The Management of Urticaria Pigmentosum

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ABSTRACT

Background: Urticaria pigmentosum is the most common skin manifestation of cutaneous mastocytosis. This disease has similarity with others, therefor misdiagnose is common occurrence.

Methods. Literature searching was conducted using databases such as PubMed, Google Scholar, and Web of Science using Search terms included "urticaria," "mastocytosis," "treatment," and "mast cell.". Systematic reviews of peer-reviewed articles, reports, and case studies were chosen.

Discussion: The management of urticaria pigmentosa consists of three lines of therapy, which can be utilized based on each patient's response.

Conclusion: The proper management of urticaria pigmentosum is important to eliminate symptoms and improve the patient's quality of life.

Key words: Urticaria pigmentosum, mastocytosis, management

Introduction

The skin is a vital organ of the body with functions as a covering and protector. The skin contains connective tissue, which includes components of the immune system such as leukocytes, macrophages, and mast cells. Mast cells function as the primary effector cells in inflammatory reactions related to immunoglobulin E. They also act as releasers of various active mediators.[1] Excessive numbers of mast cells in the skin or systemically can lead to a

condition known as mastocytosis. Urticaria pigmentosa is the most common variant of cutaneous mastocytosis. The term "urticaria pigmentosa" was first used by Sangster in 1878 to describe a type of skin lesion.[2] The exact prevalence of urticaria pigmentosa is still unknown. Mastocytosis can occur at any age, from birth to adulthood. About 15-50% of mastocytosis cases are cutaneous mastocytosis, of which 45-75% are urticaria pigmentosa. Urticaria pigmentosa is more commonly found in children but can also occur in adults. This condition does not show a gender predilection and has been reported in all races.[1]

Methods

A systematic review of peer-reviewed articles, reports, and case studies from 2013 to 2024 was conducted using databases such as PubMed, Google Scholar, and Web of Science. using Search terms included "urticaria," "mastocytosis," "treatment," and "mast cell.". Systematic reviews of peer-reviewed articles, reports, and case studies were chosen.

Discussion

Cutaneous mastocytosis is a variant of mastocytosis that aligns with the World Health Organization (WHO) criteria, as outlined in Table 1. Its manifestations include *urticaria pigmentosa*, characterized by dark to brown papules and macules in children, and reddish-brown macules and papules in adults. The hallmark diagnostic feature is Darier's sign.[1]

Table 1. Cutaneous mastocytosis based on WHO criteria[1]

Varian	Abbreviation	Subvarian
Cutaneous Mastocytosis	CM	Urtikaria Pigmentosum
		CM difus
		Mastositoma kulit
Indolen Systemic Mastocytosis	ISM	*Smoldering-SM*
		Isolated bone marrow mastocytosis
Systemic Mastocytosis with an associated clonal hematologic non-mast cell lineage disease	SM-AHNMD	*SM-acute myelogenous leukemia*
		SM-myelodisplastic syndrome
		SM-myeloproliferative disease
		SM-chronic myelomonocytic leukemia
		SM-non-Hodgkin lymphoma

Varian	Abbreviation	Subvarian
Aggressive Systemic Mastocytosis	ASM	
Mast Cell Leukemia	MCL	*Aleucemic MCL*
Mast Cell Sarkoma		
Extra-cutaneous mastocytoma		

Mast cells were first identified by Paul Ehrlich in 1878. These cells, essential components of the human immune system, are connective tissue cells found in all body tissues. They are predominantly located in areas prone to interaction with foreign organisms and antigens, such as the dermis, mucosa, intestinal submucosa, conjunctiva, pulmonary alveoli, and respiratory tracts.[4] Mast cells are mononuclear, round cells with cytoplasmic granules ranging from 0.3 to 0.8 micrometers. Originating from the bone marrow and spleen, they derive from pluripotent CD34+ stem cells, differentiate along the myeloid pathway, and leave the hematopoietic tissue as committed progenitors. These progenitors migrate to specific tissues outside the circulatory system.[1]

