Apparent Third Patient With Cutaneous Mastocytosis, Microcephaly, Conductive Hearing Loss, and Microtia

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Mastocytosis refers to a heterogeneous group of rare disorders characterized by an abnormal accumulation of mast cells in one or more organ systems. Cutaneous mastocytosis (CM) is the most frequent form in children and is characterized by hyperpigmented macules or papules symmetrically distributed over the trunk, and less so over the limbs, neck, and scalp. Two published articles have reported on unrelated girls presenting with mastocytosis, microcephaly, hearing loss, and hypotonia. Based on the original observation, this disorder was defined as CM with short stature, conductive hearing loss, and microtia (OMIM 248910). Here we report on a girl with similar manifestations who corroborates the existence of this rare disorder. CM, microcephaly, microtia, and/or hearing loss are the minimal diagnostic criteria. All the known patients were sporadic, but parental consanguinity in the first case argues for a possible autosomal-recessive inheritance.

How to Cite this Article:

Key words: cutaneous mastocytosis; microcephaly; microtia; deafness

INTRODUCTION

The term mastocytosis refers to a heterogeneous group of rare disorders characterized by abnormal accumulation of mast cells in one or more organs. Mastocytosis has many clinically related variants [Heide et al., 2008], including a rare systemic form (SM) and a more common cutaneous form. Cutaneous mastocytosis (CM) can manifest as four clinical variants: urticaria pigmentosa, the most common presentation; solitary mastocytoma; diffuse CM; and telangiectasia macularis eruptiva perstans [Valent, 2006; Briley and Phillips, 2008]. The onset is usually between 2 and 15 years. Most pediatric CM patients develop symptoms by the age of 2 years and improvement of symptoms occurs over time [Briley and Phillips, 2008].

Wolach et al. [1990] and Hennekam and Beemer [1992] reported on two 5-year-old unrelated girls presenting with mastocytosis, microcephaly, hearing loss, and hypotonia. Based on the original observation, this disorder was defined as CM with short stature, conductive hearing loss, and microtia (OMIM 248910). Here we report on a girl with similar manifestations who corroborates the existence of this rare disorder.

This girl was evaluated by us at age 16 years. Weight was 33 kg (<3rd centile), height 160 cm (25th centile), OFC 52.5 cm. She was born normally at term after a uneventful pregnancy. Birth weight was 3,050 g (25th centile), length 50 cm (50th centile), OFC 32 cm (−2 DS). Examination at birth disclosed dry skin and a camptodactylous right 5th finger. By the age of 3 years, she developed diffuse macules and papules on neck and trunk. Her parents never reported pruritus, feeding difficulties, or recurrent infections. She had mild mental retardation and hypotonia. Head control was reached at the age of 9 months, sitting unsupported at 10 months, walking unsupported at 22 months, and first monosyllables at 7 months. First menstruation occurred at 13 years.

This girl was evaluated by us at age 16 years. Weight was 33 kg (<3rd centile), height 160 cm (25th centile), OFC 52.5 cm.
She had diffuse hyperpigmented macules and papules on the trunk and fewer over the limbs. Face, scalp, palms, and soles were spared. There was also dermographism. The face was “triangular” with prominent supraorbital ridges, upward slanted palpebral fissures, wide nasal bridge, long and prominent nose, hypoplastic nares, full lips, high-arched palate, micrognathia, bilateral short ears (5.5 cm, −2 SD), long slender fingers, complete distal palmar crease at left hand, camptodactyly of the right 5th finger, and small (3rd centile) asymmetric feet (left foot was 2 cm shorter) (Fig. 1A–E).

She had been investigated extensively. Results of laboratory tests including metabolic, liver, renal, and thyroid functions, abdomen ultrasound, cardiologic evaluation, ophthalmologic and audiologic examinations were all normal. Standard karyotype analysis at 550-band resolution was normal. Radiographs disclosed dislocation of the right proximal 5th finger interphalangeal joint. A skin biopsy showed prominent mast cell infiltration and confirmed the diagnosis of CM.

