

A solitary mastocytoma presenting with urticaria and angioedema in a 14-year-old boy

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ABSTRACT

Urticaria with angioedema is a common clinical presentation that often poses a challenge for allergists. The differential diagnosis for urticaria is broad, making the evaluation and pinpointing the underlying cause difficult and frustrating for both families and physicians. Certain causes of urticaria such as infections or medications are more common and easier to identify whereas less frequently seen conditions are often overlooked because of their rarity. One such condition is mastocytosis. Mastocytosis is a rare disease that very seldom presents with urticaria but may be associated with significant morbidity and mortality if not recognized in a timely manner. We are presenting a case of a 14-year-old boy who presented with urticaria and angioedema possibly caused by a solitary mastocytoma. The learning points from this case are that mastocytosis should be considered in the differential diagnosis of urticaria and solitary mastocytomas may remain active into adolescence, raising concern for systemic progression.

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CASE PRESENTATION

Chief Complaint

Urticaria with angioedema.

History of Present Illness

A 14-year-old white boy presented with a 4-week history of urticaria with angioedema. Urticarial lesions were appearing daily diffusely over his body before fading within 30–45 minutes without leaving any hyperpigmentation. The lesions were extremely pruritic. He also experienced several episodes of lip swelling each week (Fig. 1). The lip swelling would last ~24 hours before resolving and was not associated with breathing difficulties or other symptoms. He took 25 mg of diphenhydramine every 4–6 hours as needed for pruritus. He could not identify a specific pattern or an obvious trigger for his urticaria and angioedema. He had no other systemic symptoms. He did not take any other medications. His medical history was unremarkable. The family history was negative for autoimmune disorders and angioedema. His review of systems was normal.

Physical Examination

On physical exam, his vital signs were normal. His height and weight were both in the 75th–90th percentile. His physical exam was remarkable for a 4 × 6-cm oval-shaped, dusky red-colored, blanchable macule on his inner right thigh (Fig. 2). Stroking the lesion did not elicit a Darier's sign. There were no other similar skin lesions. According to his mother, this lesion has been present since infancy. His pediatrician told his mother that the lesion was a "nonpigmented birthmark." The remainder of his physical exam was normal.

Initial Laboratory and Diagnostic Findings

His initial laboratory screen for an underlying cause for his urticaria and angioedema included a complete blood count with differential, metabolic profile with liver enzymes, and sedimentation rate, all of which were normal. No further laboratory or diagnostic testing was performed at this time.

QUESTIONS

What Is the Differential Diagnosis of the Patient's Urticaria and Angioedema?

The differential diagnosis for urticaria with angioedema is extensive (Table 1), often making the evaluation difficult. The evaluation begins with a thorough history and physical to provide clues to help identify an underlying cause of urticaria. Laboratory evaluation (screening and/or specific tests) and diagnostic testing may be helpful in detecting an underlying etiology,

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Figure 1. Edema of upper lip that frequently occurred during the patient's episodes of urticaria.



Figure 2. Appearance of the patient's skin lesion on right inner thigh during an asymptomatic period.

Table 1 Causes of urticaria and angioedema

Foods or food additives
Drug reactions
Inhalation, ingestion of, or contact with antigens
Transfusion reactions
Infection (viral, bacterial, fungal, and parasitic)
Stinging insects
Collagen vascular diseases
Thyroid disease
Malignancy
Physical urticarias
Mastocytosis
Chronic autoimmune urticaria and angioedema
Chronic idiopathic urticaria and angioedema

particularly if a cause can not be discerned from the history.

Certain causes of urticaria are much more common than others. Typical causes of urticaria include food and/or food additives, drug reactions, infections,

physical urticarias, thyroid disease, and autoimmune urticaria. Food and/or food additives can be identified by use of food diaries. Drug reactions involve eliminating the putative medication(s) and monitoring response. If an underlying infection is suspected, a detailed evaluation to document the organism should be performed. Physical urticarias (*i.e.*, vibratory, pressure, and cold) can be elicited from the history in conjunction with simple procedures to reproduce symptoms. Thyroid disease secondary to thyroid autoantibodies has been reported to cause urticaria. Autoimmune urticaria can be identified by the presence of the anti-Fcε-receptor autoantibody.