Nearly all mast cell growth is influenced by stem cell factor (SCF), produced by stromal cells in the bone marrow, fibroblasts, keratinocytes, endothelial cells, and reproductive tissues like Sertoli and granulosa cells. The surface receptor for SCF is the tyrosine kinase receptor c-kit (CD117), which is expressed by stem cells and plays a crucial role during myeloid differentiation. KIT, derived from the *c-kit proto-oncogene* located on chromosome 4q12, is a key marker for mast cell precursors and remains expressed throughout their lifespan. SCF is essential at all stages of mast cell growth and differentiation, regulating proliferation, chemotaxis, adhesion, and survival. The SCF gene, located on chromosome 12, encodes a protein localized on the cell membrane. Other growth and differentiation factors, including type 2 T-helper cell cytokines, also influence mast cell function.[1]

Mast cell mediators are categorized into three types:[1]

1. **Preformed mediators**: Stored in secretory granules and released extracellularly within seconds of mast cell activation.
2. **Newly synthesized lipid mediators**.
3. **Cytokines and chemokines**.

Preformed mediators are responsible for the acute symptoms of allergic reactions triggered by mast cells. These mediators, stored in secretory granules, include histamine, neutral proteases, heparin proteoglycans, and cytokines like TNF-α. Mutations in the *c-kit* gene

play a critical role in mastocytosis disorders. Somatic mutations at codon 816 of *c-kit* lead to amino acid substitutions (D816V, D816Y, D816F, D816H), causing persistent activation of KIT and uncontrolled mast cell growth and development. These mutations are commonly observed in adult patients. The active mutation at codon 560 (V560G) is also noted in some adult mastocytosis cases but is rare. Similar active mutations in *c-kit* have been reported in pediatric patients as well.[1]

The classic presentation of Darier's sign is induced by gently rubbing or pressing a visible skin lesion. Within 2 to 5 minutes, this results in localized itching, erythema, and the formation of wheals. The reaction may last anywhere from 30 minutes to several hours. In children, vesicles may develop at the site of rubbing. This phenomenon occurs due to an increase in normal mast cells in the dermis. When the skin is rubbed, mast cells undergo degranulation, releasing mediators such as histamine, which is thought to be responsible for the reaction. Although Darier's sign is commonly observed in mastocytosis, it has also been reported, albeit rarely, in conditions such as juvenile granulomas and acute lymphoblastic leukemia. The reaction is more frequently seen in children than adults, likely due to a 40-fold higher concentration of mast cells compared to normal skin.[1]

Pediatric-onset urticaria pigmentosa typically presents as lesions shortly after birth or during infancy. According to literature, nearly 80% of cases present within the first nine months of life, compared to only 20% at birth. Similar findings were observed in retrospective studies of 112 patients and prospective studies of 67 patients.[5-7] The lesions appear as brown to dark papules or macules (rarely), measuring 1–2.5 cm in diameter, primarily on the trunk. They usually spare the central face, scalp, palms, and soles.[1] Blistering may occur in the first year of life, often resolving without scarring unless secondary infection complicates the lesions. The exact mechanism of blistering is unclear but may involve histamine-induced transudates or other chemical mediators.[8]

In adults, urticaria pigmentosa presents as reddish-brown macules and papules measuring approximately 0.5 cm in diameter. Close inspection reveals varying degrees of hyperpigmentation and fine telangiectasia. Lesions are most commonly found on the trunk and proximal extremities, with occasional involvement of the face, distal extremities, palms, and soles. Unlike in children, lesions in adults may appear and resolve within a few months. Over recent years, adult-onset cases have been increasingly reported. Adult urticaria pigmentosa is often associated with systemic mastocytosis subtypes, such as indolent systemic mastocytosis (ISM), SM-AHNMD, aggressive systemic mastocytosis (ASM), or mast cell leukemia (MCL).[1]

