

# Prenatal ultrasound findings and a new ultrasonographic sign of epidermolysis bullosa with congenital pyloric atresia: a report of three cases

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**Abstract** Epidermolysis bullosa with pyloric atresia (EB-PA) is a rare autosomal recessive disease that is characterized by fragility of the skin and mucous membranes. The course of EB-PA is usually severe and often lethal in the neonatal period. In most cases, prenatal diagnosis of this syndrome is considered in pregnancies at risk for recurrence. EB-PA can be described during pregnancy with sonographic signs such as polyhydramnios with a dilated stomach, the “snowflake sign”, which are echogenic particles in the amniotic fluid, and several other anomalies. In this report, we present three cases of EB-PA suggested by the results of prenatal sonography, and describe a new ultrasonographic sign, i.e., complete chorioamniotic membrane separation, which can be helpful for the diagnosis. The prenatal diagnoses were confirmed postnatally. Two of the three cases had no family history, and one of these two cases was the product of a non-consanguineous couple.

**Keywords** Epidermolysis bullosa · Pyloric atresia · Prenatal diagnosis · Ultrasonography · Echogenic amniotic fluid · Chorioamniotic membrane separation

## Introduction

EB comprises a group of genetically determined skin fragility disorders manifesting with blistering of the skin and mucous membranes as a result of mechanical trauma [1]. EB can be classified into three broad categories, i.e., EB simplex, junctional EB, and dystrophic EB, depending on the level of tissue separation at the cutaneous basement membrane zone [2].

EB-PA is a severe clinical subtype that includes lethal and nonlethal variants. The three forms of EB have been reported in association with PA, although junctional EB is the most common type [3]. This condition is inherited in an autosomal recessive pattern and can be caused by mutations in the ITGA6, ITGB4, and PLEC genes [2]. Prenatal diagnosis of EB-PA became possible by fetal DNA analysis if the responsible mutation is known or by analysis of fetal skin biopsies using electron microscopy and indirect immunofluorescence. EB-PA without a history can be difficult to diagnose during pregnancy, but some ultrasound signs can be suggestive of EB-PA in these patients. We present three cases in which the diagnosis of EB-PA was suggested by ultrasound findings even when there was no family history, and we propose a new ultrasonographic sign for prenatal diagnosis of EB-PA.

## Case 1

A 24-year-old primigravid woman was referred to our department for a sonographic evaluation because of

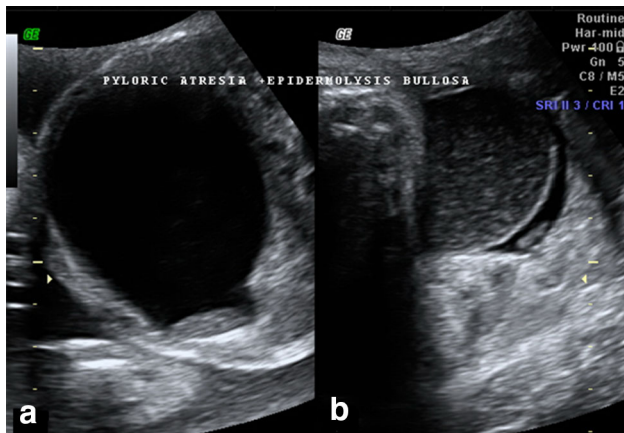
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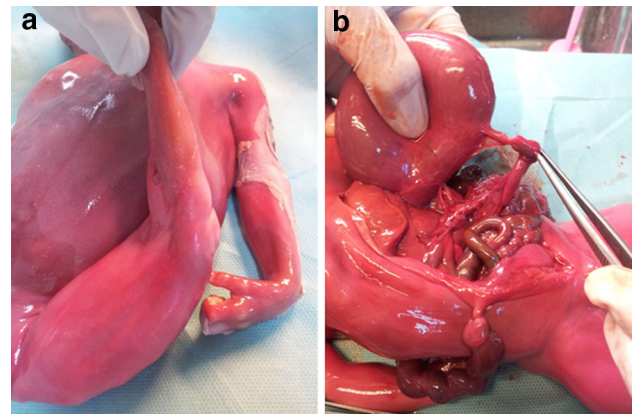


**Fig. 1** Ultrasound scan of case 1 at 30 weeks' gestation. **a** Dilated stomach. **b** Echogenic particles in the amniotic fluid and complete chorioamniotic membrane separation

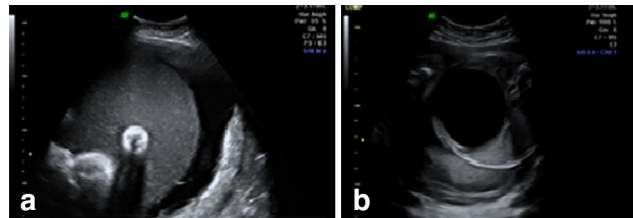
polyhydramnios associated with fetal gastric dilatation at 30 weeks' gestation. The couple was non-consanguineous and had no family history of genetic disease. The results of triple screening test were normal.

