ISSN 2692-4374

TheGMS
The Gazette of Medical Sciences

INOVACUS

Dermatology | Case report

open access

Managing pregnancy in a patient with Recessive Dystrophic Epidermolysis Bullosa: A case report

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Submitted: 13 October 2020

Approved: 26 October 2020

Published: 27 October 2020

How to cite this article: Flewelling K, Hebert D, Walworth K, Effiong U. Managing pregnancy in a patient with Recessive Dystrophic Epidermolysis Bullosa: A case report. G Med Sci. 2020; 1(5): 068-072. https://www.doi.org/10.46766/thegms.derma.20101302

ABSTRACT

Epidermolysis Bullosa (EB) is a rare, heritable skin disease that encompasses several subtypes, which vary widely in presentation and prognosis. One subtype, Recessive Dystrophic Epidermolysis Bullosa (RDEB), is especially rare and debilitating. It occurs due to a mutation in the COL7A1 gene that encodes for type VII collagen leading to chronic, diffuse skin and mucosal blistering. Given the rarity of the disease, guidelines for treatment of pregnant patients with RDEB do not currently exist. This case describes the pregnancy course of a 21-year-old female with RDEB. She conceived vaginally and had a term normal vaginal delivery complicated by postpartum hemorrhage. She declined genetic testing of her infant, but he was born with no cutaneous signs of EB. Key aspects of care were a multidisciplinary evaluation with maternal-fetal medicine assistance and close follow-up. A discussion of several interesting aspects of the case follows the report.

* This case report has been approved per Central Michigan University's guidelines and written consent for publication was obtained from the patient due to the rarity of her condition.

Introduction

Epidermolysis Bullosa (EB) is a rare group of inherited skin conditions characterized by extreme weakness in the skin and mucous membranes, resulting in blister formation following minor trauma [1]. The overall incidence of inherited EB in the United States is 19.57 per 1 million live births [2]. The four major types of EB are classified by the skin layer affected [3]. There are many additional subtypes and mutations beyond the scope of this case, but the major classifications can be viewed in Table 1. These classifications are based solely on the affected layer of the skin.

Table 1: Major classifications of EB based on affected skin layer.

Type of EB	Skin layer affected
EB simplex	Epidermis
Junctional EB	Dermal-epidermal junction
Dystrophic EB	Below the basement membrane
Kindler Syndrome	Mixed layers

This case focuses on a pregnant patient with presumed autosomal Recessive Dystrophic subtype of Epidermolysis Bullosa (RDEB). The incidence of RDEB is estimated to be just 3.05 per million people [4]. It is caused by mutations in the COL7A1 gene on chromosome 3 [5], which encodes the crucial skin protein type VII collagen. The exact mutation dictates the severity of cutaneous involvement, but all patients are at high risk for wound infection [2] and squamous cell carcinoma [6].

Extracutaneous manifestations may affect nearly all internal organs including the urogenital tract, which can make conception and childbirth complex. Despite this added complexity, limited reports have shown that pregnancy in patients with RDEB is not contraindicated [1][7]. Pregnancy does not seem to impact the progression of the skin condition [8-10], and the available literature suggests that having EB does not innately increase the risk of typical pregnancy-related complications like preeclampsia or eclampsia [5][11-14]. Risk of labor and delivery-related complications may be higher due to the nature of the disease. Some reports suggest that normal vaginal delivery (NVD) is the safest delivery option, but many EB patients request a cesarean section (CS) due to vaginal blistering and heightened risk of damage to the pelvic floor [1][9][10][15]. CS's do have unique risks in these patients including delayed wound healing, infection, and blistering at incision sites [8][9]. Anesthesia is also challenging. Epidural anesthesia may be complicated by blistering of the skin, and if intubation is necessary the trauma from the procedure can cause serious postoperative complications [8][9]. It is recommended that a delivery plan, including mode of anesthesia, be determined well in advance with input from maternal-fetal medicine (MFM). Limited literature about pregnancy in patients with EB means there are no guidelines available for management. Therefore, clinical judgment from a multidisciplinary team should be used in each individual case with guidance from MFM.