Both children and adults with urticaria pigmentosa may experience systemic symptoms due to mast cell mediators, including histamine, eicosanoids, and cytokines. Symptoms range from itching and flushing to abdominal pain, nausea, vomiting, diarrhea, palpitations, dizziness, and syncope. Flushing occurs in about 50% of cases, while alcohol intolerance and itching are less common.[4] Wheezing is rare. Musculoskeletal pain is reported in 19% to 28% of patients. Neuropsychiatric symptoms, including reduced concentration, memory impairment, headaches, irritability, and depression, are also noted. Depression may stem from chronic disease or be mediated by mast cell activity.

Diagnosis of urticaria pigmentosa relies on detecting increased mast cell numbers in one or more tissues. In skin biopsies, toluidine or Giemsa staining, or monoclonal antibodies recognizing mast cell tryptase or CD117 (KIT), confirm mast cell infiltration.[1] Histopathology reveals normal-appearing mast cells in the dermis, with spindle-shaped or cuboidal cells arranged in perivascular or nodular patterns. Pigmentation due to increased basal melanin is often observed.[9]

Detecting circulating mast cell mediators or metabolites provides indirect evidence of mastocytosis. Systemic involvement must be ruled out through complete blood counts (anemia, thrombocytopenia, leukocytosis, eosinophilia), liver function tests, and bone marrow examinations to detect mast cell leukemia. Radiological imaging may help identify bone lesions such as osteolytic or osteosclerotic changes. Specialized tests, including serum tryptase levels, 24-hour urinary N-methylhistamine, and prostaglandin D2 metabolites, are less commonly performed but correlate with disease severity.[10]

In pediatric patients with supporting biopsy results but no abnormalities in complete blood counts, hepatomegaly, splenomegaly, or lymphadenopathy, the diagnosis of cutaneous mastocytosis can be established. If systemic involvement is suspected, bone marrow biopsy and aspiration are necessary. Negative findings in these evaluations confirm cutaneous mastocytosis.[11]

In children, urticaria pigmentosa lesions are distinct and rarely confused with other skin conditions. Temporary urticarial lesions, which resolve within hours, are rarely associated with the hyperpigmentation seen in urticaria pigmentosa. Conditions that may mimic pediatric blistering mastocytosis include bullous impetigo, arthropod bites, linear IgA dermatosis, bullous pemphigoid, toxic epidermal necrolysis, and incontinentia pigmenti. In adults, urticaria pigmentosa lesions may initially resemble lentiginous or atypical melanocytic nevi but are typically associated with erythema (telangiectasia) not present in melanocytic lesions. Other

conditions that may mimic adult urticaria pigmentosa include papular sarcoidosis, drug eruptions, and papular urticaria.[1]

TREATMENT

The management of urticaria pigmentosa focuses on alleviating symptoms. This includes counseling patients and caregivers about the clinical presentation of the disease, avoiding triggers that promote mast cell mediator release, and addressing symptoms caused by these mediators. For mild cases, therapy aims to relieve clinical symptoms. Asymptomatic children with urticaria pigmentosa generally do not require treatment.[1]

Lifestyle modifications are essential in managing urticaria pigmentosa. Patients are advised to bathe with warm water, use air conditioning during hot weather, and avoid triggers that may induce mast cell degranulation, such as alcohol, anticholinergic medications, aspirin, NSAIDs, narcotics, and polymyxin B sulfate. Friction, which can provoke local or systemic symptoms, should also be avoided. Certain systemic anesthetics, including lidocaine, d-tubocurarine, etomidate, thiopental, succinylcholine, enflurane, and isoflurane, have been implicated in exacerbating clinical symptoms.[3] Patients are encouraged to avoid foods containing mast cell mediator triggers, such as salicylates, seafood (shrimp and lobster), spicy foods, hot beverages, alcohol, and aged cheeses.[12] First-Line Therapy includes topical corticosteroids and avoiding triggers. Furthermore, second-Line Therapy options include topical methoxypsoralen with UVA radiation (PUVA), pulsed-dye laser treatment, and systemic therapies such as leukotriene antagonists, sodium cromolyn, ketotifen, and 5-lipoxygenase inhibitors and third-Line Therapy include intralesional corticosteroids, surgical excision for mastocytomas, and omalizumab.[13]

