The Genetics Corner: A Genetics Consultation for Agenesis Cutis Congenita and Methimazole Exposure

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Case History:

A genetics consult was requested for a term male infant with cutis aplasia congenita. The pregnancy was complicated by maternal hyperthyroidism, treated with methimazole (10mg/day), until around 12 weeks' gestation, when her endocrinologist changed her medication to propylthiouracil (PTU). All medication was discontinued in the second trimester when she became euthyroid. She also took Buspar, PRN (approximately once a day) for depression until 12 weeks gestation. Other teratogenic exposures were denied.

The baby was delivered in a community hospital at term by vaginal delivery to a 25-year old G2P1 mother. APGAR scores were 91 and 95. BW 2960 gm (20.54th %ile), BL 49.5 cm (42nd%ile), HC 33 cm (13th%ile). The baby was transferred to our facility because of his scalp defect. Head and abdominal ultrasound exams and echocardiogram were normal.

The family history was obtained by phone from the mother who was still at the birth hospital. She reported an area of congenital cutis aplasia of about 1 cm in diameter on her own scalp, but no one else in the family was similarly affected to her knowledge. Both parents are 25 years old. There is a healthy 4-year old sibling. There was no parental consanguinity; father is Caucasian, and mother is Asian.

On physical exam, the baby was alert, responsive and active in ambient air. He had a normal 1.5 cm anterior fontanel and a full thickness 3 x 6 cm scalp defect with irregular borders at the vertex (figure 1).. A cephalohematoma was palpable at the margin of the scalp defect. The frontal bones could be palpated at the anterior edge of the scalp defect and appeared to be intact. The extremities were normal, with normal nails, digits, and creases. There were no other dysmorphic features or congenital anomalies.

Consultant's report:

Aplasia cutis congenita (ACC) is a rare congenital skin defect characterized by focal or extensive absence of the epidermis, dermis, subcutaneous tissue and sometimes bone. Most lesions are localized to the scalp at the vertex, although lesions can appear anywhere on the body. ACC can occur as an isolated anomaly, after focal necrosis related to placental infarction, a dead co-twin (fetus papyraceous) or an intrauterine infection (varicella) (Alexandros B et al., 2017), as a sporadic or familial single gene disorder, or in combination with various anomalies in over 50 multiple congenital anomaly syndromes.

Hereditary forms of ACC can be isolated and nonsyndromic or associated with other anomalies. A family with nonsyndromic autosomal dominant ACC (MIM 107600) in 5 generations had a pathogenic variant in BMS1, a gene involved in skin morphogenesis (Marneros AG et al., 2013). Adams-Oliver syndrome (MIM 100300) comprises a group of autosomal recessive and autosomal dominant disorders of variable severity in which aplasia cutis congenita occurs with transverse terminal limb defects. It is caused by variants in ARHGAP31 and many other genes. In Scalp-Nipple-Ear syndrome, also called Finlay-Marks syndrome (MIM 181270), ACC occurs with breast anomalies (athelia), ear anomalies, nail dystrophy, cutaneous syndactyly, and renal malformations. A heterozygous variant causes this autosomal dominant disorder in KCTD1. In Setleis syndrome (MIM 227260), an autosomal recessive condition caused by variants in TWIST2, the symmetric bitemporal areas of cutis aplasia have been likened to "forceps marks." Recognizable facial features in Setleis syndrome include thin, wrinkled periorbital skin and distichiasis (double eyelashes).

Gestational hyperthyroidism, which occurs in 1-2/1000 pregnancies, confers an increased risk for serious consequences on the exposed neonate. Hyperthyroidism in pregnancy is associated with preeclampsia, preterm labor and delivery, and admission to the NICU. The commonly used antithyroid drugs, methimazole (MMI) and carbimazole (CMZ), a pro-drug of methimazole, are associated with congenital anomalies in exposed fetuses. While propylthiouracil (PTU) has been the preferred agent for the treatment of hyperthyroidism during the first trimester of pregnancy, it is associated with maternal liver failure. More recently PTU-exposed fetuses have been shown to have an increased risk of mild teratogenic effects, primarily preauricular sinuses/cysts/fistulas and urinary tract anomalies.

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Methimazole is a thioamide that crosses the placenta. It causes fetal thyroid suppression in both animals and humans, with subsequent fetal hypothyroidism and goiter. Concern about its teratogenicity was first reported in 1972 when Milham & Elledge briefly described gestational exposure to MMI in 2 of the 11 mothers of 12 infants with aplasia cutis (1 affected singleton, one set of concordant affected twins). More severe birth defects have subsequently been reported leading to the description of methimazole/carbimazole embryopathy. Recently, two large series of treated mothers in Japan and Denmark have confirmed an increased risk of 2-3% risk for congenital anomalies after early in utero MMI exposure. These MMI-associated congenital malformations made up about half of the excess cases of congenital anomalies: aplasia cutis congenita, omphalocele, omphalomesenteric duct, choanal atresia, esophageal atresia/ tracheoesophageal fistula, microtia, septal defects, eye, and urinary tract defects. Laurberg and Andersen (2014) noted, in their meta-analysis of 92 publications on the topic, that the period of highest risk for anomalies in MMI/CMZ-exposed pregnancies was 6-10 weeks gestation. Song et al. (2017) evaluated ten studies with over 5000 pregnancies treated with antithyroid medications and reported an almost doubled risk for congenital malformations among MMI/CBZ-exposed pregnancies compared to those exposed to PTU alone (OR 1.90; 95% 1.3-2.78; P=0.001).