Case Report

A 21-year-old G1P1000 female with congenital EB presented to our clinic with a pregnancy of 27 weeks' gestation to establish care with a new primary care physician (PCP). Prior to conception she met with a genetic counselor regarding pregnancy. Genetic testing revealed one frameshift mutation in the COL7A1 gene. The specific mutation had never been previously reported, but was believed to indicate RDEB based on historical mutation data and family history. The presumptive diagnosis of RDEB was made with some uncertainty due to the rarity of the mutation. Recommendation to meet with a maternal-fetal medicine (MFM) specialist was made. Carrier testing for her partner was recommended and the use of preimplantation genetic diagnosis with in-vitro fertilization (IVF) was discussed.

The patient was born with diffuse skin blistering and bullae which persisted throughout her life with moderate severity. Multiple care providers noted that blisters were especially prominent on her hands and feet, and she often experienced intraoral blistering and periodic dysphagia. Importantly, the vaginal mucosa was not affected. She did not receive regular wound care but consulted with a wound care specialist early in her pregnancy. She had no other medical issues.

There was no known family history of EB and no known consanguinity. Her father died of lung cancer at 50. Her mother had two early miscarriages of unknown etiology, for which her parents received genetic testing and discovered they were both heterozygous carriers for EB. This test result could not be confirmed by the authors, but supported the presumptive diagnosis of RDEB. Figure 1 depicts the patient's three-generation pedigree. The patient had four half-siblings, all healthy. Her partner's family history was noncontributory and he declined carrier testing.

