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Case Report

A novel association of an uncommon pigmentation pattern: coexistence of cutis tricolor with intracranial teratoma and holoprosencephaly

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Abstract

Cutis tricolor was first described in a 17-year-old male patient by Happle et al. as a rare coexistence of circumscribed hyperpigmentation and hypopigmentation close to each other on a background of normally pigmented skin. Cutis tricolor has been reported as an isolated cutaneous finding or in various associations. To the best of our knowledge, cutis tricolor in association with teratoma and holoprosencephaly has not been reported in the literature. Herein, we report a male patient who presented with a teratoma and a combination of whorl-like hypopigmentation together with hyperpigmented patches adjacent to each other on intermediately pigmented skin. This case report supports the view that cutis tricolor may be a marker of an underlying neurological abnormality.

Keywords: cutis tricolor, holoprosencephaly, Ruggieri-Happle syndrome, teratoma

Introduction

Since the first description of cutis tricolor [1] there have been many isolated case reports about this peculiar combination of pigmentation, which is now believed to be a result of the "twin-spotting phenomenon" [1-5]. Nicita et al. emphasized in their article [5] that cutis tricolor is not a single entity. It has been reported in association with various abnormalities or as an isolated cutaneous finding (Table 1 [1-18]). Its coexistence with facial dysmorphism, neurological and behavioral abnormalities and skeletal dysplasia has been defined as Ruggieri-Happle syndrome [2-5]. We report a novel case of cutis tricolor without the dysmorphic features or skeletal abnormalities suggestive of this syndrome. The unique presentation of our case with teratoma and holoprosencephaly highlights the hypothesis that neurological abnormalities can accompany cutis tricolor even when the characteristic syndromic findings are absent.

Case synopsis

Our patient, now 6 years old, was born from non-consanguineous healthy parents after an uneventful pregnancy and a spontaneous delivery. Birth weight was 2400 g (< 3rd percentile) and birth length was 42 cm (< 3rd percentile). He had one healthy 7-year-old sister. At the age of 6 months, he presented with inability to sit with support and hold his head up. Cranial magnetic resonance imaging (MRI) revealed holoprosencephaly and a large mass in the frontal lobe. At the age of 1 year, the mass was surgically resected and the histopathology was consistent with teratoma. 6 months later, residual lesions were noted on cranial MRI. At the age of 2 years, the tumor was completely resected via a subfrontal approach (Figure 1). He had to be

hospitalized several times for severe hyponatremia related to diabetes insipidus, requiring treatment with vasopressin analogues. In addition, he was treated with phenobarbital and carbamazepine for epileptic seizures. During follow-up he was not able to catch up in developmental milestones. Psychomotor and language development were markedly delayed.