In our unit, a detailed sonographic examination revealed gastric dilatation (60 × 50 mm) with dilated distal esophagus, polyhydramnios, complete chorioamniotic membrane separation, and multiple echogenic particles in the amniotic fluid in a normally growing fetus (Fig. 1a, b). A dilated stomach and polyhydramnios were suggestive of a gastric outlet obstruction, and EB-PA was suspected on the basis of these ultrasound findings. Cordocentesis was performed because polyhydramnios associated with digestive tract obstruction can be associated with trisomy 21; the fetal karyotype was normal (46, XX). After detailed genetic counseling, the parents decided to continue with the pregnancy.

Follow-up ultrasound scan after one week showed intrauterine fetal death. The cause of fetal death was unclear, but could be related to a cord complication due to complete chorioamniotic membrane separation. However, there was no sign of umbilical cord strangulation. Labor was induced with intravaginal misoprostol. The dead female fetus weighing 1315 g was delivered in two days and presented large areas of desquamation of the epidermis and erosions located in patches throughout the body, especially around the left and right knee and elbow, the dorsal surface of both legs and arms, and the trunk. There were sharply demarcated areas of absent skin localized especially on the dorsal surface of the legs, and these findings were compatible with EB in association with aplasia cutis congenita (Fig. 2a). Autopsy showed a distended stomach, with neither any pyloric opening nor antral web at the exploration of the distal stomach consisting of pyloric atresia (Fig. 2b).



**Fig. 2** Autopsy of case 1. **a** Sharply demarcated areas of absent skin. **b** Pyloric atresia



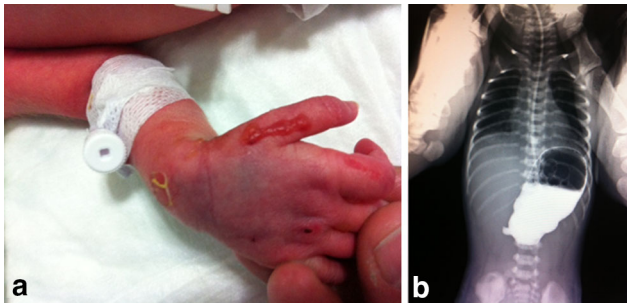
**Fig. 3** **a** Ultrasound scan at 35 weeks' gestation demonstrating echogenic particles in the amniotic fluid and complete chorioamniotic membrane separation (case 2). **b** Dilated stomach with no evidence of a "double-bubble" sign (case 2)

## Case 2

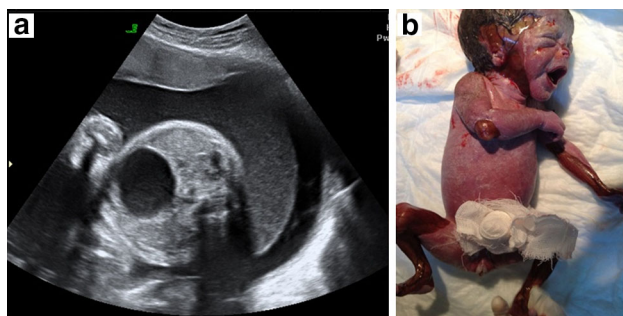
A 40-year-old primipara woman was admitted to our unit at 35 weeks' gestation, and ultrasound examination revealed polyhydramnios with snowflake-like echogenic amniotic fluid and complete chorioamniotic membrane separation (Fig. 3a). There was a dilated fetal stomach, but there was no evidence of a "double-bubble" sign (Fig. 3b).

She did not undergo screening tests or regular follow-up during her pregnancy. Her previous pregnancy had ended with the delivery of a male infant with junctional epidermolysis bullosa. The parents were first cousins. EB-PA was suspected based on these findings. Preterm birth occurred spontaneously within 24 h.

