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Cutaneous Manifestations in Trisomy 13 Mosaicism: A Rare Case and Review of the Literature

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Trisomy 13 mosaicism is a rare genetic disorder affecting a small minority of all trisomy 13 cases. It occurs when two cell populations that are karyotypically different are present in the same individual and are derived from a single zygote. As a rule, the phenotype is mitigated to a less dysmorphic appearance and longer survival, making genetic counseling a difficult task. Capillary hemangiomas are a common feature of full trisomy 13, seen in 27–56% of all cases. We report on an 18-months-old girl with extensive cutaneous anomalies, mild dysmorphic features, and slight psychomotor delay, without structural defects and provide an up-to-date review of all cases of trisomy 13 mosaicism with skin involvement. To our knowledge, this is the second clinical report of a patient with trisomy 13 mosaicism with hemangiomas and port wine stains, but no structural defects. © 2015 Wiley Periodicals, Inc.

Key words: trisomy 13; trisomy 13 mosaicism; hemangioma; cutaneous vascular anomaly; cutaneous manifestation

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INTRODUCTION

As the third most common autosomal trisomy in live birth, trisomy 13 is a well described chromosomal abnormality with characteristic features such as microcephaly, microphthalmia, mental retardation, cleft lip and palate, polydactyly, cardiac and renal diseases, and rocker bottom feet [Patau et al., 1960]. The incidence is reported with 1:10.000 to 1:20.000 births [Carey, 2010] with a median survival of 10 days [Wu et al., 2013]. As well as complete trisomy and trisomy resulting from unbalanced Robertsonian translocation, partial trisomies (8%), and mosaic forms (1–5%) of this disorder do exist [Alberman et al., 2012]. Over the years, collected clinical observations have identified more than 100 different abnormalities for both trisomy 13 [Jones, 2006] and its mosaic forms [Griffith et al., 2009]. With a reported range from 27% to 56% [Petry et al., 2013], capillary hemangioma is a common feature in full trisomy 13. We present one patient with trisomy 13 mosaicism with hemangiomas and port wine stains but a mild phenotype. Furthermore, we provide an up-to-date review of 27 published cases of skin involvement in trisomy 13 mosaicism.

CLINICAL REPORT

The patient is an 18-months-old female who was born to a 44-year-old mother. She is the second child of healthy and unrelated parents. The mother has a previous history of one live born child and three spontaneous abortions. She was delivered at 28 weeks of gestation by emergency cesaren section due to prolonged fetal bradycardia. The mother denied the use of any medications that could be related to these findings. The first trimester of pregnancy was uneventful. Due to advanced maternal age, first trimester screening was performed showing nuchal translucency of 1.2 mm, a visible nasal bone, and no anatomical abnormalities. Maternal serum PAPP-A was 0.3369 multiples of the median (MoM); ß-hCG was 0.6286 MoM. The combined test revealed a risk reduction from 1:28 to 1:427 for trisomy 21 and from 1:49 to 1:166 for trisomy 13/18. Further invasive genetic testing as well as a detailed second trimester anatomy scan were declined by the parents. The mother was referred to our tertiary care center for maternal fetal medicine because of substantial growth retardation and abnormal fetal Doppler in the 28th week of gestation. She was

Conflict of interest: none

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transferred to the delivery ward for continuous fetal heart rate monitoring. After 1 day, the patient was delivered via emergency cesarean because of prolonged fetal bradycardia. At birth, microcephaly of the infant was observed. The birth weight was 534 g, body length was 33cm, and head circumference was 22 cm (all parameters below 3rd percentile). Apgar scores were seven at 1 min, nine at 5 min and nine at 10 min.

A prominent single palmar crease was visible as well as small and pointed fingers with type V brachymesophalangy on both hands. On physical examination, the patient exhibited normal muscle tone and mobility and the absolute strength of the extremities and reflexes were within normal range. A thorough dermatologic examination revealed a large port wine stain on the left forehead spreading to the right frontal area, upper eyelids, philtrum, and the occipital scalp. In addition, a 4 cm^2 large hemangioma planotuberosum was observed on the forearm extending to the wrist (see Fig. 1A and C). Due to a very poor sucking reflex exhibited by our patient, a gastric tube was placed after delivery. The hemangiomas were systemically treated with propranolol [Léauté-Labréze et al., 2008] and showed good regression tendency.