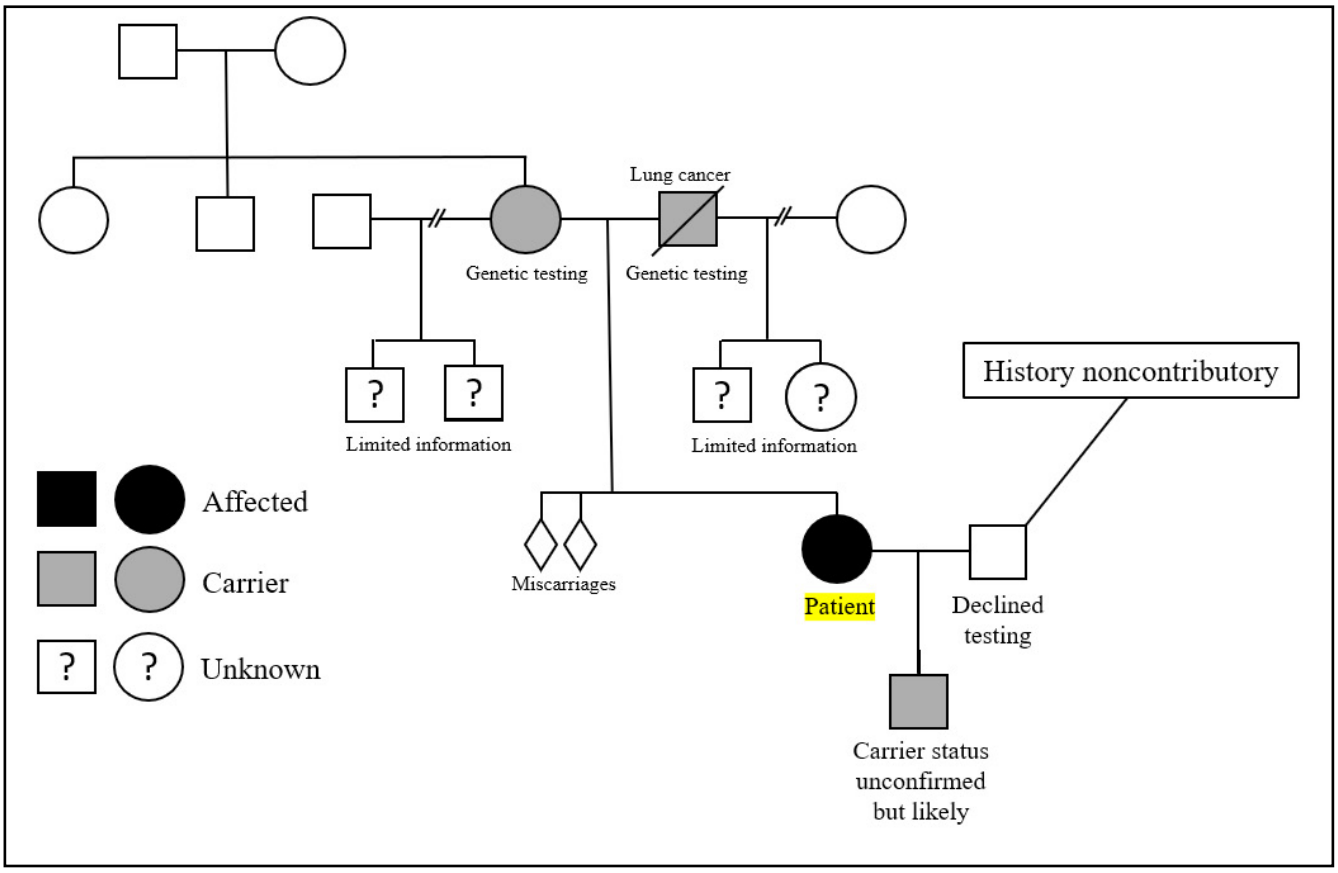

Figure 1: Patient's three generation pedigree

A full panel of updated laboratory screening tests were obtained at her PCP visit, several of which were abnormal but expected given her EB. Treatment was initiated for these minor abnormalities and her pregnancy progressed well. Conception was vaginal. Fetal growth was consistently on track, and there was no gestational diabetes, preeclampsia, or eclampsia. Despite the previous recommendation to consult with MFM, she declined and only saw her regular obstetrician. She received regular prenatal care but declined all prenatal genetic testing. At the onset of labor, she was transferred to a nearby hospital with MFM because the local anesthetists were not comfortable with her disease. She gave birth vaginally at 39 weeks and 5 days of gestation to a healthy male with no cutaneous signs of EB. Labor was complicated by postpartum hemorrhage of 1600mL due to several genital lacerations and the patient received a transfusion. The patient and infant were discharged home in stable condition.

Case Discussion

The patient had a history of probable RDEB with a singular frameshift mutation in the COL7A1 gene. She gave birth to a male infant who had no cutaneous abnormalities at birth or in the following weeks. A family history of EB was not noted, but her parents stated they had both tested positive as heterozygous carriers of EB many years earlier. Given this information inherited RDEB was the patient's likely diagnosis, but a de novo mutation could not be entirely ruled out without confirming parental carrier status.

The patient's partner declined genetic testing to determine whether he was a carrier for EB, which would have allowed for determination of the likelihood of the child being born with RDEB. Confirmed negative carrier status would have guaranteed the child to be a silent carrier and may have offered the parents peace of mind. Conversely, positive carrier status would have better guided decision-making. We believed that the potential benefits to be gained from paternal genetic testing outweighed the risks.

Use of IVF with preimplantation genetic diagnosis (PGD) was also declined. PGD allows for genetic analysis of oocytes

or embryos before they are implanted into the uterus. Since the patient had EB, PGD of oocytes would not have revealed new information. PGD of embryos would have been highly useful if the father was a confirmed carrier by allowing for selection of a heterozygous carrier embryo. In this case, the distribution of blistering allowed the patient to conceive comfortably through vaginal intercourse. Considering all of this, foregoing IVF was probably a good choice for this couple. However, IVF and PGD are critical options to discuss with EB patients seeking pregnancy.

The care team consisted of several doctors, including a geneticist, obstetrician, PCP, wound care specialist, dermatologist, and MFM specialist, all of whom helped to ensure the safety of mother and child during the pregnancy. Although RDEB increases the risk of some maternal complications [5][11-14], there is currently no recommendation against pregnancy. While our patient did not suffer consequences for declining regular care with MFM, there is no substantial evidence that this was a safe decision and all pregnant patients with EB must be strongly encouraged to seek MFM advice.

Patients should establish consistent care with a PCP prior to pregnancy as EB can cause anemia, renal damage, elevated copper levels, and deficiencies in iron, zinc, and several vitamins [16-20]. Correction and monitoring of these abnormalities is desirable before and after pregnancy.

Conclusion

Very few case reports exist on pregnant patients with RDEB. Consequently, guidelines for best practices do not exist. Reports to date suggest that some maternal complications are more likely in RDEB patients [5][11-14] but that pregnancy is not contraindicated [1][7]. Most literature suggests that NVD is the preferred method of delivery when feasible [8-10][13][15], but labor and delivery require detailed planning on a case-by-case basis because both NVD and CS are associated with unique risks. A MFM specialist should always be consulted when managing RDEB patients. Genetic testing and counseling would be beneficial for all EB couples, with consideration given to IVF and PGD. Finally, regular PCP follow up is critical pre and postnatally to monitor for organ dysfunction and to correct vitamin and mineral abnormalities.

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