www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2021;10(1):e100123
doi: 10.7363/100123
Received: 2019 Jul 31; revised: 2020 Jan 12; accepted: 2020 Jan 12; published online: 2020 Dec 02

Case report

Neonatal inflammatory skin and bowel disease type 2: a very rare disease associated with EGFR mutation

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Abstract

Homozygous Epidermal Growth Factor Receptor (EGFR) mutation is associated with neonatal inflammatory skin and bowel disease type 2.

We present the case of a preterm female infant with severe growth restriction and a severe and complex clinical course. She presented from birth with erosive and inflammatory skin lesions as well as several malformations (sparse scalp hair, craniofacial abnormalities, thin and long limbs, arachnodactyly, absence of subcutaneous fat, arthrogryposis and severe congenital heart disease). She developed recurrent skin and respiratory infections, failure to thrive, severe electrolyte imbalances and progressive heart failure. Neonatal inflammatory skin and bowel disease type 2 was suspected and directed genetic testing confirmed the presence of an EGFR gene mutation in homozygosity. Despite the optimization of medical therapy, the infant died of progressive cardiac failure at 3 months of age.

Keywords

Rare disease, genetics, EGFR, mutation, neonatal.

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How to cite

Lemos M, Gonçalves JS, Correia CR, Maria AT. Neonatal inflammatory skin and bowel disease type 2: a very rare disease associated with EGFR mutation. J Pediatr Neonat Individual Med. 2021;10(1):e100123. doi: 10.7363/100123.

Background

Epidermal Growth Factor Receptor (EGFR) belongs to a tyrosine kinase family of receptors. These receptors are situated on the cellular surface and bind to EGF and other factors, inducing cell proliferation [1]. The EGFR gene is located on chromosome 7p11. Mutations of the EGFR gene are associated with neoplastic diseases in the adult, but mutations in the child and the newborn are rarer and, therefore, not well documented.

More specifically, the homozygous EGFR mutation is associated with neonatal inflammatory skin and bowel disease type 2. So far, only a hand few of cases have been reported [2, 3].

The present case demonstrates the key clinical features associated with this disease and its complex management.

Case presentation

We present the case of a preterm female infant, born at 28 weeks of gestation via emergency cesarean due to non-reassuring fetal status, with severe growth restriction, weighing 650 grams. She was the fifth child of consanguineous parents. Pregnancy was otherwise uneventful and the fetal ultrasounds at 9, 14 and 19 weeks were described as normal. No fetal maturation induction was performed. Her Apgar score was 4 at the first minute and 7 at the fifth and tenth minutes. She was intubated in the delivery room and was transferred to a Neonatal Intensive Care Unit (NICU).

On physical examination, she had several apparent malformations: alopecia, protuberant frontal and parietal bones, hypoplastic facial bones, downslanting palpebral fissures, thin and long limbs, arachnodactyly, absence of subcutaneous fat and arthrogryposis (**Figures 1-4**).

Additionally, she presented with very fragile skin with extensive erythema, requiring permanent skin care and minimal handling (**Figures 2-4**).

While in the NICU, she was on continuous mechanical ventilation and presented with recurrent infections (sepsis and recurrent respiratory infections), requiring multiple courses of broad-spectrum antibiotics.

Additionally, she developed anemia and thrombocytopenia, requiring multiple transfusions. Furthermore, she presented failure to thrive, with weight percentiles consistently below the 3rd percentile of Fenton preterm growth chart for girls.

Echocardiography revealed a severe congenital heart disease with ventricular disproportion with hypoplastic left ventricle, severe aortic arch hypoplasia, complete atrioventricular septal defect (**Fig. 5**) and a patent ductus arteriosus.

Figure 1. Demonstrating the particular phenotype: alopecia, protuberant frontal and parietal bones, hypoplastic facial bones, downslanting palpebral fissures, thin and long limbs, arachnodactyly, absence of subcutaneous fat and arthrogryposis.