This infant had isolated ACC without other associated congenital anomalies. A single gene disorder had to be considered because of the family history of scalp defect in this mother. Genetic testing was ordered with negative results for pathogenic variants on a multigene panel for Adams-Oliver syndrome, with add-on testing for BMS1. A chromosome microarray analysis was also normal.

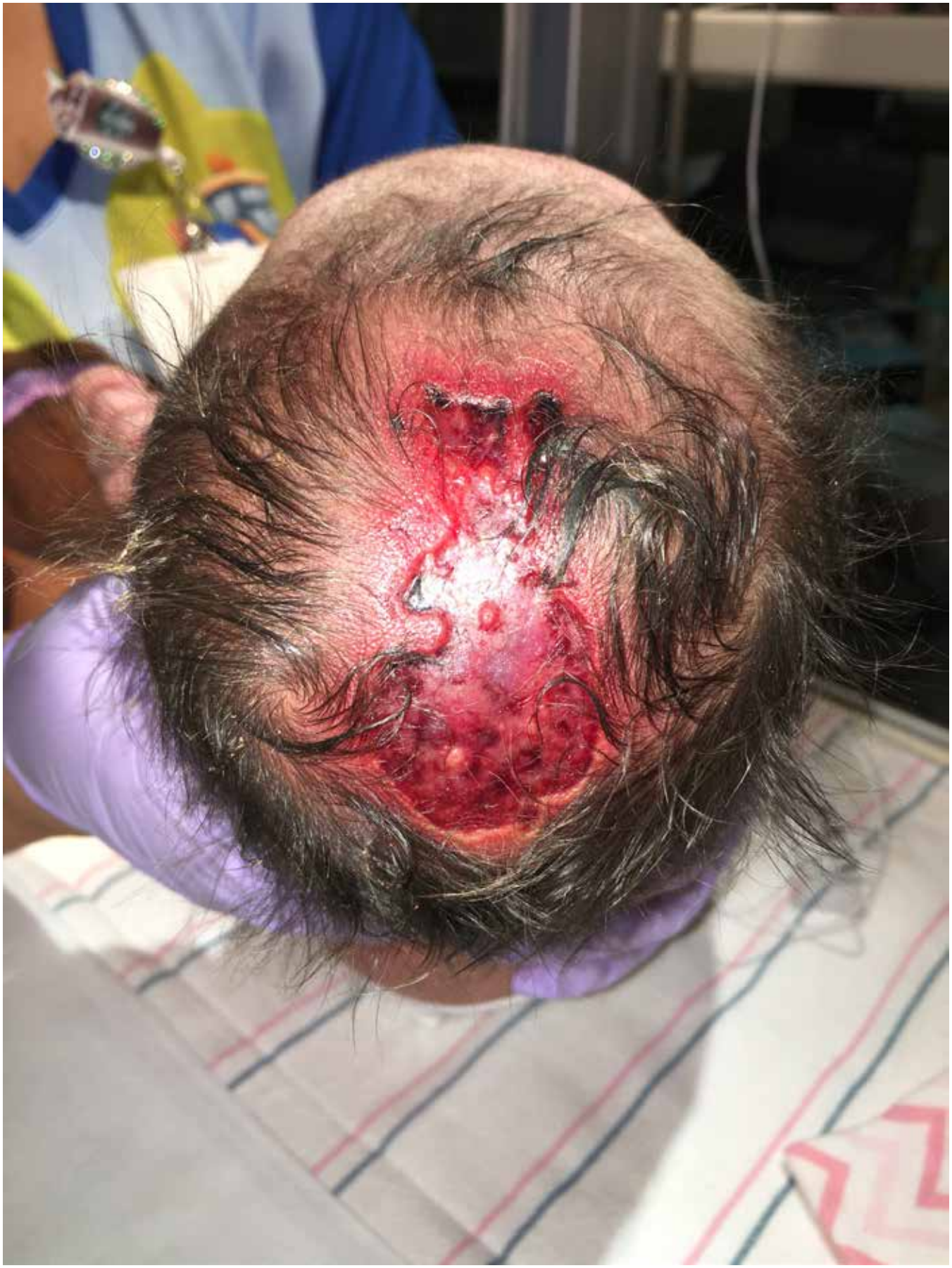

Figure 1: Full thickness scalp defect at vertex 3x6 cm, with irregular borders

We concluded that this infant's ACC was due to his first-trimester exposure to methimazole. However, in his case, it is possible, and perhaps likely, that a permissive genetic background enhanced the teratogenic action of the drug.

Practical applications:

- Examine infants of hyperthyroid mothers for aplasia cutis congenita and other teratogenic effects of antithyroid medications.
- Consider placental, teratogenic, monogenic syndromes and multifactorial disorders in the differential diagnosis of ACC.
- Distinguish isolated from syndromic ACC.
    - Evaluate infants with ACC for associated birth defects. Order echocardiogram, renal/abdominal ultrasound.
- Take your own detailed pregnancy and family history directly from the mother.
    - When you copy and paste the family history from the mother's chart, you risk missing important key information.
- Order appropriate genetic testing when the family history is positive for ACC or when other anomalies are present.
- Counsel women with pregestational hyperthyroidism prior to conception regarding available treatments and their potential adverse effects.
    - When you talk to the mother of your patient, take advantage of the opportunity for preconceptional counseling.
    - Hyperthyroid women should plan their pregnancies in order to avoid MMI/CBZ during the sensitive periods of organogenesis in the first trimester.

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The authors have no relevant disclosures.

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