Rare causes of urticaria include collagen vascular diseases, malignancy, and mastocytosis. These conditions often present with atypical urticaria (*i.e.*, persist for >24 hours or leave a hyperpigmented mark on remitting) in conjunction with systemic symptoms such as arthralgia, weight loss, diarrhea, or unexplained fever. If the aforementioned causes have been excluded, a diagnosis of chronic idiopathic urticaria is assigned until the urticaria spontaneously remits or a cause is discovered.

What Additional Investigations Would Be Helpful in This Patient?

Because both the history and the initial laboratory screen did not provide clues to an underlying cause for his urticaria. A trial of symptomatic treatment with an antihistamine was started and close follow-up was arranged. Although a more thorough laboratory evaluation may be conducted at the initial encounter, it is not practical or cost-effective and often does not yield additional information given the low pretest probability. If he does not respond to antihistamine therapy or the interim history and/or physical exam provides new insight into an underlying cause, further evaluation is certainly warranted.

CLINICAL COURSE

The initial history and laboratory evaluation did not provide an underlying cause for his urticaria and angioedema. He was started on 25 mg of hydroxyzine nightly. He was instructed to keep a food diary to potentially identify a trigger for his urticaria. He was to follow-up in 2 months or sooner if he had any problems. His urticaria was controlled with hydroxyzine over the next 2 months so his mother discontinued the hydroxyzine. He did not have problems with urticaria or angioedema for 10 months. Unfortunately, the urticaria and angioedema reoccurred but this time his mother reported that the so-called "birthmark" on his right inner thigh would turn bright red, swell, itch, and develop small hives around it minutes before the appearance of new urticarial lesions elsewhere on his

body. This history made us suspicious that the lesion was a solitary mastocytoma. A serum tryptase level obtained when diffuse urticaria were not present was normal. Plasma histamine and urine prostaglandin D₂ levels were not drawn when the urticaria was present. A skin punch biopsy of the lesion was positive for c-kit and mast cell tryptase on immunohistochemical staining, consistent with a mastocytoma. We speculated that the solitary mastocytoma was presumably the most likely underlying cause of his urticaria. Unfortunately, there is no practical approach to definitively prove his urticaria and angioedema were caused by activity of the solitary mastocytoma. However, based on the history provided by his mother that the mastocytoma would swell, itch, and develop small hives around it a few minutes before the appearance of new urticaria elsewhere provides the best evidence to suggest the relationship between his urticaria and the mastocytoma.

His urticaria and angioedema have been controlled with 10 mg of hydroxyzine nightly. He was also instructed to do occlusive dressings with a high potency topical steroid for 2 weeks by his dermatologist in an attempt to shrink the mastocytoma. More importantly, we will need to continue to follow this patient closely to monitor for signs and symptoms such as generalized flushing, diarrhea, or hepatosplenomegaly, and serum tryptase, which may suggest systemic involvement.

DISCUSSION

Urticaria with angioedema is a common presentation with a broad differential diagnosis. The history is critical in identifying the etiology as depicted in this case. When his mother provided the history that the lesion on his right inner thigh would swell within minutes of the appearance of new urticaria, we became highly suspicious that the lesion was a solitary mastocytoma, which was confirmed by a skin punch biopsy by the presence of positive staining for c-kit and mast cell tryptase. Although rare, mastocytomas can present with urticaria and should be considered in the differential diagnosis for urticaria.

Mastocytosis is a heterogeneous group of rare disorders characterized by abnormal proliferation and accumulation of mast cells, involving either only the skin (cutaneous mastocytosis) or the bone marrow and other extracutaneous organs (systemic mastocytosis). The majority of cases of mastocytosis in children are limited to the skin.¹ Cutaneous mastocytosis is further divided into four clinical variants (Table 2): urticaria pigmentosa, solitary mastocytoma, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans.² The pathogenesis of cutaneous mastocytosis is not well understood. A

Table 2 Forms of cutaneous mastocytosis in children

Urticaria pigmentosa
Solitary mastocytoma
Diffuse cutaneous mastocytosis
Telangiectasia macularis eruptiva perstans

transient dysregulation of stem cell factor, a growth factor necessary for mast cell differentiation and growth, has been implicated as the underlying defect in cutaneous mastocytosis.³