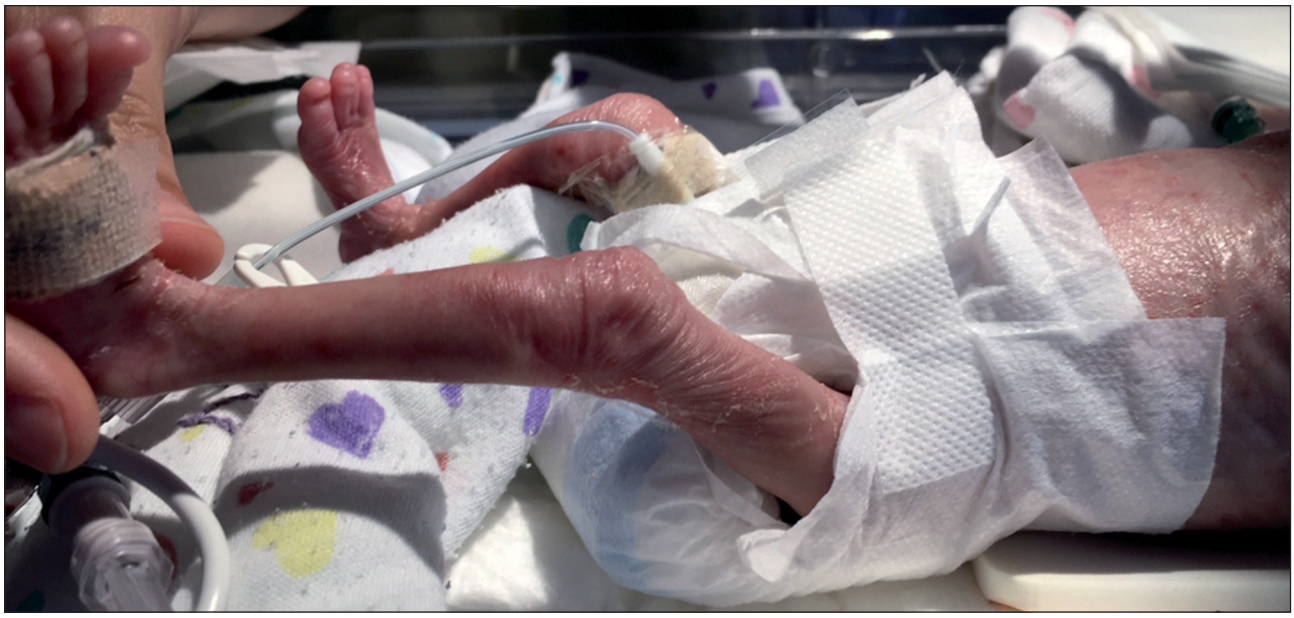

Figure 2. Arthrogryposis and erythematous cutaneous lesions.

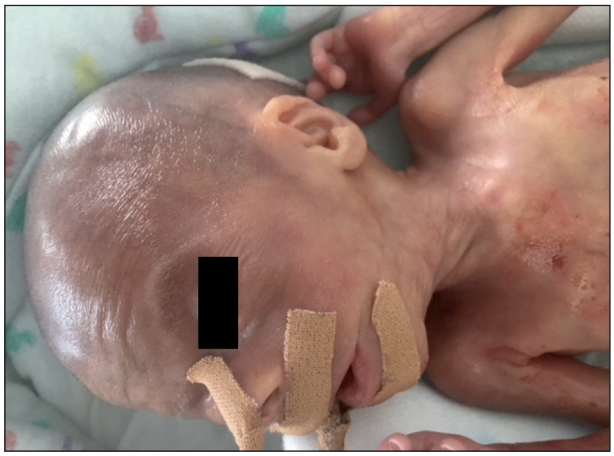

Figure 3. Detail of the face. Additionally, the erythematous cutaneous lesions are visible in the thorax.

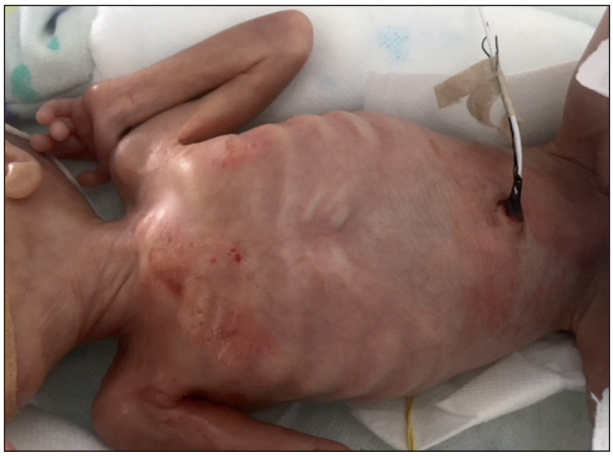

Figure 4. Inflammatory skin lesions and absence of subcutaneous fat visible in the thorax.