**DISCUSSION**

Mastocytosis includes a spectrum of clinical disorders. Criteria for diagnosis were reported by Valent [2006] and Valent et al. [2001]. SM can affect the gastrointestinal tract, liver, spleen, bone, and bone marrow and at time can be complicated by anaphylaxis. Pathologic mast cell infiltration may be observed in the affected tissues. Multiple molecular, genetic, and chromosomal defects are likely to contribute to mast cell growth, and somatic c-kit (receptor tyrosine kinase) gene mutations have been found in several patients [Briley and Phillips, 2008; Foster et al., 2008; Heide et al., 2008; Kirsch et al., 2008]. The diagnosis of CM is based on the absence of SM criteria. Systemic mastocytosis is defined by the organs involved. Major criteria are multifocal infiltrates of mast cells observed in bone marrow biopsies and/or mast cells stained for tryptase in biopsies from extracutaneous organs. Diagnostic procedures aimed to identify the organs involve the following: determination of serum tryptase levels, abdomen ultrasound (organomegaly), platelets and leukocyte counts, differential cell count, and liver and renal function analyses [Heide et al., 2008]. CM is the most frequent form in children and is characterized by hyperpigmented macules or papules symmetrically distributed over the trunk, and less so over the limbs, neck, and scalp. The prognosis is favorable in most CM pediatric patients [Briley and Phillips, 2008]. While familial occurrence of CM is rare, pedigrees displaying both autosomal-recessive and -dominant inheritance with reduced penetrance of the cutaneous and SMs have been reported [Fowler et al., 1986; Hennekam and Beemer, 1992; Chang et al., 2001; Lappe et al., 2003]. Treatment is based on the avoidance of mast cell degranulators, including physical stimuli and chemical substances, and the use of H1 or H2 blockers or steroids, but novel therapeutic options are under evaluation [Hoffmann et al., 2008].

The present patient had CM confirmed by skin biopsy, and microcephaly, mental retardation, hypotonia, minor facial anomalies, short ears, unilateral 5th finger camptodactyly, and asymmetrically small feet. This condition was previously reported in two children [Wolach et al., 1990; Hennekam and Beemer, 1992]. Wolach et al. described a 5-year-old girl with CM, short stature, hypotonia, microcephaly, upslanted palpebral fissures, highly arched palate, micrognathia, bilateral “dysplastic” microtic ears, clinodactyly of 5th fingers, conducive hearing loss, and feeding problems. Hennekam and Beemer [1992] reported another 5-year-old girl, who presented with a similar constellation of symptoms, including CM, short stature, hypotonia, microcephaly, upslanted palpebral fissures, highly arched palate, micrognathia, clinodactyly

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**FIG. 1.** The proposita at age 16 years. A: Frontal view; (B) short ears, hypoplasia nasal alae, and micrognathia; (C) cutaneous mastocytosis; (D) the hands show camptodactyly of the right 5th finger and complete distal palmar crease at left; and (E) asymmetric small left foot.
of 5th fingers, mixed hearing loss, feeding problems, mental retardation, and convulsion (Table I).

Major differences in the present case included absence of the feeding problems and normal hearing. The audiologic involvement in the three affected girls consisted of microtia with/without deafness and malformed ears. Nonoverlapping skeletal abnormalities were recorded in the three patients. While our patient had right 5th finger camptodactyly and asymmetric small feet, the other two girls had scoliosis and 5th finger clinodactyly. Short stature was recorded only in the original report.

Mastocytosis in association with hearing loss has been reported in a few patients. Trevisan et al. [2000] described two siblings with mastocytosis and neurosensory hearing loss, in a family segregating hereditary deafness, and Ina et al. [2007] reported a 30-month-old girl with CM and bilateral neurosensory hearing loss. Mental retardation and dysmorphic features were not found in these cases, although cerebral MRI in the Ina’s patient disclosed bilateral symmetric subcortical lesions in the temporo-occipital and fronto-parietal lobes.

Published cases suggest that mastocytosis may manifest with a variable spectrum of clinical features. Cerebral and audiological disorders could result from mast cell infiltration in these organs, although encephalopathy induced by systemic mastocytosis is rare and more frequent in the adult patients manifesting acute symptoms of cerebral dysfunction. To our knowledge, mental retardation was not reported in association with systemic mastocytosis. Hennekam and Beemer [1992] found unremarkable neuroradiological findings and normal level of histamine in the spinal fluid. Unfortunately, the parents of our patient did not consent cerebral MRI and spinal fluid investigation. However, both clinical and laboratory results did not favor the diagnosis of SM. Mental retardation in the present syndromic case and in the Wolach et al. [1990] and Hennekam and Beemer [1992] patients was likely related to microcephaly.

In conclusion, our patient provides confirmatory evidence to the existence of a rare syndrome originally reported by Wolach et al. [1990], CM, microcephaly, microtia, and/or hearing loss could be the minimal diagnostic criteria for this disorder. All the known patients were sporadic, but parental consanguinity (parents were first cousins) in the first case suggested autosomal-recessive inheritance. Therefore, a one in four recurrence risks seems appropriate for the parents of affected patients.

ACKNOWLEDGMENTS

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TABLE I. Clinical Features in the Present Case and in the Two Published Patients


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