Aside from the significant cutaneous manifestations, the girl showed no structural defects and all further work-up—echocardiography, head and abdomen ultrasound, brain magnetic resonance imaging, and ophthalmologic exam—showed no abnormalities. The parents consented to a chromosome analysis, and the karyotyping of blood leukocytes showed 47,XX,+13[12]/46,XX[38] mosaicism with 24% of the cells being trisomic at the time of examination.

The patient lives with her family and has not been critically ill or admitted to the hospital since delivery. She receives nutritional supplement (Infantrini^{TM}) three times a day in addition to her

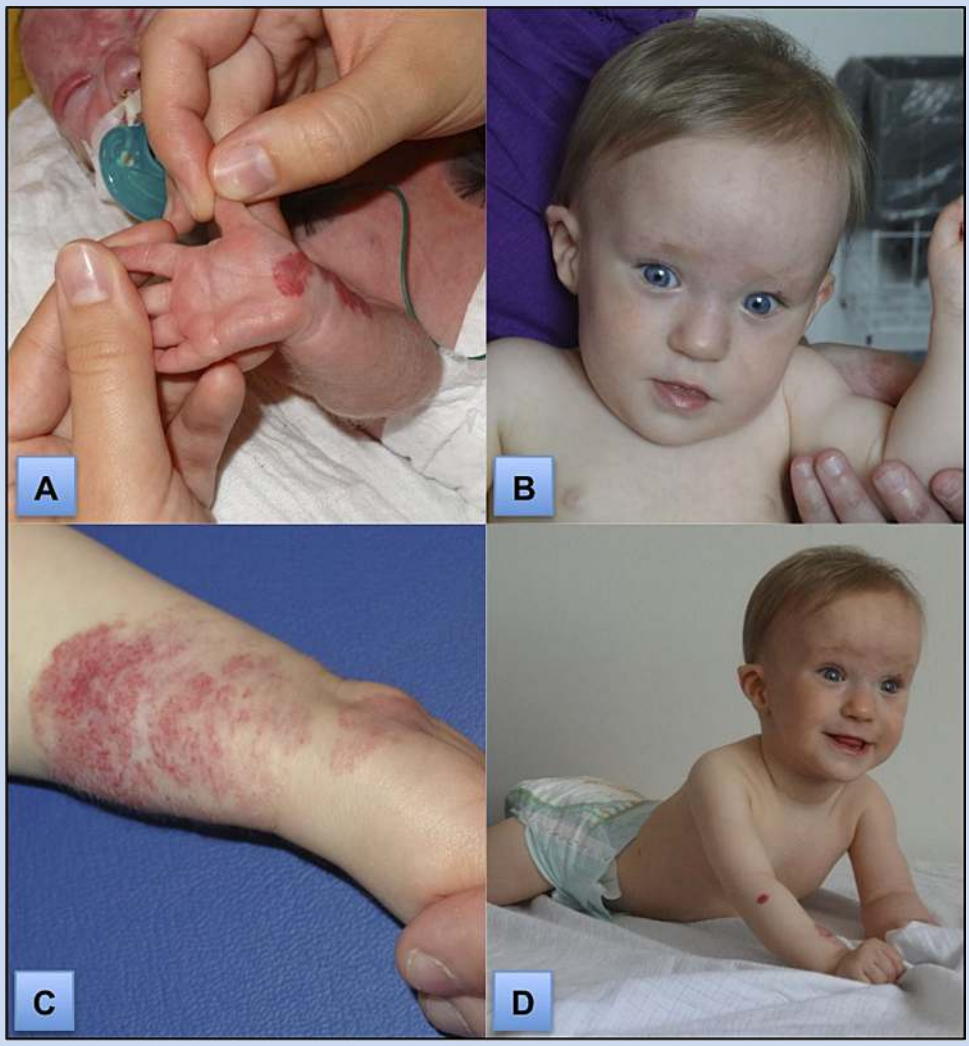

FIG. 1. A: Patient at the age of 3 weeks. Note the hemangioma on the right arm and the port wine stain on the right frontal region; B: Patient at the age of 11 months, picture taken at a follow-up appointment at the department for Clinical Genetics. C: Right arm of the patient at the age of 11 months showing the regression tendency of the hemangioma under propanolol therapy. D: Patient at the age of 11 months.