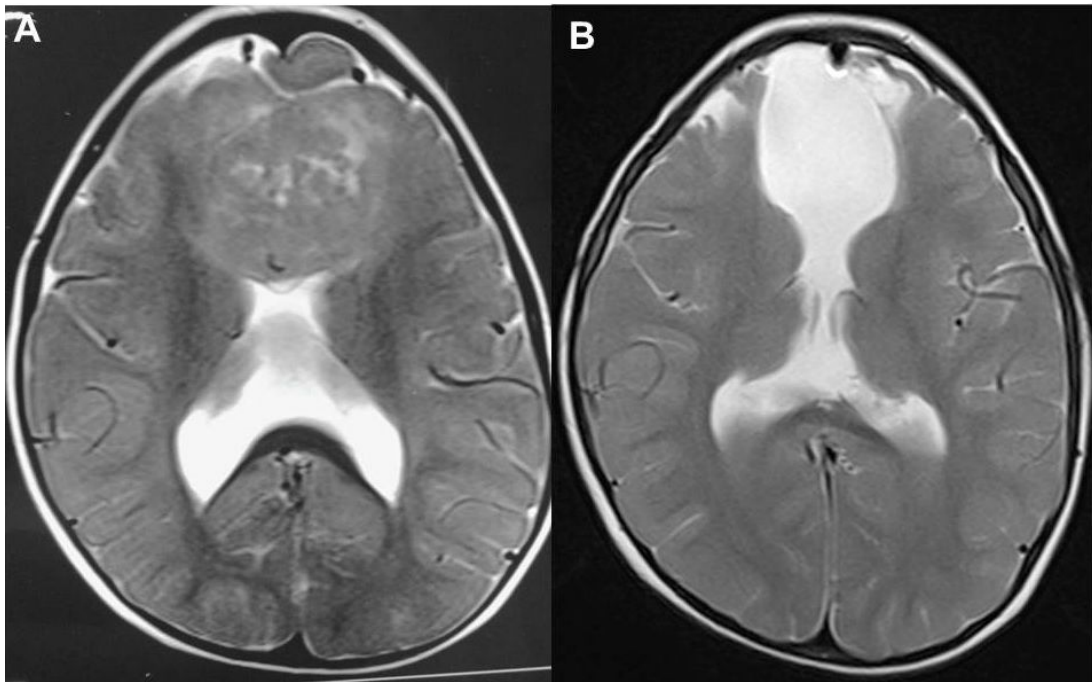


Figure 1. (A) Preoperative MRI of the teratoma. (B) Postoperative MRI.

At the age of 3 years, he was consulted for peculiar skin pigmentation. On physical examination, hypopigmented macules occupying a large area on the abdomen were noted. On the anterior side, hypopigmented macules reached the subcostal region superiorly. On the right side, they extended from the abdomen to the back, following the lines of Blaschko. Hypopigmented lesions showed sharp midline demarcation on the posterior trunk. Surrounded by this area of hypopigmentation, there were three circumscribed block-like light brown patches on the right lower abdomen. Interspersed within these areas of hypo- and hyperpigmentation, areas of normally pigmented skin were also noted (Figure 2, 3). In addition, a 2x2 cm brown patch and two smaller hypochromic patches were present in a background of normally pigmented skin on the anterior thigh. These pigmentary features were present since birth and grew proportionately to the patient's size. No additional findings that might be suggestive of tuberous sclerosis or neurofibromatosis were found on physical examination.



Figure 2. Hyperpigmented, hypopigmented and normally pigmented skin in close proximity on the abdomen



Figure 3. Small hypopigmented macules extending to the back in a curvilinear pattern and scattered small hypopigmented macules in their periphery in the right lumbar region

The diagnosis of cutis tricolor was considered. The parents and sister did not have any similar pigmentary abnormalities. No change was observed in the size and shape of the dermatological findings during the 3 year follow-up period, except for slight enlargement proportionate to the body size.

Discussion

Cutis tricolor is described as the coexistence of circumscribed hyperpigmentation and hypopigmentation in close proximity to each other on a background of normally pigmented skin [1-3]. The hypothesized genetic explanation is post-zygotic crossing-over ("*twin-spotting phenomenon*"), which gives rise to two different homozygous clones from a doubly heterozygous embryo during embryogenesis [5, 6, 12]. Cutis tricolor can appear in different phenotypes, which are explained by the timing of crossing-over and different types of didymosis.

Various neurological manifestations have been described in patients with cutis tricolor. In the largest case series (comprising 14 of the 30 published cases of cutis tricolor) [10] the frequency of neurological manifestations was found to be 71.4 %. In the same series neurological manifestations were found to accompany all cases (100 %) of syndromic cutis tricolor (i.e., Ruggieri-Happle syndrome), whereas no neurological abnormalities were found in cases with isolated skin manifestations. The most common neurological manifestations were found to be mild-to-severe mental retardation, language delay, epilepsy, behavioral disturbances and EEG abnormalities. No intracranial tumor was reported in this series [10].

Aside from this large series, other neurological findings were also reported (Table 1). The first case defined as cutis tricolor parvimaclata [13] presented with a large oligodendroglioma involving the left frontal lobe. In the two cases of cutis tricolor affected by the ring chromosome 15 syndrome, microcephaly was attributed to the underlying genetic disorder [14]. Similarly, neurological manifestations could be explained by ataxia-telangiectasia in the case report by Khumalo et al [17]. In a more recent case report [15] enlarging subcortical and periventricular mass lesions were found on cranial MRI of a 3-year-old girl with a disseminated presentation of cutis tricolor. The authors used further imaging techniques and concluded that these lesions suggested tumoral growth, but couldn't prove their diagnosis because they weren't able to biopsy the lesions owing to their location.

