

A Diagnostic Challenge: Prenatal Ultrasound Findings in Severe Epidermolysis Bullosa

Eine diagnostische Herausforderung: schwere Verlaufsform der Epidermolysis Bullosa im pränatalen Ultraschall

Introduction

Epidermolysis bullosa is a rare condition with clinical and genetic heterogeneity. This report describes the prenatal clinical manifestations in a case with a severe form of junctional epidermolysis bullosa with pyloric stenosis. We discuss the diagnostic challenge but also the ultrasound signs emerging to be reminiscent of this condition.

Case description

A 31 year-old, gravida III, para I, patient of Turkish descent, presented for routine second trimester anomaly scan after first trimester screening at low risk for the frequent trisomies. The pregnancy was complicated by insulin-dependent gestational diabetes. The patient received antiepileptic treatment (Levetiracetam 1500 mg/d) for an epilepsy diagnosed in childhood. Family history was uneventful, there was suspected distant consanguinity. Detailed anomaly scan at 22 weeks gestational age revealed edematous swelling of the right dorsal foot; the left foot and lower leg were slim and appeared hypotrophic, the tibia shorter, in comparison to the right lower limb (► Fig. 1, 2a, b). There were no additional anomalies. Based on the clinical findings parents were counselled about an uncertain diagnosis ranging from a possible isolated localized finding of non-genetic etiology to a first sign of a systemic or syndromic condition with unknown outcome at this point of pregnancy. The patient opted for amniocentesis for chromosomal microarray analysis revealing a normal molecular karyotype [arr(1–22)x2,(XY)x1]. Stretches of loss of heterozygosity (chromosomes 3, 5, 7, 12, 13 and 17) indicated consanguinity and an increased risk for recessive conditions. Amniotic fluid alpha-fetoprotein was excessively increased (AFAFP: 112'705 IU/ml = 136'373ug/l), and subsequent measurement of acetylcholinesterase (AChE) was weak positiv. In the absence of ultra-

sound findings of neural tube defects and fetal structural anomalies known to cause fetal leakage such as e. g. abdominal wall defects the patient and her husband were counselled for an increased risk for a rare systemic disease in the child and opted to continue the pregnancy.

Ultrasound follow-up of the pregnancy detected additional anomalies such as progressive polyhydramnios and hydronephrosis starting at 27 weeks of the right kidney and a dilated stomach without depictable obstruction at 33 weeks (► Fig. 3).

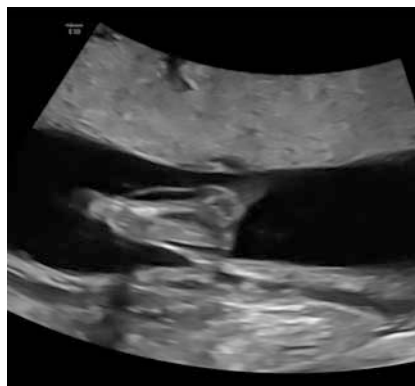
The boy was delivered prematurely at 34 weeks of gestation and presented with extensive skin areas of aplasia cutis (head, face, thorax, back, limbs, genitals), a dystrophic external left ear, esophageal atresia type I and pyloric atresia, bilateral pye-

lectasia with a right ureterocele and a hypoplastic lower left leg (► Fig. 4). The newborn deceased on day 5 after birth.

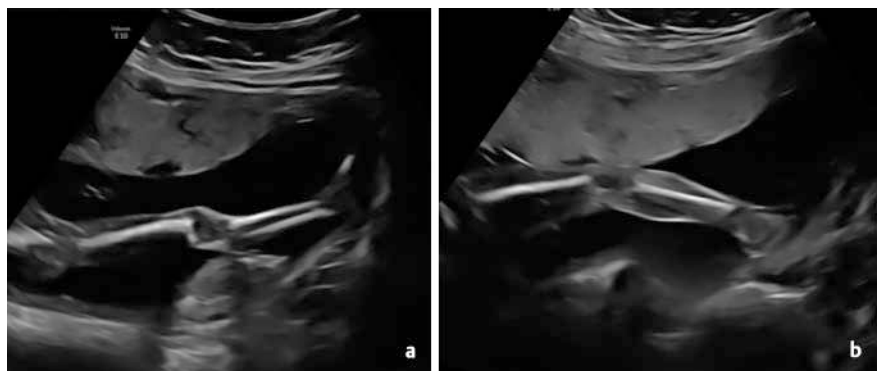
The clinical diagnosis of junctional epidermolysis bullosa (EB) with pyloric atresia (EB-PA) was confirmed by a loss of integrin alpha6 / beta4 in a skin biopsy using immunofluorescence staining. Genetic testing of the *ITGA6* and *ITGB4* genes identified a novel homozygous mutation c.1761 + 3A>C in the *ITGB4* gene, not previously described, but in association with the clinical diagnosis and skin biopsy results likely causal for the EB-PA in the child. Other mutations in the *ITGB4* gene are known to cause autosomal recessive EB with and without pyloric atresia.

