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CASE REPORT

Like Father, Like Daughter—inherited cutis aplasia occurring in a family with Marfan syndrome: a case report

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Key Clinical Message

We present the case of a newborn with co-occurrence of Marfan syndrome and aplasia cutis congenita (ACC) and a family history significant for Marfan syndrome and ACC in the father. This case details a previously unreported mutation in Marfan syndrome and describes a novel coinheritance of Marfan syndrome and ACC.

Keywords

Aplasia cutis congenita, Marfan Syndrome.

Case Report

A female newborn was noted to have round superficial erosions on the vertex and occipital scalp, measuring 2 × 3 and 1 × 1 cm, respectively (Figs 1 and 2). There was with no palpable calvarium beneath the lesions. Findings were consistent with aplasia cutis congenital (ACC). She was also noted to have elongated fingers (Fig. 3), leading to suspicion of Marfan syndrome. The mother was homeless and had limited prenatal care, as well as documented tobacco, cocaine, opiate, and marijuana abuse. Fluconazole for treatment of vaginal candidiasis was the only prescription medication given during the pregnancy. The infant was born via spontaneous vaginal delivery at 39 weeks of gestation, at which time the mother's drug screen was negative. The infant was treated empirically with ampicillin and gentamicin for acute chorioamnionitis. The infant was adopted at birth and has no current contact with her biological family.

Multiple imaging studies were performed perinatally. The infant was found to have a mildly dilated aortic root ($Z = 2.8$) on echocardiogram at birth. Retroperitoneal ultrasound and MRI of the brain within the first 2 days of life showed no anatomic abnormalities. A concern for Marfan syndrome resulted in ophthalmology consultation and exam, which revealed no abnormalities.

Chart review and discussion with the biological father prior to our patient's adoption confirmed documented Marfan syndrome in the father, who was diagnosed clinically based on the presence of aortic dilation and other features consistent with the disease; he is followed by a cardiologist. He also has been diagnosed clinically with scalp ACC, based on physical exam findings consistent with the disease, present since birth. The paternal grandfather was also diagnosed clinically with Marfan syndrome. The mother's past medical history is significant only for spina bifida.

Genetic evaluation of the proband revealed a heterozygous mutation on FBN-1 sequencing, c.6391T>C

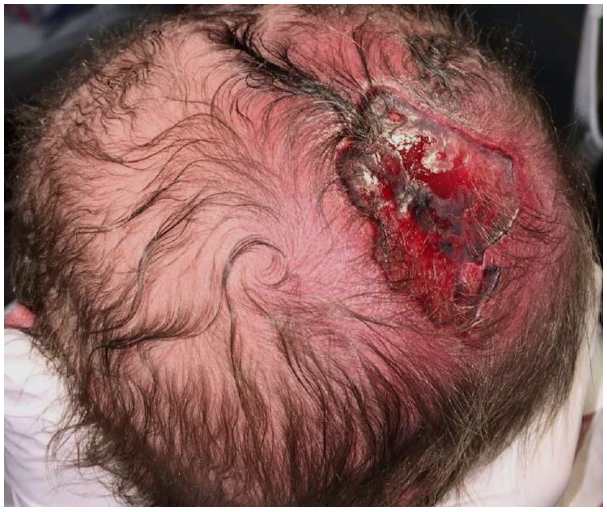

Figure 1. 2 × 3 cm superficial erosion on the vertex scalp on day of birth. The calvarium was not palpable beneath the lesion.

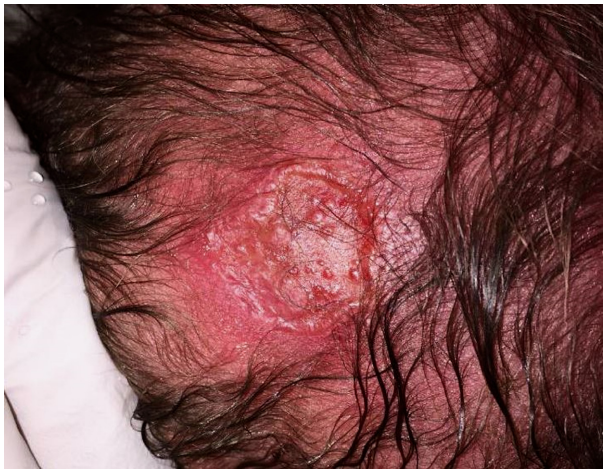

Figure 2. 1 × 1 cm superficial erosion on the posterior scalp on day of birth.

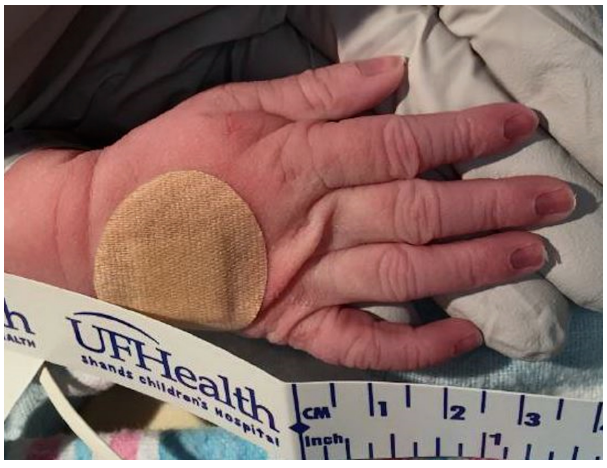

Figure 3. Arachnodactyly and dolichonychia pictured on day of birth.

