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Case Series

Five Cases of Pediatric Cutaneous Mastocytosis and Autism Spectrum Disorder

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ABSTRACT

Here we report five cases of children with both Cutaneous Mastocytosis (CM), a pediatric condition of skin lesions containing mast cells, and autism spectrum disorder (ASD), a neurodevelopmental condition characterized by impaired communication and obsessive behaviors. This apparent comorbidity is intriguing given that the co-occurrence of these two conditions would be expected to be infrequent in the general population. The possible association between CM and ASD is supported by increasing evidence indicating a strong association between atopic dermatitis (AD), which involves mast cells, and ASD. Activated mast cells in CM and AD could contribute to their pathogenesis, hence inhibiting mast cell activation may have considerable benefit.

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

1. Introduction

Cutaneous mastocytosis (CM) is a disorder manifesting in children during the first two years of life. (1) The exact prevalence is not known due to lack of sufficient epidemiological data, but it is estimated to be about 1:10,000 children (0.001%) (2). Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired communication and obsessive behaviors affecting 1 in 31 (3.2%) children in the USA (3). There is no distinct pathogenesis or effective treatment for either CM or ASD (4, 5).

2. Methods

All children had been diagnosed with ASD by trained child psychiatrists using cutoff scores on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as well as the validated scales of Autism Diagnostic Observation Schedule, Second Edition 1 (ADOS-2) and Diagnostic Interview-Revised (ADI-R). All children had mild to moderate ASD, as determined by using a composite score of 20-40 on the Childhood Autism Rating Scale (CARS), with the lowest score of 15 indicating normal behavior on all 15 scales, while the highest score of 60 indicates behavior is severely abnormal on all 15 scales). Fragile X, Tuberous Sclerosis, Rett and PTEN syndromes had been excluded on clinical evaluation and appropriate genetic analysis. Brain MRI and EEG were also normal. Improvement in ASD-related symptoms was rated using the Clinical Global Impression-Improvement (CGI-I) scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change from baseline; 5=minimally worse; 6=much worse; 7=very much worse). Children were referred to TCT for unusual skin lesions. Diagnosis of CM was made based on history of symptoms, clinical observation. and a positive of Darier's sign (itching and redness upon stroking of the affected lesion).

3. Results

Here we report five cases of children with CM and ASD (Table I). All patients were Caucasian (3-11 years old) and all but one were male. Diagnosis of CM was made). In all children, all basic blood values including liver and thyroid function tests were normal, and the serum level of the mast cell marker tryptase was <10 ng/ml.

Table I. *Demographics, CM characteristics and ASD-Symptom Improvement.*

Patient	Sex	Age (years*)	Site of Lesion	Type of Lesion	CGI-I
1	M	6	Arm	Solitary	2
2	F	11	Back	Solitary	2
3	M	3.5	Arm	Solitary	2
4	M	5.5	Back	Solitary	3
5	M	3	Leg	Diffuse	2

*Rounded up at the time of last encounter

There were four cases with solitary mastocytomas: One was present on the arm (Fig. 1a) and all others were on the torso (Fig. 1b-d); one case involved congenital diffuse CM (Fig. 1e).

