

SHORT COMMUNICATION

Congenital Linear Streaks on the Face and Neck and Microphthalmia in an Infant Girl

Nicolas Kluger^{1,2}, Antoine Bouissou³, Laurent Tautin³, Jacques Puechberty⁴ and Olivier Dereure^{2*}

¹Department of Dermatology, Allergy and Venereology, Institute of Clinical Medicine, Skin and Allergies Hospital, University of Helsinki, Helsinki, Finland, Departments of ²Dermatology, and ⁴Medical Genetics, INSERM U1058, University of Montpellier I, Hôpital Saint-Eloi, 80 avenue Augustin Fliche, FR-34295 Montpellier Cedex 5, and ³Neonatal Intensive Care Unit, Territorial Hospital Centre, Nouméa, New Caledonia, France. *E-mail: o-dereure@chu-montpellier.fr Accepted May 13, 2013; Epub ahead of print Oct 3, 2013

Congenital skin atrophic lesions are infrequent but may reveal general, most particularly genetic conditions. The dermatologist is at the front line for initial diagnosis and subsequent management that usually includes a multi-disciplinary approach along with genetic counselling.

CASE REPORT

A 3-month-old girl was evaluated for congenital depressed lesions on the right hemiface, neck and hand. She was born at full term by caesarean section with normal birth weight, height and head circumference. Family history was unremarkable. The non-consanguineous parents already had a healthy daughter. Dermatological examination displayed markedly depressed, sharply demarcated, red-pink streaks, predominantly affecting the right side of the face (mainly cheek and chin) and the neck (Fig. 1), along with similar, although less marked lesions on the left cheek, the left side of the neck and the right hand following Blaschko's lines. She showed small-sized or aplastic fingernails on the right hand. Ophthalmologic evaluation revealed right microphthalmia, aniridia and sclerocornea. Physical examination was otherwise normal. Chest X-ray, transfontanelar, heart and abdominal ultrasound imaging were unremarkable. A diagnosis of Microphthalmia with Linear Skin defects (MLS; MIM 309801) syndrome, also known as MIDAS (Microphthalmia, Dermal Aplasia and Sclerocornea) syndrome was made. Routine karyotyping was unremarkable in the patient. After obtaining parental consent, a peripheral blood sample of the patient was further investigated by fluorescence *in situ* hybridization (FISH) using a panel of molecular probes spanning the terminal region of the short arm of the X chromosome (Xpter, CEP-X, Kallmann, RP1-167A22, RP11-120D5, RP11-450G14 and RP11-163I1 probes). This analysis revealed a terminal deletion of at least 11.5 Mb on the short arm of one of the X chromosomes, with the karyotype 46,X,del(X)(p22.2). More specifically, hybridisation with probe RP11-163I1, covering the *HCCS* gene, revealed no signal on the deleted X chromosome. FISH analysis of the parents and relatives

disclosed the same Xp deletion in the mother of the patient who was free of any clinical sign of MLS. The maternal grandmother could not be investigated as she was deceased. At the age of 4 months, the patient developed tachycardia and limited signs of heart failure with multiple ectopic atrial tachycardia-inducing foci that were efficiently controlled by amiodarone. The right eye malformation was surgically corrected with an ocular prosthesis and a favourable outcome. Subsequent psychological and motor development was unremarkable.

DISCUSSION

MLS/MIDAS syndrome is a rare X-linked dominant neurocutaneous disease with *in utero* male lethality. Patients present with congenital linear atrophic streaks affecting face and neck associated with various ocular abnormalities (microphthalmia, anophthalmia, sclerocornea, microcornea, aniridia, cataract, etc) (1–5). Additional manifestations may include developmental delay and short stature along with heart, central nervous system and genitourinary tract structural or functional abnormalities (5). MLS is related to a variety of chromosomal aberrations leading to segmental monosomy of the Xp22.2 region (1–6). Heterozygous mutations in the *HCCS* gene encoding the holocytochrome *c*-type synthase turned out to underlie MLS syndrome (7). Recently, mutations in another X-chromosomal gene, *COX7B*, encoding a subunit of the cytochrome *c* oxidase, have been detected in 3 patients with MLS syndrome (8). Both *HCCS* and *COX7B* are involved in mitochondrial respiration and apoptosis (7–9). Exceptional cases of male infants with MLS phenotype have been reported (10, 11). A high degree of intrafamilial