Solitary mastocytomas account for 10–15% of all pediatric cutaneous mastocytosis.⁴ The majority of mastocytomas present during infancy, typically by 3 months of age, as a single indurated, red–brown macule, papule, or plaque on the trunk, extremities, head, or neck.^{1,4,5} Only 10% of mastocytomas appear beyond 2 years of age.⁶ Symptoms associated with solitary mastocytomas are secondary to the release of mast cell mediators (e.g., histamine). Symptoms may be localized to include pruritus or blistering of the lesion or generalized with flushing and rarely, urticaria. A Darier's sign may be elicited in only ~50% of patients. Hence, the absence of a Darier's sign does not exclude the diagnosis of a mastocytoma. Mast cell degranulation within solitary mastocytomas may be triggered by a variety of factors including physical stimuli (e.g., heat, cold, friction, and pressure), emotional factors, certain medications (e.g., nonsteroidal anti-inflammatory drugs, opioids, dextromethorphan, vancomycin, and general anesthetics), and radiocontrast media.^{6,7}

The diagnosis of a solitary mastocytoma is suspected by the presence of a characteristic skin lesion and confirmed by skin punch biopsy consisting of >15 mast cells/cluster and/or tryptase-positive mast cells on immunohistochemical staining.⁸ Laboratory evaluation is rarely needed unless lesions fail to regress over time or systemic symptoms are present. The initial laboratory evaluation includes a complete blood count with differential, comprehensive metabolic profile and a serum tryptase level. A bone marrow biopsy is not necessary in infants and children unless extracutaneous organ involvement is suspected.

The goal of management of a solitary mastocytoma is to prevent mast cell mediator release and alleviate symptoms associated with mediator release, particularly pruritus. The mainstay of therapy involves avoidance of potential triggers and oral antihistamines (H₁-blockers). Other therapeutic options include psoralen-UV-A, short-term application of a topical steroid under an occlusive dressing, or targeted laser therapy.⁹ Surgical excision can be curative if unresponsive to other therapies. In addition, families should be edu-

cated on the natural history of solitary mastocytomas. Fortunately, the vast majority of children with solitary mastocytomas have a good prognosis with reduction or complete resolution of symptoms by adolescence. Solitary mastocytomas rarely remain symptomatic in older children; as in this case, only 10–15% of children have symptoms that persist into adulthood.^{3,10} These children may have a higher likelihood of having systemic mastocytosis.

CONCLUSION

This case illustrates several valuable learning points. First, solitary mastocytomas seldom cause urticaria but should always be considered in the differential diagnosis for urticaria. The second point and, probably, more important is that most mastocytomas regress by adolescence while a small percentage remain active beyond adolescence, raising concern for progression to systemic mastocytosis. A skin lesion suspicious for a solitary mastocytoma should prompt a diagnostic evaluation with participation of the appropriate specialist. It is important to recognize mastocytomas early to monitor progression of the lesion.

REFERENCES

1. Akoglu G, Erkin G, Cakir B, et al. Cutaneous mastocytosis: Demographic aspects and clinical features of 55 patients. *J Eur Acad Dermatol Venereol* 20:969–973, 2006.
2. Castells MC. Mastocytosis: Classification, diagnosis, and clinical presentation. *Allergy Asthma Proc* 25:33–36, 2004.
3. Heide R, Tank B, and Oranje AP. Mastocytosis in childhood. *Pediatr Dermatol* 19:375–381, 2002.
4. Hannaford R, and Rogers M. Presentation of cutaneous mastocytosis in 173 children. *Australas J Dermatol* 42:15–21, 2001.
5. Wolff K, Komar M, and Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. *Leuk Res* 25:519–528, 2001.
6. Briley LD, and Phillips CM. Cutaneous mastocytosis: A review focusing on the pediatric population. *Clin Pediatr (Phila)* 47: 757–761, 2008.
7. Bains SN, and Hsieh FH. Current approaches to the diagnosis and treatment of systemic mastocytosis. *Ann Allergy Asthma Immunol* 104:1–10, 2010.
8. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: Consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 37:435–453, 2007.
9. Heide R, Beishuizen A, De Groot H, et al. Mastocytosis in children: A protocol for management. *Pediatr Dermatol* 25:493–500, 2008.
10. Kettelhut BV, and Metcalfe DD. Pediatric mastocytosis. *J Invest Dermatol* 96(suppl):15S–18S, 1991. □

Errata

Angioedema in a child with a liver transplant, intussusception, and normal c4 levels

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On page e63 of the July–August 2010 issue, there are two errors in the Abstract.

The seventh sentence of the Abstract should begin: “Serial C1 esterase inhibitor levels . . .”.

The ninth sentence should read: “Although 95% of cases of hereditary angioedema (HAE) have low C4 levels, . . .”

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