Discussion

Junctional epidermolysis bullosa with pyloric atresia (EB-PA) is a usually severe and often lethal condition in the neonatal period. It is characterized by fragility of the skin and mucous membranes manifesting with blistering with little or no trauma, and congenital localized aplasia cutis affecting predominantly limbs and the head. Atresia in the gastrointestinal tract, ureteral and renal anomalies, contractures, nail dystrophy, scarring alopecia, hypotrichosis and dilated cardiomyopathy are variably present. Most affected children succumb as neonates. Non-lethal milder variants exist [1]. It is debated



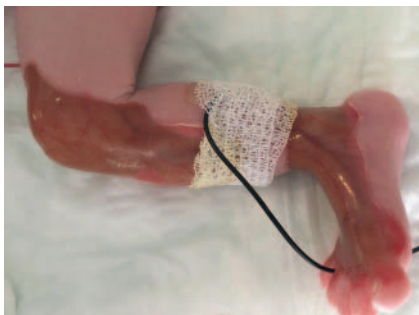
► Fig. 1 Right dorsal foot with edematous swelling.



► Fig. 2 a Slim and hypotrophic left leg. b In comparison normal right lower limb.



► **Fig. 3** Severe dilated stomach without depictable obstruction at 33 weeks.



► **Fig. 4** Leg of the newborn presenting extensive skin areas of aplasia cutis.

whether the variably associated esophageal, pyloric, duodenal and intestinal atresia are primary malformations or occur as secondary stenoses or constrictions as a result of mucous membrane lesions.

In the absence of a previous family history the prenatal diagnosis of EB and EB-PA is notoriously difficult. We illustrate this challenge since the postnatal recognizable clinical sign of aplasia cutis cannot be appreciated by ultrasound, and other indirect signs such as dilated stomach and polyhydramnios as a consequence of oesophageal atresia, may only manifest later in pregnancy, if present at all. Unilateral oedematous tissue and lower leg deformation were the first, but subtle and unspecific findings recognized at the 2nd trimester anomaly scan. These signs may occur in a large spectrum of conditions associated with diverse outcomes including genetic but also non-genetic etiologies such as localized constriction and defor-

mation due to e. g. amniotic band or vascular compromise. However, excessively increased AFAFP and weak positive AChE in the absence of neural tube defects and major fetal structural anomalies pointed to a likely systemic or syndromic disease, but the differential diagnosis is vast [2]. Novel genomic approaches for monogenic disorders such as prenatal exome sequencing may be beneficial in some cases, but still of limited clinical utility because of the expected number of variants of unknown clinical significance and because of turn-around-time.

The prenatal phenotype of EB and EB-PA is described only in a few other cases [3–8], but in review, including our observations, a variable combination of unspecific ultrasound signs including gastric dilations, double bubble, polyhydramnios, snowflake sign, anomalies of the kidney and urinary tract, ear-nose deformities, complete chorioamniotic membrane separation, shortening or deformity of limbs and excessively increased AFAFP may prompt to consider the diagnosis of EB/EB-PA. Of note, that elevated AFAFP can be attributed to the skin lesions that lead to AFP leakage, but may not be present until the first 20 weeks of pregnancy or at all, depending on the severity and onset of skin lesions.

In summary, we suggest that increased AFAFP, deformity of limbs and ultrasound signs of gastrointestinal obstruction should prompt to consider severe forms of epidermolysis bullosa in prenatal differential diagnosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors

Julie De Geyter^{1,2}, Isabel Filges^{1,2,3}, Sevgi Tercanli⁴

¹ Medical Genetics, Institute of Medical Genetics and Pathology, University-Hospital and University of Basel, Basel, Switzerland

² University of Basel, Basel, Switzerland

³ Department of Clinical Research, University-Hospital Basel, Basel, Switzerland

⁴ Ultraschallpraxis Freie Strasse, Basel, Switzerland

Correspondence

Julie De Geyter

Schönbeinstrasse 40

4031 Basel

Switzerland

Tel.: ++41/61/3 28 66 45

julie.degeyter@usb.ch

References

- [1] Pfender EG, Lucky AW. Epidermolysis bullosa with pyloric atresia. *Gene reviews*. 2017
- [2] Milunsky A, Milunsky JM. *Genetic Disorders and the Fetus*. Wiley. 2016; 7th edition
- [3] Yacoub T et al. Maternal serum and amniotic fluid concentrations of alpha-fetoprotein in epidermolysis bullosa simplex. *Br Med J* 1979; 1: 307
- [4] Meizner I, Carmi R. The snowflake sign. A sonographic marker for prenatal detection of fetal skin denudation. *J Ultrasound Med* 1990; 9: 607–609
- [5] Lepinard C et al. Prenatal diagnosis of pyloric atresia-junctional epidermolysis bullosa syndrome in a fetus not known to be at risk. *Prenat Diagn* 2000; 20: 70–75
- [6] Katorza E et al. Unusual prenatal sonographic findings of epidermolysis bullosa mimicking an amniotic band constriction ring. *J Ultrasound Med* 2009; 28: 73–75
- [7] Dural O et al. Prenatal ultrasound findings and a new ultrasonographic sign of epidermolysis bullosa with congenital pyloric atresia: a report of three cases. *J Med Ultrasonics* 2014; 41: 495–498
- [8] Jeong BD et al. Unusual prenatal sonographic findings without an elevated maternal serum alpha-fetoprotein level in a fetus with epidermolysis bullosa. *J Clin Ultrasound* 2016; 44: 319–321

Bibliography

DOI <https://doi.org/10.1055/a-0720-8983>

Published online: 2018

Ultraschall in Med 2018; 39: 600–601

© Georg Thieme Verlag KG, Stuttgart · New York
ISSN 0172-4614