more apparent	less apparent
Association	-SM much less occur -DCM(exclusively)	-SM more occur -TMEP(exclusively)
Prognosis	-usually resolve after months and good prognosis	-depend on associated forms of SM. CM or ISM are good prognosis

Diagnosis of urticaria pigmentosa can be established by skin biopsy and mast cell identification using special stain such as Giemsa, toluidine, or monoclonal antibodies to tryptase or CD117 (KIT). However, other investigations are needed to be done if signs and symptoms of SM are indicated such as unexplained GI ulcer, malabsorption, hepatosplenomegaly, skeletal and hematologic abnormalities.[1, 9] Laboratory tests include 24 hr. urine histamine metabolite (MelmAA or Methylhistamine), skeletal x- ray and bone marrow biopsies with antitryptase or CD 117 immunostaining. In this patient, there are no symptoms and signs of SM. Laboratory tests including CBC and total serum tryptase are also normal, therefore UP is the diagnosis. Annual measurement of total serum tryptase is planned for this patient to evaluate mast cell burden.

Since there is no cure for this disease, management in this patients is directed to alleviate symptoms. This patient is instructed to avoid potential mast cell stimuli such as alcohol, anticholinergic drugs, aspirin, NSAID, heat, friction and certain systemic anesthetic drugs (local lidocaine can be used). Antihistamine H1 and H2 are given to this patient in order to reduce symptoms. PPI may be used in secondary treatment if this patient develops GI symptoms.[9] Potent topical steroid with occlusion reduces the numbers of UP lesion but the lesion may recur after discontinuation within the year.[10] Oral steroid have some efficacy in both cutaneous and GI symptoms. Other reported beneficial treatments such as cromolyn sodium,[11] antileukotrienes,[9] ketotifen and azelastine[12] and PUVA[13] can be used.

Some patients with SM may have life-threatening episode of anaphylaxis, thus self-epinephrine should be prepared. In severe disease,IFN-alpha-2b, Cladribine, Imatinib[14] has been used especially Cladribine has been shown effectively eliminate skin lesion including those with D816 c-kit mutation.[15]

In this patient, the symptom is being followed up after receiving levocetirizine, ranitidine and clobetasol cream.

References

1. Valent P, Aberer E, Beham-Schmid C, Fellinger C, Fuchs W, Gleixner KV et al. Guidelines and diagnostic algorithm for patients with suspected systemic mastocytosis: a proposal of the Austrian competence network (AUCNM). Am J Blood Res 2013;3:174-80.
2. Jensen RT. Gastrointestinal abnormalities and involvement in systemic mastocytosis. Hematol Oncol Clin North Am 2000;14:579-623.
3. Travis WD , Li CY. Pathology of the lymph node and spleen in systemic mast cell disease. Mod Pathol 1988;1:4-14.
4. Lanternier F, Cohen-Akenine A, Palmerini F, Feger F, Yang Y, Zermati Y et al. Phenotypic and genotypic characteristics of mastocytosis according to the age of onset. PLoS One 2008;3:e1906.
5. Rogers MP, Bloomingdale K, Murawski BJ, Soter NA, Reich P , Austen KF. Mixed organic brain syndrome as a manifestation of systemic mastocytosis. Psychosom Med 1986;48:437-47.
6. Sanchez-Munoz L, Teodosio C, Morgado JM , Escribano L. Immunophenotypic characterization of bone marrow mast cells in mastocytosis and other mast cell disorders. Methods Cell Biol 2011;103:333-59.
7. Chan IJ, Kasprowicz S , Tharp MD. Distinct signalling pathways for mutated KIT(V560G) and KIT(D816V) in mastocytosis. Clin Exp Dermatol 2013;38:538-44.
8. Bodemer C, Hermine O, Palmerini F, Yang Y, Grandpeix-Guyodo C, Leventhal PS et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. J Invest Dermatol 2010;130:804-15.
9. Valent P, Akin C, Sperr WR, Mayerhofer M, Fodinger M, Fritsche-Polanz R et al. Mastocytosis: pathology, genetics, and current options for therapy. Leuk Lymphoma 2005;46:35-48.
10. Barton J, Lavker RM, Schechter NM , Lazarus GS. Treatment of urticaria pigmentosa with corticosteroids. Arch Dermatol 1985;121:1516-23.
11. Horan RF, Sheffer AL , Austen KF. Cromolyn sodium in the management of systemic mastocytosis. J Allergy Clin Immunol 1990;85:852-5.
12. Kettelhut BV, Berkebile C, Bradley D , Metcalfe DD. A double-blind, placebo-controlled, crossover trial of ketotifen versus hydroxyzine in the treatment of pediatric mastocytosis. J Allergy Clin Immunol 1989;83:866-70.
13. Godt O, Proksch E, Streit V , Christophers E. Short- and long-term effectiveness of oral and bath PUVA therapy in urticaria pigmentosa and systemic mastocytosis. Dermatology 1997;195:35-9.
14. Agarwala MK, George R, Mathews V, Balasubramanian P, Thomas M , Nair S. Role of imatinib in the treatment of pediatric onset indolent systemic mastocytosis: a case report. J Dermatolog Treat 2013.
15. Tefferi A, Li CY, Butterfield JH , Hoagland HC. Treatment of systemic mast-cell disease with cladribine. N Engl J Med 2001;344:307-9.