(p.Cys2131Arg). Single-nucleotide polymorphism–comparative genomic hybridization studies found no copy number variations, but did demonstrate a region of homozygosity on chromosome 4p of 6 Mb [4p15.1 (29,725,379-35,729,486)]. Genetic testing on the paternal side of the family was unable to be performed to evaluate the potential causative gene(s) of her ACC because of no contact with her biological father.

Physical examination at 10 months of age showed a 6-cm round alopecic plaque on the vertex of the scalp, and a 2.5 × 2.0 cm similar lesion on the posterior scalp. Nodularity was noticed underneath these lesions, worse at the vertex, leading to clinical concern for abnormal fusion of the cranial sutures. The hair collar sign was not present. She was noted to have continued arachnodactyly, as well as dolichonychia and an elongated wingspan. Her facial appearance was normal without evidence of dysmorphism.

Discussion

Aplasia cutis congenita is a rare group of disorders that is characterized by absent or scarred areas of skin from birth. Involved layers of skin may include the epidermis, dermis, and subcutaneous fat. The midline posterior scalp is the most commonly affected area of the body. It can be associated with other malformations in 37% of cases [1]. For example, in Adams–Oliver syndrome, ACC accompanies limb deformities, cutis marmorata telangiectasia congenita, and/or structural brain abnormalities [2]. As in our patient, most defects heal spontaneously, with a resultant scar and alopecia [3]. The etiology remains unclear, but theories include infection, defects in amniogenesis, teratogens, and vascular malformations [4]. ACC does occur with genetic syndromes, including Trisomy 13, 4p- syndrome, and Johanson–Blizzard syndrome [5]. Frieden described a classification system for ACC in 1986 that is used to this day [5].

Marfan syndrome is a disease of connective tissue that commonly causes aortic root dilation, ocular lens dislocation, overgrowth of the long bones, pes planus, and pectus excavatum. It is secondary to mutations in *FBN1,* which encodes for fibrillin-1, an extracellular matrix protein that polymerizes to form the microfibrils of elastin. Dermatologic manifestations of Marfan syndrome include striae atrophicae, arachnodactyly, and dolichonychia [6].

The autosomal dominant transmission of Marfan syndrome is well established [6]. ACC has been suggested by multiple authors to be inherited in an autosomal dominant fashion, among other modes of inheritance [7]; however, cooccurrence with Marfan syndrome has not previously been reported.

Our patient's mutation in c.6391T>C was first described by B. Loeys in a 2014 personal communication [8]. This mutation alters a highly conserved cysteine residue in one of the epidermal growth factor (EGF)-like domains. According to the revised Ghent criteria, an alteration in a cysteine residue is a major criterion for diagnosing Marfan syndrome [9]. These cysteine residues are predictably spaced to bond via disulfide linkage that determines protein folding, resulting in the binding of calcium to fibrillin-1. An alteration in these cysteine residues leads to protein misfolding and enhanced proteolytic degradation of fibrillin-1 [6]. This patient's region of homozygosity on chromosome 4 contains 10 known genes, none of which is known to cause disease in humans.

The only known gene associated with nonsyndromic ACC is *BMS1*, a ribosomal ATPase located on chromosome 10q11, involved in preribosomal processing. A study of one family with autosomal dominant severe ACC found that a p.R930H mutation in this gene resulted in a cell cycle delay at the G1/S phase checkpoint, mediated by p21 [10]. However, a review of the literature has yielded no reports of mutations in *FBN1* associated with ACC.

This case further questions the possibility of nonsyndromic inherited ACC and also illustrates co-occurrence of two rare genetic conditions. It is possible there is an unknown link between the two conditions. A limitation of this study includes the inability to identify the father's genetic mutations, particularly for ACC; however, specific gene testing for ACC does not currently exist, as the genetic basis for this disease is an ongoing research endeavor. The father's ACC and Marfan syndrome was diagnosed and documented clinically, but because contact with the father is no longer possible, genetic studies are unable to be obtained. It cannot be proven if the region of homozygosity on chromosome 4p is the causative mutation for ACC and Marfan syndrome coinheritance in this patient; however, many genetic causes of ACC remain unknown. There also remains the possibility that these two diseases were coinherited coincidentally. In order to help elucidate some of these ties, trio whole-exome sequencing may have been a useful tool if the biological parents were available for testing. This case, and those reported prior, suggests further research into the potential for heritable forms of ACC associated with and without other genetic syndromes.

Conflict of Interest

The authors attest to no reportable conflict of interests.

Authorship

YI: involved in data interpretation, drafting of the work, and final approval of the work; CW and IA: involved in data acquisition and interpretation, revising the draft, and final approval of the work; JS: involved in data interpretation, revising the draft, and final approval of the work.

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