BRIEF REPORT

Acquired Monosomy 7 Myelodysplastic Syndrome in a Child With Clinical Features Suggestive of Dyskeratosis Congenita and IMAGe Association

Sharon McDonald, MD,1*, David B. Wilson, MD, PhD,1,2 Elena Pumbo, BS,3 Shashikant Kulkarni, PhD,1 Philip J. Mason, PhD,3,4 Tobias Else, MD,5 Monica Bessler, MD, PhD,2,3 Thomas Ferkol, MD,1 and Shalini Shenoy, MD1

We describe a case of acquired monosomy 7 myelodysplastic syndrome (MDS) in a boy with congenital adrenal cortical insufficiency, genital anomalies, growth delay, skin hyperpigmentation, and chronic lung disease. Some of his clinical manifestations were suggestive of dyskeratosis congenita (DC), while other features resembled IMAGe association. DC has been linked to mutations in telomere maintenance genes. The genetic basis of IMAGe association is unknown, although mice harboring a mutation in a telomere maintenance gene, Tpp1, have adrenal hypoplasia congenita. We considered the possibility that this patient may have defective telomere function resulting in features of both DC and IMAGe association.

CASE REPORT

The Caucasian male was born at 32 weeks gestational age to non-consanguineous parents. The family history was unremarkable. The pregnancy was complicated by placenta previa and IUGR. Delivery was via caesarian section. APGAR scores were 7 at 1 min and 8 at 5 min, and the birth weight was 1,157 g. As a neonate, he was noted to have bifrontal bossing, broad nasal bridge, low-set ears (Fig. 1A), and genital anomalies (microphallus, hypospadias, and bilateral cryptorchidism). Chromosome analysis revealed a 46,XY genotype. He received testosterone replacement therapy with a good response in phallic and testicular enlargement and underwent orchiopexy to correct his cryptorchidism.

In the first week of life he developed hyponatremia and hyperkalemia. Endocrinologic evaluation revealed an elevated plasma adrenocorticotrophic hormone level with a low plasma cortisol level at less than 0.7 μg/dl (normal range 4–22 μg/dl) and plasma adrenocorticotrophic hormone level with a low plasma cortisol level at less than 0.7 μg/dl (normal range 4–22 μg/dl) and low plasma aldosterone level (normal range 9–76 pg/ml; 0.14–4.4 pmol/l).

We considered the possibility that this patient may have defective telomere function resulting in features of both DC and IMAGe association.

REF: 1Department of Pediatrics, Washington University School of Medicine, St. Louis Children’s Hospital, St. Louis, Missouri. 2Department of Developmental Biology, Washington University School of Medicine, St. Louis Children’s Hospital, St. Louis, Missouri. 3Department of Internal Medicine, Washington University School of Medicine, St. Louis Children’s Hospital, St. Louis, Missouri. 4Department of Genetics, Washington University School of Medicine, St. Louis Children’s Hospital, St. Louis, Missouri. 5Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

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*Correspondence to: Sharon McDonald, Department of Pediatrics, Washington University School of Medicine, 660 S. Euclid Ave., Box 8116, St. Louis, MO 63110. E-mail: mcdonald_s@wustl.edu

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normal plasma 17-hydroxyprogesterone level at 40 (normal range 26–568) resulting in the diagnosis of adrenal hypoplasia congenita. A co-syntropin stimulation test at 20 days of age revealed a baseline cortisol level of <0.7 µg/dl and a stimulation level of 3.2 µg/dl, supporting the diagnosis of primary adrenocortical insufficiency.

As a toddler he had feeding difficulties due to uncoordinated swallowing and esophageal stricture. He underwent esophagoscopy with dilation at 2 and 4 years of age. Esophageal biopsy showed ballooning degeneration of the squamous epithelium. Despite adequate caloric intake, his weight and length remained <3rd percentile throughout childhood. At the chronologic age of 4.3 years, his bone age was 3.7 years. MRI of his brain at 16 months of age showed a large extracerebral cerebrospinal fluid space in his left frontal region and multiple diffuse periventricular white matter lesions with abnormal myelination. Extensive genetic testing was performed on the patient, and the results are summarized in Table I.