Our case did not have the dysmorphic features or skeletal abnormalities suggestive of Ruggieri-Happle syndrome. We could not say with certainty whether the neurodevelopmental anomaly (holoprosencephaly), seizures, psychomotor retardation, and delayed language development of our patient were related to an incomplete form of this syndrome or because of the teratoma and its complications. Because our case did not display the other manifestations of Ruggieri-Happle syndrome, we preferred not to categorize it under the syndromic cases (Table 1). Our patient is also different from the purely cutaneous cases, so a proper classification seems difficult. Like the authors, who reported the only proven association of cutis tricolor with an

intracranial tumor before our case [13], we also think that a causal relationship between the cutaneous presentation and the cerebral tumor is likely. This report further supports the view by Lionetti et al. [10] that cutis tricolor may be a marker of underlying neurological involvement. Patients with cutis tricolor should be closely followed-up for neurological abnormality and referred accordingly if there should be any sign or symptom suggesting neurological involvement.

Table 1. Characteristics of the published cases of cutis tricolor with reference numbers and years (based on the classification proposed in the references [5], [10] and [11]).

	Reference number	Reference year	Age, gender	Associated anomalies	Distinguishing feature
Cutis tricolor as an isolated skin manifestation	2	2000	11, m	Mild scoliosis not associated with skeletal dysplasia or other bone abnormalities, developed cataract at the age of 15 years [4].	
	6	2003	12, f	None	First familial cases (sisters)
			15, f	Unilateral breast hypoplasia	
	7	2004	33, m	None	
	8	2005	4, f	None	
			35, f		
	9	2008	16, m	None	
	10, 11	2010	10, f	Brushy eyebrows	Largest case series published to date
			17, m	None	
22, f			Pectus excavatum, prominent chin, thick lips, brushy eyebrows		
12	2013	13, f	None		
Our Case	2014	6, m	Teratoma, holoprosencephaly, seizures, psychomotor retardation, delayed language development, diabetes insipidus		
In the context of Ruggieri–Happle syndrome	1	1997	17, m	Neurological findings: developmental delay, mental retardation, language delay, behavioral disturbances,	First published case
	2	2000	6, m	seizures, muscular weakness, poor coordination,	
	10, 11	2003	11, f	hypotonia, nystagmus, walking imbalance, EEG abnormalities, hearing defect [5, 10]	Largest case series published to date
			2, f	Neuroimaging findings: hypoplasia of the corpus callosum, dilatation of lateral ventricles, white matter abnormalities [5]	
			2, m		
			5, f		
			8, m		
			11, m		
			14, f		
14, m	Ophthalmological findings: strabismus, hyperopia, astigmatism [1], cataract [4]				
5	2012	10, f	Skeletal findings: scoliosis, kyphosis, prognathism, leg length discrepancy, clinodactyly, pectus excavatum, vertebral scalloping, rib anomalies, small skull [11] Facial abnormalities: coarse face, hypertelorism, facial asymmetry, thick lips, brushy eyebrows, prominent chin, deep nasal bridge, epicanthus [10, 12] Other abnormalities: ventricular septal defect [1], cardiac ventricle anomalies [12]		
As a distinct phenotype first defined by Larralde et al. [13] and named cutis tricolor parvimaclata	13	2005	11, f	Oligodendroglioma, seizures, small teeth, enamel pitting, periungual fibromas	First description of cutis tricolor parvimaclata
	14	2011	3, f	Growth retardation, microcephaly, hypertelorism, clinodactyly of the fifth fingers, triangular facies	Both patients affected by ring chromosome 15 syndrome
			7 months, f		
15	2012	3, f	Developmental delay, dysmorphic face, EEG abnormalities, subcortical and periventricular mass lesions in cranial MRI (tumors?)		
In association with order skin disorders	16	1997	8, f	Recurrent episodes of pneumonia	Coexistence with phacomatosis pigmentovascularis
	17	2001	6, f	Cerebellar ataxia, posterior fossa atrophy, low serum immunoglobulin A, raised levels of alpha-fetoprotein	Coexistence with ataxia-telangiectasia, but no oculocutaneous telangiectases present
	18	2008	8, m	Developmental delay, dysmorphic face, mental retardation, skeletal abnormalities, multiple subcutaneous aneurysmatic nodules	Coexistence with cutis marmorata telangiectatica congenita

(EEG: electroencephalography, f: female, m: male, MRI: magnetic resonance imaging).

¹A complete list of extracutaneous features of Ruggieri-Happle syndrome is not intended. For a complete list please consult the references [5], [10], [11] and [12].

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