Fig. 1. Congenital sharply demarcated, depressed red-pink streaks following Blaschko's lines, mainly on the right side of the face and neck of the infant girl.

phenotypic variability has already been emphasized in this syndrome, even between identical twins (2, 4, 10) and this tendency is very strikingly illustrated by our observation with complete absence of clinical features in the mother, carrying the same genetic abnormality as her affected daughter. A postzygotic *de novo* mutation leading to somatic mosaicism might be one factor protecting from an MLS phenotype in females with a terminal Xp deletion or a sequence-level *HCCS* mutation. Alternatively, non-random X-inactivation in favour of the active wild-type X chromosome in the early embryo might be even more crucial for the absence of any obvious clinical feature in these females (3).

The authors declare no conflict of interest.

REFERENCES

1. al-Gazali LI, Mueller RF, Caine A, Antoniou A, McCartney A, Fitchett M, Dennis NR. Two 46,XX,t(X; Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3. *J Med Genet* 1990; 27: 59–63.
2. Allanson J, Richter S. Linear skin defects and congenital microphthalmia: a new syndrome at Xp22.2. *J Med Genet* 1991; 28: 143–144.
3. Wimplinger I, Rauch A, Orth U, Schwarzer U, Trautmann U, Kutsche K. Mother and daughter with a terminal Xp deletion: implication of chromosomal mosaicism and X-inactivation in the high clinical variability of the microphthalmia with linear skin defects (MLS) syndrome. *Eur J Med Genet* 2007; 50: 421–431.
4. Morleo M, Franco B. Dosage compensation of the mammalian X chromosome influences the phenotypic variability of X-linked dominant male-lethal disorders. *J Med Genet* 2008; 45: 401–408.
5. Sharma VM, Ruiz de Luzuriaga AM, Waggoner D, Greenwald M, Stein SL. Microphthalmia with linear skin defects: a case report and review. *Pediatr Dermatol* 2008; 25: 548–552.
6. Zvulunov A, Kachko L, Manor E, Shinwell E, Carmi R. Reticulolinear aplasia cutis congenita of the face and neck: a distinctive cutaneous manifestation in several syndromes linked to Xp22. *Br J Dermatol* 1998; 138: 1046–1052.
7. Wimplinger I, Morleo M, Rosenberger G, Iaconis D, Orth U, Meinecke P, et al. Mutations of the mitochondrial holocytochrome c-type synthase in X-linked dominant microphthalmia with linear skin defects syndrome. *Am J Hum Genet* 2006; 79: 878–889.
8. Indrieri A, Van Rahden VA, Tiranti V, Morleo M, Iaconis D, Tammaro R, et al. Mutations in *COX7B* cause microphthalmia with linear skin lesions, an unconventional mitochondrial disease. *Am J Hum Genet* 2012; 91: 942–949.
9. Indrieri A, Conte I, Chesi G, Romano A, Quartararo J, Tatè R, et al. The impairment of *HCCS* leads to MLS syndrome by activating a non-canonical cell death pathway in the brain and eyes. *EMBO Mol Med* 2013; 5: 280–293.
10. Anguiano A, Yang X, Felix JK, Hoo JJ. Twin brothers with MIDAS syndrome and XX karyotype. *Am J Med Genet A* 2003; 119: 47–49.
11. Kutsche K, Werner W, Bartsch O, von der Wense A, Meinecke P, Gal A. Microphthalmia with linear skin defects syndrome (MLS): a male with a mosaic paracentric inversion of Xp. *Cytogenet Genome Res* 2002; 99: 297–302.