As an infant and toddler he had numerous hospitalizations for recurrent pneumonia. Chest radiographs and computed tomography of the chest showed diffuse bilateral ground glass opacities superimposed on bronchiectasis and bronchiolectasis (Fig. 1B). Bronchoscopy revealed a normal tracheal lining, increased mucosal vascularity, and thick, clear secretions throughout the bronchial tree. Biopsy of the respiratory epithelium demonstrated normal cilia on electron microscopy. In addition to lung infections, he had frequent episodes of otitis media with associated hearing loss, necessitating myringotomies with tympanostomy tube placement. An immuno-deficiency workup revealed a low *Haemophilus influenzae* titer and low IgG for which he received intravenous immunoglobulin replacement therapy.

At 3 years of age, he developed persistent neutropenia. Bone marrow evaluation revealed myeloid hyperplasia with atypia, neutrophil hypolobation, and hypergranulation. Cytogenetic analysis revealed monosomy 7 in 18 of 20 metaphases. FISH analysis of buccal mucosal cells and fibroblasts revealed no monosomy 7. With written informed consent of the parents and approval of the Institutional Review Board, peripheral blood mononuclear cell (PBMC) telomere length measurements [16] were performed on the patient and his family (Fig. 1C). There was no telomere shortening present in either the patient or his parents. A series of telomere maintenance genes were also sequenced (*TERC*, *TERT*, *TINF2*, *TPP1*, and *DKC1*), but no mutations were detected.

At 6 years of age, he underwent allogenic HSCT from a 10/10 allele matched unrelated donor. The preparative regimen included fludarabine 120 mg/m² and melphalan 140 mg/m² [17]. Graft-versus-host disease (GVHD) prophylaxis included methotrexate, cyclosporine A, and prednisone. He tolerated HSCT without acute complications. A skin rash developed 8 months after transplant and was consistent with GVHD restricted to the skin. Topical hydrocortisone induced minimal improvement but therapeutic levels of cyclosporine (250–350 ng/ml) induced remission with residual localized hyperpigmentation. Mucus membranes and other organs remained unaffected and cyclosporine was weaned again.
gradually. Complete donor engraftment with no evidence of monosomy 7 was documented at 1 year.

In the post-transplant period, he developed several lower respiratory infections, likely secondary to immunosuppression and underlying bronchiectasis. Accordingly, he was maintained on alternating courses of levofloxacin and ciprofloxacin prophylaxis until 1 year post-transplant, and monthly infusions of intravenous immunoglobulin therapy (400 mg/kg/dose) for 15 months.

DISCUSSION

Although he lacked the classic mucocutaneous features of DC, the proband had other hallmarks of DC including IUGR, MDS, esophageal stricture, lung disease, and hypospadias. DC is a telomere maintenance disorder and is often, but not always, associated with very short telomeres [16]. Although the PBMC telomere length was normal, this was measured after the diagnosis of MDS, and the surviving MDS hematopoietic cells may not have reflected the average telomere length in other tissues. For this reason telomere length measurements must be interpreted with caution [16]. He did not harbor a mutation in TERC, TERT, DKC1, or TINF2, but only about half of patients with DC have an identifiable mutation in these telomere maintenance genes.

A cardinal finding in our patient, congenital adrenal insufficiency, has not been linked to DC in humans. However, mice harboring a hypomorphic allele of Tpp1, a component of the shelterin complex that protects telomeres, exhibit a complex phenotype that includes adrenocortical hypoplasia with cytomegaly [14,15]. This allele, termed Tpp1<sup>ad</sup> (for the adrenocortical dysplasia strain), results in telomeres that are dysfunctional, leading to an increase in senescence-associated markers in adrenocortical cells. These findings suggest that Tpp1 is essential for proper function of progenitor cells in the adrenal cortex and that abnormalities in telomere maintenance can, at least in mice, manifest as adrenocortical dysfunction. Investigators are currently searching for mutations in telomere maintenance genes in humans with certain forms of congenital adrenocortical insufficiency [7,18,19]. We did not detect a TPP1 mutation in our patient.

One other patient with monosomy 7 syndrome, congenital adrenal hypoplasia with cytomegaly, and male pseudohermaphroditism has been previously described by Le and Kutteh [20]. We speculate that our patient and that of Le and Kutteh have a still undefined defect in telomere function with features of both DC and IMAGe association. Clinically well-delineated cases such as these may help elucidate the molecular pathogenesis of MDS and telomere maintenance disorders. While the hematopoietic manifestations of MDS and monosomy 7 were successfully tackled in our patient with reduced intensity allogeneic HSCT, other systemic manifestations such as adrenal and pulmonary complications continue to require ongoing management.

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