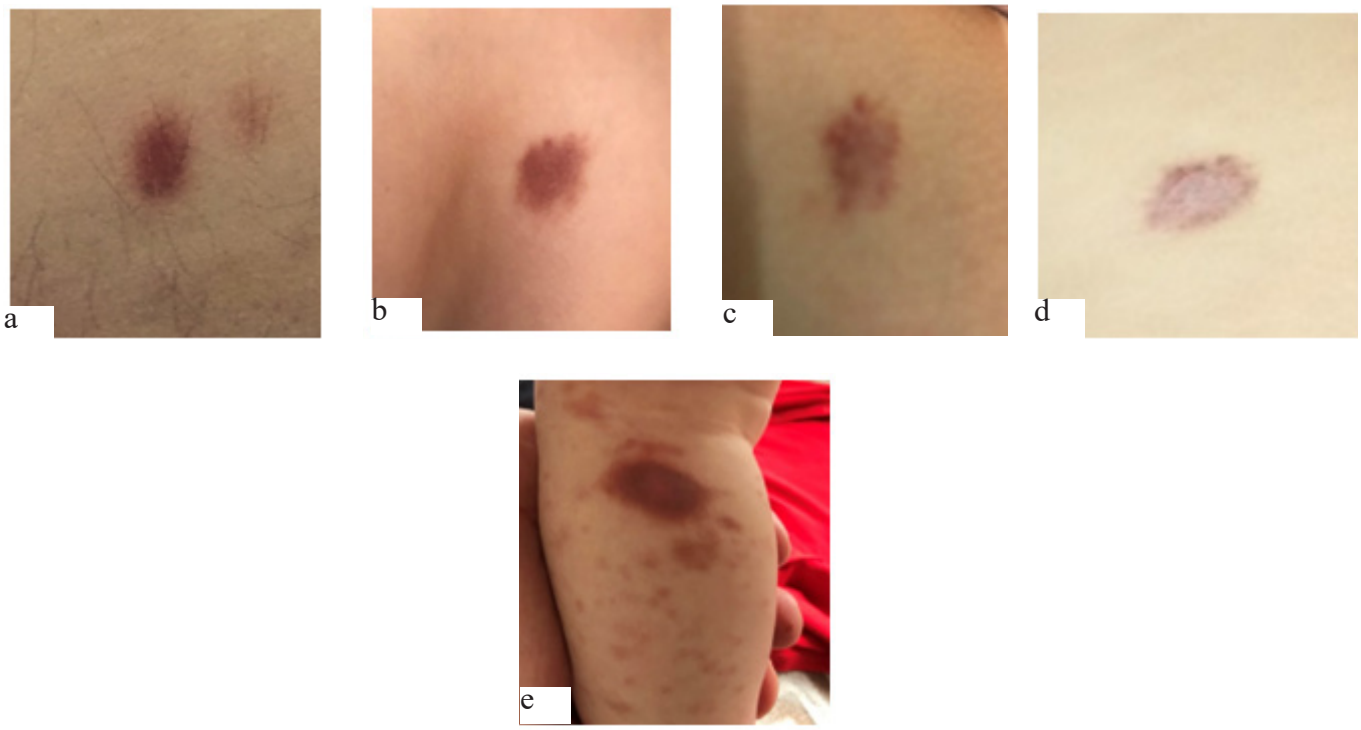

Fig. 1. *Photomicrographs of skin lesions:* ***a****. solitary mastocytoma lesion from the back of a 11-year-old Caucasian male;* ***b****. Photomicrograph of a solitary mastocytoma lesion from the arm of a 6-year-old Caucasian male;* ***c****. Photomicrograph of a solitary mastocytoma lesion from the abdomen of a 5.5-year-old Caucasian male;* ***d****. Photomicrograph of a solitary mastocytoma lesion from the abdomen of a 4-year-old Caucasian female;* ***e.*** *Photomicrograph of diffuse CM lesions from the leg of a 3-year-old Caucasian male.*

All children were administered a dietary supplement (NeuroProtek®, one softgel capsule twice per day for 6 months) containing the flavonoids luteolin, quercetin and rutin formulated in olive pomace oil (6). Additionally, a skin lotion containing the luteolin structural analogue tetramethoxyluteolin (7) (GentleDerm®) was applied on the lesional skin twice per day. All children continued with speech therapy sessions. Six months after initiation of thisintervention , parents reported that the skin lesions had "faded" and there was significant overall ASD symptom improvement using the CGI-I .

4. Discussion

We had previously reported that children born to mothers with systemic mastocytosis, which is characterized by a greater number of hyperactive mast cells (8), had a higher risk of being diagnosed with ASD than the general population (9).

The comorbidity of CM and ASD is intriguing especially since the prevalence of pediatric CM has been reported to be about 0.0001% and that of ASD is about 3.0% making the possibility of these two conditions co-occurring (3 in 1,000,000 or 0.0003%) extremely unlikely (Table II).

Table II. *Calculation of Chance of Comorbidity of CM and ASD.*

To determine the chance of comorbidity for two conditions, one multiplies the individual prevalence rates, assuming the conditions are independent. This means that one condition does not influence the likelihood of developing the other. To calculate the chance of comorbidity:

1. **Define the prevalence rates as probabilities:**
   - Condition A: 1 in 10,000, or $P(A)=1/10,000=0.0001$
   - Condition B: 3 in 100, or $P(B)=3/100=0.03$
2. **Multiply the probabilities.**
   - The probability of two independent events both occurring is
   - $P(A \text{ and } B)=P(A)\times P(B)$
   - $P(\text{Comorbidity})=0.0001\times 0.03=0.000003$
3. **Result**

The chance of comorbidity for these two conditions is 3 in 1,000,000, or 0.0003%.

Only one case of pediatric CM in a male child with motor and intellectual delay has been reported (10). Epidemiological studies have shown a statistically significant association between ASD and atopic dermatitis (AD) (11, 12), as well as other atopic diseases (13), all of which also involve activation of mast cells (14).

Mediators released from mast cells (15) could contribute to the pathogenesis of ASD by: (a) increasing the permeability of the blood-brain barrier (BBB) and allowing toxins to enter into the brain where they stimulate microglia leading to focal brain inflammation (14) and releasing metalloproteinases that could disrupt neuronal connectivity (16).

The flavonoids in the supplement and skin lotion used have been reported to inhibit human mast cells (17) and microglia (18). Moreover, the dietary supplement used had been reported to result in a significant decrease in serum levels of pro-inflammatory markers in children with ASD (19). A recent review stressed the possible significance of mast cells in the pathogenesis of ASD (20).

There are a number of limitations to be considered. The number of subjects was small and this case study was open-label; moreover, the improvement was subjective even though the scale used has been utilized in numerous investigators. The apparent improvement of symptoms noted may also be due to the natural course of the conditions. However, pediatric CM does not improve on its own until puberty and ASD-related symptoms do not typically resolve within 6 months regardless of speech therapy.

4. Conclusion

The apparent co-occurrence of CM and ASD is intriguing and could point to associations important for understanding pathophysiological interactions that may contribute to the development of both conditions in at least a subgroup of children. Any allergic manifestations and suspicious skin lesions in children with ASD should be investigated and addressed.

Abbreviations

ADOS-2 = Autism Diagnostic Observation Schedule, Second Edition
ADI-R = Diagnostic Interview-Revised
ASD = Autism Spectrum Disorder
BBB = blood-brain barrier
CARS-2 = Childhood Autism Rating Scale, Second Edition
CGI-I = Clinical Global Impression-Improvement
CM = cutaneous mastocytosis
DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

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Disclosures
TCT is on the Medical Advisory Board of the Mastocytosis Society. He is also the Scientific
Director and shareholder in Algonot, LLC (Sarasota, FL).

Ethical considerations
This study conforms to the Declaration of Heksinski and the US Federal Policy for the Protection of Human Subjects. There is NO identifying patient information, and the author has permission to publish from the respective parents.

Community involvement
There was no community involvement other than the families of children with ASD reaching out to me because of the unusual skin lesions.

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