TABLE I. Reported Dermatologic Features in Children with Trisomy 13 Mosaicism

				Major congenital anomalies reported												
Year	Author	Cutaneous manifestation	Sex	Atypical facial features	Cleft lip/ palate	Eye anomaly	Ear anomaly	Brain/ CNS anomaly	Developmental delay	Cardiovascular anomaly	Genitourinary anomaly	Intestinal anomaly	Limb anomaly	Polydactyly	Respiratory anomaly	Mosaicism
2015	Wieser et al.	Hemangioma Port wine stain	f				X		X							Blood: 24%
2014	González-del Angel et al.	Pigmentary abnormalities Hemangioma	f	X		X	X		X		X		X			Blood: 36% Fibroblasts light skin: 0.8% Fibroblasts dark skin: 92%
2013	Pachajoa and Meza Escobar	Hemangioma	f	X	X											Blood: 20%
2011	Aypar et al.	Hemangioma	f	X			X								X	Blood: 42%
2009	Griffith et al.	Teleangiectatic nevus	m	X		X	X			X	X		X	X		Blood: 40% Skin: 45%
2009	Griffith et al.	Teleangiectatic nevus	m	X	X		X				X	X	X		X	Cartilage: 72%
2007	Di Giacomo et al.	Hemangioma	f						X							Blood: 16% Skin: 5% Urinary cells: 23% Amniocytes: 80%
2005	Yamanouchi et al.	Hemangioma	m					X		X	X	X				Blood: 73%
2002	Yakinci et al.	Hypomelanosis of Ito	m	X				X	X		X	X		X		Blood: 54%
2003	Ronger et al.	Hypomelanosis of Ito	f	X			X	X	X			X				Blood: 3% Skin: 12% (only hypopigmented area)
2001	Schepis et al.	Pigmentary abnormalities & Phylloid hypomelanosis	f	X			X	X	X				X			Blood: 70% Skin: 25%
1992	Ohashi et al.	Pigmentary abnormalities	m	X		X		X	X							Blood: 9% Skin: 61% normally pigmented area 71% hyperpigmented area
1997	Horn et al.	Phylloid hypomelanosis	f	X		X	X		X				X			Blood: 4%, 10% Skin: 7%
1988	Sperber and Honoré	Skin redundency	f	X			X						X			Placental chorionic palate: 4%
1979	Fryns et al.	Hemangioma	f	X				X	X		X		X	X		Blood: 25% Skin: 56%
1976	Beer et al.	Hemangioma	m	X	X				X	X	X					Blood: 10%
1975	Loevy et al.	Hemangioma	m		X				X	X						Mosaic[a]
1975	Loevy et al.	Hemangioma	f	X	X	X			X				X			Mosaic[a]
1974	Schinzel et al.	Skin redundency	f	X		X	X	X		X	X		X			Blood 24% Skin 34%
1970	Taylor et al.	Skin redundency	f	X	X		X	X	X	X	X	X	X	X		76% (translocation trisomy) with other 22% having a D chromosome with a terminal centrosome
1967	Wilson and Melnyk	Hemangioma	f	X	X	X		X	X		X		X			Blood: 41% Skin 100% Bone marrow: 33%
1965	Bain et al.	Port wine stain	f	X	X			X		X	X		X			Thymus: 26% Spleen: 64%
1965	Bain et al.	Skin redundancy	m	X			X			X			X			Blood: 27%

TABLE I. (*Continued*)

Year	Author	Cutaneous manifestation	Sex	Major congenital anomalies reported										Mosaicism
				Atypical facial features	Cleft lip/palate	Eye anomaly	Ear anomaly	Brain/CNS anomaly	Developmental delay	Cardiovascular anomaly	Genitourinary anomaly	Intestinal anomaly	Limb anomaly	Polydactyly	Respiratory anomaly	
1963	Beçak et al.	Pigmentary abnormaliets	m					X	X							30%
1963	Beçak et al.	Pigmentary abnormaliets	m					X	X							25%
1963	Therman et al.	Hemangioma Port wine stain Teleangiectatic nevus	f	X	X	X			X			X				Blood: 55% Skin: 62% Bone marrow: 36%
1962	Warkanay et. al.	Skin redundency	m	X	X	X	X	X	X		X		X			Blood: 80%, 62% Skin: 56%

Abbreviations: f = female, m = male.
[a]not stated by the authors.

normal meals and continues to grow along the 3rd centile in both weight and height. At 11 months, the patient crawls appropriately, is reactive to her mother and smiles when tended to. She plays properly, sits without help and is able to switch from a crawling into a sitting position by herself (see Fig. 1B and D). The patient forms two syllable words like "dada" and "baba." She receives early support by physiotherapists twice a week. The family requires no home nurse or psychological counseling.

DISCUSSION

To our knowledge, this is the second reported case of a patient who has trisomy 13 mosaicism with defects restricted to cutaneous manifestations. Though suffering from port wine stains and hemangiomas along with mild dysmorphic features, our patient had no evident structural defects.

