Restrictive dermopathy: A baby with taut skin, facial dysmorphism, joint contractures, and pulmonary hypoplasia

Wei Di Ng, MBBS, MMED (Paed),a Ai Ling Koh, MB, ChB, MRCPCH, MMED (Paed),b Mark Jean Aan Koh, MBBS, DIP, MRCPCH, Dip Pract Derm (UK), DipDermatopathology (ICDP-UEMS, Austria),c and Juin Yee Kong, MD (Jefferson, FAAP, Diplomate of American Board of Pediatrics) (Peds) (Neonatology)a

Key words: fetal akinesia deformation sequence; laminopathy; restrictive dermopathy; ZMPSTE24.

INTRODUCTION
Restrictive dermopathy (RD) is a rare, lethal, and genetically heterogeneous congenital laminopathy. It is usually diagnosed postnatally by the presence of tight adherent skin with superficial vasculature, distinctive facies, joint contractures, and pulmonary hypoplasia. Prenatal diagnosis by chorionic villus sampling or amniocentesis and providing genetic advice to affected families play an important role. To our knowledge, we report the first case of genetically confirmed RD in Southeast Asia.

CASE PRESENTATION
Our patient is the first child of non-consanguineous Chinese parents with an unremarkable family history. Her mother presented at 32 weeks gestation with preterm premature rupture of membranes. Antenatal ultrasound scans then showed fetal growth restriction, but maternal TORCH (Toxoplasmosis, Others, Rubella, Cytomegalovirus, Herpes simplex) serologies and autoimmune screen were negative. There was no polyhydramnios.

The baby girl was born at 33 weeks' gestation and had severe respiratory distress at birth. She weighed 1540 g (14th centile) with a length of 43 cm (49th centile) and a head circumference of 29 cm (24th centile).

Physical examination showed generalized tight and shiny skin with prominent superficial blood vessels. She had widened sutures, a large fontanelle, and matted hair. Facial dysmorphisms included absent eyelashes, ectropion with conjunctival chemosis, low-set ears, small, pinched nose, eclabium, microstomia, and micrognathia. Multiple joint contractures with restricted limb movements were prominent (Fig 1).

Chest X-ray showed a bell-shaped chest and small lung volumes. The clavicles were dysplastic, and there was a suggestion of overtubulation of the humerus (Fig 2).

Given the clinical presentation at birth of a baby with tight skin associated with ectropion and eclabium, differential diagnoses included congenital ichthyosis; however, the baby did not show the classical erythema and scaling of congenital ichthyosis; however, the baby did not show the classical erythema and scaling of congenital ichthyosis. The presence of other facial dysmorphisms and skeletal and pulmonary abnormalities were also not in keeping.

She was referred to a pediatric dermatologist and geneticist. Skin biopsy performed on day 4 of life showed flattened epidermis and attenuated rete pegs, markedly thin dermis with compact collagen bundles oriented parallel to the surface, reduced elastic fibers, thickened subcutaneous fat, and underdeveloped skin appendages (Fig 3, A-C).
Exome-based trio sequencing gene panel (PreventionGenetics) was performed on the baby's and parents' blood samples, which showed that the infant had a maternally-inherited heterozygous frameshift variant (c.1085dupT(p.Leu362Phefs*19)) and a paternally-inherited heterozygous splice site variant (c.1059-1G>T) in ZMPSTE24.

Treatment and outcome

Supportive treatment consisted of emollients, nursing in a humidified incubator, strict hand hygiene, eye lubricants, parenteral nutrition, broad-spectrum antibiotics, and analgesia. Ventilation was challenging because of pulmonary hypoplasia, restricted chest wall movements, and persistent pulmonary hypertension of the newborn. Her respiratory condition deteriorated, and she demised on day 11 of life.

DISCUSSION

Witt et al. coined the term “restrictive dermopathy” in 1986 and hypothesized that the rigid skin severely restricts fetal movements, breathing, sucking, and swallowing, leading to polyhydramnios, facial dysmorphisms, joint contractures, and pulmonary hypoplasia. This phenomenon is known as fetal akinesia/hypokinesia deformation sequence. RD was later identified as a laminopathy in 2004. To date, almost 120 cases have been reported world-wide.