Initial clinical examination of the newborn showed bullous skin lesions, especially over the elbows and hands, consisting of EB (Fig. 4a). A gastric outlet obstruction was confirmed with barium contrast radiography (Fig. 4b). Laparotomy revealed a dilated stomach with a membrane at the pylorus. Gastroduodenostomy was performed. The postoperative period was uneventful.



**Fig. 4** **a** Picture of the newborn with bullous lesion on the dorsal surface of the right hand (case 2). **b** Barium contrast radiography at birth confirming the pyloric atresia and major gastric dilatation (case 2)



**Fig. 5** **a** Ultrasound scan at 32 weeks' gestation demonstrating echogenic particles in the amniotic fluid, complete chorioamniotic membrane separation, and dilated stomach (case 3). **b** Picture of the newborn with bullous lesion (case 3)

### Case 3

A 28-year-old primigravid woman was referred to our department with a suspicion of obstruction of the gastrointestinal tract at 32 weeks' gestation. Ultrasound examination revealed polyhydramnios with snowflake-like echogenic amniotic fluid, complete chorioamniotic membrane separation, and fetal gastric dilatation with dilated distal esophagus (Fig. 5a).

The couple was consanguineous (2nd degree) and had no family history of genetic disease. She did not undergo screening tests or regular follow-up during her pregnancy. EB-PA was suspected. After detailed genetic counseling, the parents decided not to allow any testing, and spontaneous preterm birth occurred 12 days after the examination.

Clinical examination of the female fetus weighing 1450 g showed widespread bullous skin lesions (Fig. 5b). A gastric outlet obstruction was confirmed with barium contrast radiography. Gastroduodenostomy was planned, but the newborn died due to septic shock before the surgery.

### Discussion

While the majority of prenatal diagnoses for EB are currently based on analyzing the fetal DNA if the responsible mutation is known, fetal skin biopsy remains an option for families in which the mutation cannot be identified or where the mutation analyses are not available or unaffordable to be used for prenatal diagnosis. However, while EB-PA without a history or abnormal laboratory findings may be difficult to diagnose during pregnancy, some ultrasound signs can be suggestive of EB-PA in these patients.

Gastric dilatation, which is a sonographic sign for EB-PA, can occur as a result of pyloric atresia or duodenal stenosis. A differential diagnosis of these two malformations can usually be made by ultrasound. Prenatal diagnosis of duodenal stenosis is based on the demonstration of the characteristic “double bubble” appearance of the dilated stomach and proximal duodenum, while a markedly distended stomach is suggestive of pyloric atresia [4]. PA is a very rare condition and constitutes about 1 % of all gastrointestinal anomalies [4]. PA is treated with surgery and shows a satisfactory survival rate, but the association with junctional EB is a highly lethal disease.

In addition to skin lesions and gastrointestinal tract involvement, some affected individuals are also born with a number of systemic manifestations, including enamel pitting, nail dystrophy, corneal erosions, and tracheal and urinary tract involvement [5]. In general, maternal serum  $\alpha$ -fetoprotein (AFP) and amniotic fluid AFP and acetylcholinesterase (AChE) levels are elevated in pregnancies complicated by fetal EB [6, 7]. As seen in case 1, maternal serum AFP levels at routine Down syndrome screening can be normal because skin lesions that lead to AFP leakage may not be present in the first 20 weeks of pregnancy.

EB-PA may be suspected based on prenatal ultrasound, especially in families with a known genetic risk. So far, gastric dilatation associated with polyhydramnios as an expression of pyloric atresia [8], the “snowflake sign,” which may be a sign of in utero skin denudation syndromes [9], anomalies of the kidney and urinary tract [10], and ear-nose deformities have been reported as prenatal ultrasound findings of EB-PA. Prenatal ultrasound findings in our three cases were gastric dilatation, snowflake sign, and complete chorioamniotic membrane separation. In our three cases, the diagnosis of EB-PA was considered based on ultrasound findings alone, even in the cases with no previous family history. Complete chorioamniotic membrane separation usually occurs following an invasive intrauterine procedure and is associated with poor perinatal outcomes, including miscarriage, in utero fetal death, umbilical cord complications, and preterm delivery [11]. There are no other reports on the relationship between EB

and complete chorioamniotic membrane separation. In this report, complete chorioamniotic membrane separation was observed in all three cases, which can be associated with genetic skin diseases because the amniotic membrane is believed to have an ectodermal origin [12], and this sign can be helpful in the diagnosis of EB-PA.

**Conflict of interest** There are no financial or other relations that could lead to a conflict of interest.

**Ethical Considerations** This article does not contain any studies with human or animal subjects performed by any of the authors.

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