Due to the severe cutaneous manifestations with all other clinical testing being negative, the genetic background was hiding behind the phenotype. Eventually, the parents consented to karyotyping which revealed mosaicism with 24% of the cells being trisomic. Compared to other patients with trisomy 13 mosaicism and skin involvement, our patient reveals a very mild phenotype. It is important to note that the proportion of trisomic cells vary considerably between different tissues and one cannot correlate mosaic proportions in lymphocytes with the clinical picture (see Table I).

As the severe dermatologic features were the ultimate reason for genetic testing, we collected data on dermatologic features in trisomy 13 mosaicism to provide physicians and parents with additional information and to aid family counseling.

In 2009, Griffith and co-workers published a very detailed review of 49 patients with trisomy 13 mosaicism. Since then four new cases have been published [Chen et al., 2009; Aypar et al., 2011; Pachajoa and Meza Escobar, 2013; González-del Angel et al., 2014]. Of the 53 clinical reports, along with our patient, dermatologic features were explicitly described in 27 patients (Table I).

Hemangiomas were the most common reported feature and were found in 44% of patients with cutaneous manifestations (nine female and three male). Apart from our patient, one other patient was described having both port wine stains and hemangiomas [Therman et al., 1963].

The presence of teleangectatic nevi were reported in another three patients [Therman et al., 1963; Griffith et al., 2009 (two cases)].

Reviewing the literature dating back to 1962, it is important to note that "hemangioma" was the commonly used term for any vascular anomaly. This suggests that not all were appropriately classified according to the current understanding [Griffith et al., 2009; Hoeger and Colmenero, 2014]. Hemangiomas are vascular tumors in infancy that are characterized by their dynamics of growth and the potential to regress spontaneously. In contrast, vascular malformations are usually present at birth and do not show postnatal tendency to grow or involute. [Cohen, 2006; Hoeger and Colmenero, 2014]. Apart from the bias, hemangiomas account for a high proportion of all dermatologic symptoms reported in trisomy 13 mosaicism and warrant further investigation with a more precise classification.

TABLE II. A Summary of the Most Common Observed Dermatologic Features in Trisomy 13 Mosaicism

Dermatologic feature	Total	%	Definition
Hemangioma	12/27	44.4	An infantile vascular tumor that is mostly not present at birth, but is characterized by a rapid postnatal growth followed by slow involution [Hoeger and Colmenero, 2014].
Port wine stain	3/27	11.1	A capillary malformation that tends to persist throughout childhood and darkens and thickens in adulthood [Cohen, 2013].
Teleangiectatic nevus	3/27	11.1	An erythematous macula that forms branches from a central point of the lesion resembling the legs of a spider [Donsky, 1968].
Phylloid hypomelanosis	2/27	7.4	A pattern of hypopigmentation with multiple oval to round lesions resembling leafs. The term phylloid is derived from the Greek (phyllon = leaf and eidos = form) [Happle, 2001].
Hypomelanosis of Ito	2/27	7.4	A cutaneous symptom with hypopigmented lesions following the Blaschko lines [Happle, 2011].
Pigmentary abnormalities	6/27	22.2	Abnormal patterns of pigmentation, either hypopigmentation or hyperpigmentation.
Skin redundency	5/27	18.5	The presence of extra skin.

There was only one other patient [Di Giacomo et al., 2007] who had hemangiomas without structural defects in other organ systems. In contrast to our patient's case, the mother had an amniocentesis, which helped to establish a much earlier diagnosis [Di Giacomo et al., 2007].

Although not present in our patient, pigmentation changes have been reported in trisomy 13 mosaicism as well: two reports of hypomelanosis of Ito, a cutaneous manifestation associated with an underlying mosaicism or chimerism, have been found [Yakinci et al., 2002; Ronger et al., 2003]. It is characterized by a pattern of hypopigmentation along the Blaschko lines. This is in contrast to phylloid hypomelanosis, which does not follow the course of the Blaschko lines and might be associated with trisomy 13 and its mosaic forms as well [Happle, 2001]. Other poor defined patterns of hyperpigemantation were observed in four cases [Beçak et al., 1963 (two cases); Ohashi et al., 1992; Schepis et al., 2001].

For an overview of dermatologic features and the observed incidence in trisomy 13 mosaicism, see Table II.

In conclusion, dermatologic features are, although not representing a homogeneous pattern, commonly described in trisomy 13 mosaicism. In some cases, skin involvement, presenting either as vascular anomaly or pigmentary changes, may be the final clue to an underlying genetic syndrome.

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