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Patient Report

Asthma and gastroesophageal reflux in a girl with urticaria pigmentosa

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Urticaria pigmentosa is a relatively rare disorder, but is the most common form of mastocytosis. It is characterized by abnormal aggregates of mast cells in the skin and occurs primarily in infants and children. These abnormal aggregates of mast cells can, under some physical stresses, abruptly release vasoactive mediators and may produce pruritus, episodic flushing, tachycardia, respiratory distress, wheezing, hypotension, syncope, shock, headache, abdominal pain, diarrhea and gastric hypersecretion.[1,2] A computerized search of the MEDLINE database from 1966 to 1998 identified only two articles reporting an association between urticaria pigmentosa and asthma[3,4] and two articles reporting an association between urticaria pigmentosa and gastro-esophageal reflux (GER).[5,6]

In the present report, we describe a girl with urticaria pigmentosa who also suffered attacks of dyspnea, cough, wheezing, abdominal pain and GER. A possible mechanism of the association of these clinical entities is discussed.

Case Report

Diffuse hyperpigmented spots appeared in the girl when she was 3 months of age. Histopathology of a skin sample (hematoxylin and eosin stain) showed an increased number of mast cells distributed uniformly throughout the dermis with perivascular localization in places. Urticaria pigmentosa was diagnosed by clinical suspicion and with biopsy of the skin, and the patient was treated with ketotifen. Some worsening of the affected skin was caused by mechanical irritation or after sun exposure. When she was 9 years of age, attacks of dyspnea, cough, wheezing and abdominal pain began, particularly after physical exertion. Respiratory symptoms often disappeared following the inhalation of salbutamol.

The 13-year-old girl was, on admission, without symptoms and in good general condition. Hyperpigmented macular lesions were present on the skin of the trunk and limbs. They were symmetrically distributed and their size was approximately 1 cm.

Laboratory analysis showed normal values of routine hematological and serum chemistry profiles. The absolute number of eosinophils and total and specific serum IgE was within the normal limits for the patient's age. Skin testing (prick) did not reveal an immediate reaction to inhalant and nutritive allergens. The sweat chloride test was normal.

We decided to do pH monitoring because the patient had uncontroled nonatopic asthma.[7] According to the Vandeplas and Sacre-Smith reflux index (RI) $> 5\%$ was considered positive; the same cut-off limit was used for the oscillatory index.[8] Simultaneous 24 h esophageal and gastric pH monitoring showed pathological GER (Table 1.). Median fasted intragastric pH was 2.2 and, after meal, it was 3.2. Endoscopic evaluation revealed esophagitis stage one, but a biopsy was negative for esophagitis.

The patient was treated with cisapride and disodium cromoglicate and, 6 months later, she had only two short attacks of dyspnea, which disappeared without therapy. Control pH recording was significantly better (Table 1.).

Discussion

Urticaria pigmentosa is a cutaneous form of mastocytosis that usually occurs sporadically in childhood and is considered a benign disorder because spontaneous regression of lesions occurs in 50% of cases by puberty. In persistent cases, 30% have systemic involvement.[1,2] Physical exertion, alcohol, narcotics, non-steroidal analgesics, aspirin and bathing in very hot or cold water provokes symptoms of the systemic mastocytosis.

Clinical symptoms occur from the release of chemical mediators and the pathologic infiltration of cells.[9–11]

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Table 1 24 Hour esophageal pH monitoring before and after treatment with cisapride and disodium cromoglicate

	Before treatment	After treatment
No. reflux episodes	148	103
No. reflux episodes > 5 min	3	1
Longest reflux episode (min)	23	12
Reflux index	8.4	5.1
Median pH value	4.7	5.8
Oscillatory index	11.7	2.7
DeMeester score	43.2	31.9

Normal values according to Colleti *et al.*,[7] Vandeplas and Sacre-Smith[8] and Vandeplas.[13]

Histamine is the most prominent product of mast cell degranulation and its main actions are in increasing vascular permeability, contraction of gastrointestinal smooth muscles, gastric acid hypersecretion, bronchoconstriction and mucus hypersecretion. Other mediators generated after stimulation of the mast cell include prostaglandins, leukotriene and cytokines. Prostaglandin D_2 is the principal cyclo-oxygenase product of mast cells during a spontaneous episode of IgE-indepedent systemic mast cell activation. It is a potent bronchoconstrictor and is thought to have a role in the pathogenesis of asthma. Leukotrienes are also potent bronchoconstrictors, inducers of airway microvascular leakage, edema, mucus secretion and decreasing mucociliary transport. Triadafilopoulos *et al*. suggest that leukotriene B_4 mediates the inflammatory phenomenon of reflux esophagitis.[12]

The association of asthma, abdominal pain and GER in our patient with urticaria pigmentosa is probably the result of systemic effects of mast cell-derived mediators. These mediators cause bronchoconstriction, GER and hyperacidity of the stomach. Bronchoconstriction is caused by histamine, leukotriene and thromboxane receptors in the lung, which could be the reason for the dyspnea, cough and wheezing seen in our patient. Histamine also stimulates gastric acid secretion, acting through histamine H_2 receptors and, together with leukotrienes, contributes the clinical manifestations of GER disease, which corresponds to our findings on pH recording. Recent studies report that up to 75% of children with uncontrolled asthma suffer pathologic GER, although other studies report a negative correlation.[7,13] Potential mechanisms include reflex bronchospasm rather than overt or silent aspiration.[13]

The association of these three diseases (urticaria pigmentosa, asthma and GER) may be accidental, but it may also be result of the primary disease, a disorder of mast cell proliferation.

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