The main cause of RD is an autosomal recessive gene defect of the ZMPSTE24 gene. The mutations identified-to-date lead to a loss of function of the zinc-metalloproteinase ZMPSTE24. As a result, the nuclear membrane precursor protein prelamin A cannot be completely processed to form mature lamin A. This leads to an increase in the intermediate stage farnesylated prelamin A, which accumulates at the nuclear rim, causes misshapen nuclei and intrinsic toxicity to cells.2-6

There are characteristic skin, craniofacial, pulmonary, and skeletal abnormalities in RD. The skin is shiny, taut, and easily sheared at the skin flexures. There is also prominent superficial vasculature. The face is often expressionless with sparse or absent eyelashes and eyebrows, a small, pinched nose, retromicrognathia, and an “O”-shaped mouth. The lack of breathing movements and narrow, tight chest wall result in pulmonary hypoplasia. Skeletal defects include splayed sutures, large fontanelle, dysplastic clavicles, overtubulated long bones, ribbon-like ribs, joint contractures, and rocker-bottom feet.7

Histologic features in RD are a thin dermis composed of dense, horizontally arranged collagen bundles, flat dermoepidermal junction with a straight lower border, complete lack of rete ridges, and markedly reduced elastic fibers. These features were well-captured on our skin biopsy samples. Other features include epidermal hyperkeratosis, parakeratosis, epidermal acanthosis, coarse keratohyaline granules, intraepidermal and subepidermal bullae, paucity of and poorly developed skin appendages and increased subcutaneous fat.8

Our patient had the biallelic variants c.1085dupT (p.Leu362Phefs*19) and c.1059+1G>T detected in ZMPSTE24. The c.1085dupT sequence change is predicted to result in a premature translational stop signal (p.Leu362Phefs*19) leading to absent or disrupted protein production. This variant has been reported in other individuals with RD.9-4 Although the splice site variant c.1059+1G>T has not been reported in the literature, it is predicted to abolish the
consensus splice donor site near the junction of exon 8 and intron 8 in ZMPSTE24 and is expected to be pathogenic. These molecular findings confirmed RD in our patient.

The earliest manifestations of RD are in the late second or early third trimester. Affected fetuses are often growth-restricted and born moderate-to-late preterm. There may be a family history of consanguinity. The mother may present with preterm premature rupture of the membranes or decreased fetal movements. Antenatal diagnosis is challenging because ultrasound findings of polyhydramnios, spontaneous complete chorionicamniotic membrane separation, decreased fetal movements, joint contractures, or “O”-shaped mouth are nonspecific late findings. Skin biopsy can be performed by a maternal-fetal medicine specialist at centers equipped with skills and resources after 22 weeks gestation as typical features develop after this time. Placental hyperplasia and a short umbilical cord may be noticed at delivery. Prenatal testing via chorionic villus sampling or amniocentesis remains the most reliable method for antenatal diagnosis of at-risk pregnancies.

Affected patients usually have pulmonary hypoplasia and inspiratory dysfunction because of thoracic stiffness. Respiratory insufficiency is the most common cause of death. The longest reported survival was 120 days. The residual activity of ZMPSTE24-encoded zinc metalloproteinase appears to correlate with disease severity and duration of survival. Knowledge of the histopathology findings and poor prognosis associated with this condition changed our management approach from active intensive care to palliative care.

Conflicts of interest
None disclosed.

REFERENCES
1. Witt DR, Hayden MR, Holbrook KA, Dale BA, Baldwin VJ, Taylor GP. Restrictive dermopathy: a newly recognized autosomal recessive skin dysplasia. Am J Med Genet. 1986;24: 631-648.
2. Navarro CL, De Sandre-Giovannoli A, Bernard R, et al. Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. Hum Mol Genet. 2004;13:2493-2503.
3. Navarro CL, Cadinanos J, De Sandre-Giovannoli A, et al. Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of lamin A precursors. Hum Mol Genet. 2005;14:1503-1513.
4. Moulson CL, Go G, Gardner JM, et al. Homozygous and compound heterozygous mutations in ZMPSTE24 cause the laminopathy restrictive dermopathy. J Invest Dermatol. 2005; 125:913-919. https://doi.org/10.1111/j.0022-202X.2005.23846.x
5. Navarro CL, Esteves-Vieira V, Courrier S, et al. New ZMPSTE24 (FACE1) mutations in patients affected with restrictive dermopathy or related progeroid syndromes and mutation update. Eur J Hum Genet. 2014;22(8):1002-1011. https://doi.org/10.1038/ejhg.2013.258
6. Broers JL, Ramaekers FC, Bonne G, Yaou RB, Hutchison CJ. Nuclear lamins: laminopathies and their role in premature ageing. Physiol Rev. 2006;86:967-1008.
7. Wesche WA, Cutlan RT, Khare V, Chesney T, Shanklin D. Restrictive dermopathy: report of a case and review of the literature. J Cutan Pathol. 2001;28:211-218.
8. Pierard-Franchimont C, Pierard GE, Hermans-Le T, et al. Dermatopathological aspects of restrictive dermopathy. J Pathol. 1992;167:223-238.
9. Chen M, Kuo HH, Huang YC, et al. A case of restrictive dermopathy with complete chorionicamniotic membrane separation caused by a novel homozygous nonsense mutation in the ZMPSTE24 gene. Am J Med Genet A. 2009;149A:1550-1554.
10. Van Hoestenberghe M, Legius E, Vandevoorde W, et al. Restrictive dermopathy with distinct morphological abnormalities. Am J Med Genet. 1990;36:297-300.