Potent topical glucocorticoids applied under occlusion for 8 hours daily for 8 to 12 weeks can reduce lesion count. However, lesions often recur within a year after stopping treatment. Intralesional corticosteroid injections may provide temporary symptom relief but risk skin atrophy.[3] Prolonged and extensive use of potent topical glucocorticoids in infants may lead to hypothalamic-adrenal suppression.[1]

There are systemic therapies may be used:[14]

- Ketotifen: An H1 antihistamine derived from benzocycloheptathiophene with mast cell and basophil stabilizing properties, useful for gastrointestinal symptoms associated with mastocytosis.

- Leukotriene Antagonists: Effective in controlling flushing, diarrhea, and abdominal cramps by inhibiting cysteinyl-leukotrienes, potent pro-inflammatory mediators from mast cells. They block leukotriene receptors or inhibit 5-lipoxygenase to reduce leukotriene production.
- Sodium Cromolyn: Inhibits mast cell degranulation and is particularly effective for gastrointestinal symptoms in children.

Phototherapy and Laser Treatment

Methoxypsoralen with UVA (PUVA) therapy can relieve pruritus and urticaria for 1–2 months after treatment. However, pruritus often recurs within 3–6 months after discontinuation. PUVA-induced pigmentation may serve as camouflage for adult lesions, but the increased risk of skin malignancies with long-term use must be considered. Pulsed-dye lasers are used for treating adult lesions. A monoclonal antibody targeting immunoglobulin E (IgE), omalizumab is effective for adult mastocytosis patients resistant to leukotriene antagonists and antihistamines. Effective doses range from 150–450 mg monthly. Epinephrine is the treatment of choice for anaphylactic episodes. Patients should carry self-injectable epinephrine and have an emergency management plan. If subcutaneous epinephrine fails, intensive care may be required for vascular system failure. Patients with recurrent anaphylaxis episodes should continue H1 and H2 antihistamines to reduce severity.[13,15]

Targeted therapies such as KIT inhibitors are used primarily for systemic mastocytosis. Hoffmann et al.[13] reported successful treatment of cutaneous mastocytosis with the protein kinase inhibitor imatinib, which is typically used for systemic mastocytosis. Imatinib therapy begins at 100 mg daily and may be tapered as improvement occurs.

Prognosis

Childhood-onset urticaria pigmentosa has a favorable prognosis, with nearly 50% of cases resolving by adulthood. Lesions without systemic involvement often improve or disappear by puberty. Extensive skin involvement in children does not reliably predict systemic disease, unlike in adults.[16]

A study on urticaria pigmentosa subgroups found an 80.6% resolution rate, with only 56.4% achieving complete resolution, which typically occurred within 10.2 years. Partial resolution took an average of 7.1 years. In 19.4% of patients, no improvement was observed during a shorter follow-up period.[17] Most adult-onset cases involve cutaneous or indolent systemic mastocytosis and rarely progress to advanced disease.[1]

However, 25% of adults are more prone to developing systemic mastocytosis compared to children.[14] Target organs include bone marrow, bones, gastrointestinal tract, liver, spleen, and lymph nodes.[18] Adult-onset urticaria pigmentosa has a worse prognosis than childhood-onset due to its persistent nature and greater likelihood of systemic progression.[1]

Conclusion

Urticaria pigmentosa is the most common variant of cutaneous mastocytosis. Proper management can significantly improve patients' quality of life by alleviating distressing symptoms.

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