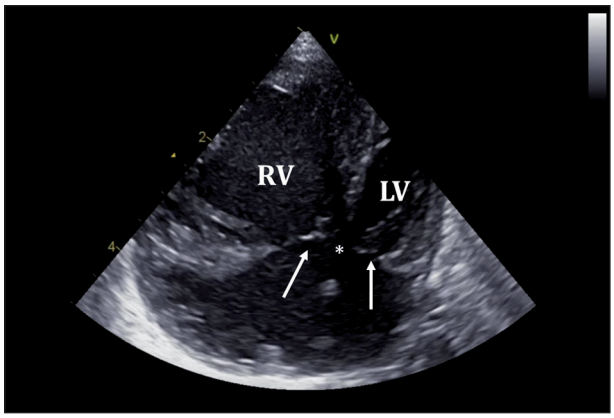

Figure 5. Transthoracic echocardiogram showing an atrioventricular septal defect and hypoplastic left heart syndrome.
LV: left ventricle; RV: right ventricle; white arrows: single atrioventricular valve; asterisk: atrioventricular septal defect.

She developed persistent hypernatremia, requiring very high volume intakes (more than 180 mL per kg per day), persistent hypokalemia, hypophosphatemia and severe hypomagnesemia requiring frequent replacement therapy. The renal function was otherwise normal. Renal ultrasound revealed bilateral renal enlargement, increased echogenicity of the parenchyma and diminished corticomedullary differentiation.

Serial cranial ultrasounds showed tetraventricular hydrocephalus (caused by bilateral ventricular hemorrhage) with severe periventricular and subcortical white matter lesion, cerebellum atrophy and a mega cisterna magna.

Due to persistently erythematous and friable skin, a skin biopsy was performed, showing para-

keratosis and neutrophils in the stratum corneum, with perifollicular pustules, consistent with ongoing inflammation. Gram staining was negative for bacteria.

Initial genetic testing with karyotype and comparative genomic hybridization were normal.

Due to the several phenotypical abnormalities present at birth, an initial diagnosis of neonatal progeroid syndrome (or Wiedemann Rautenstrauch Syndrome [WRS]) was suspected. This syndrome is characterized by intrauterine growth restriction and aged appearance at birth, absence of subcutaneous fat with thin and fragile skin, sparse scalp hair, distinctive craniofacial abnormalities (triangular face with hypoplasia of facial bones, abnormal palpebral fissures and pseudohydrocephalus, with enlarged fontanelles) as well as failure to thrive [4].

WRS is an autosomal recessive genetic condition and thus more frequent in children of consanguineous parents, which was also consistent with the present case. However, WRS also presents with natal teeth, paradoxical caudal fat accumulation, genital anomalies, endocrine abnormalities (usually hypothyroidism and hyperprolactinemia) and radiologic abnormalities, which were not consistent with our case [4].

More importantly, WRS is not associated with persistent erythematous and inflammatory skin lesions and recurrent infections and, for this reason, this hypothesis was discarded.

Upon review of the literature, inflammatory skin and bowel disease type 2 was suspected.

Findings compatible with this disease were premature birth with intrauterine growth restriction, fragile skin with erythematous lesions, recurrent infections (manly skin and respiratory), phenotypical abnormalities (arachnodactyly, downslanting palpebral fissures and sparse scalp hair), failure to thrive, heart abnormalities and enlarged kidneys [2, 3, 5].

Given the whole phenotype and clinical presentation, EGFR gene mutation was suspected. Polymerase chain reaction and direct and bidirectional gene sequencing identified the c.1283G-A, p.(Gly428Asp) mutation in homozygosity, in exon 11 of the EGFR gene.

The electrolyte imbalance (persistent hypernatremia, hypokalemia, hypophosphatemia and hypomagnesemia) presented itself as a challenge to manage. The need for high intakes of fluids contributed to fluid overload and cardiac failure, progressively refractory to medical therapy.

Palliative surgical repair of the heart defect was discussed by a multidisciplinary team (neonatology, pediatric cardiology, cardiac surgery) but, given her many co-morbidities and the disease prognosis, a conservative approach was chosen.

At 3 months of age, the infant died of progressive cardiac failure, despite optimization of medical therapy.

Discussion

The mutation c.1283G-A, p.(Gly428Asp), when in homozygosity, is associated with neonatal inflammatory skin and bowel disease type 2 [2, 3].

The inheritance of this disease seems to be autosomal recessive, and thus consanguinity is a high-risk factor [2]. Obtaining genetic information from both parents would be of incredible importance, as it would confirming and supporting the findings described by other authors.

Campbell et al. described this syndrome in an infant born to Roma parents, with extensive skin lesions presenting at birth and loss of scalp hair. Additionally, the child had probable aortic coarctation, chronic diarrhea, failure to thrive and recurrent infections (mainly skin and respiratory infections) [3].

Similarly, Alruwaithi and Sherlock described a case where whole-exome sequencing revealed homozygosity for Gly428Asp, a mutation in the EGFR gene causing fragile skin with recurrent skin infections, a ventriculoseptal defect, failure to thrive, chronic watery diarrhea, enlarged kidneys and phenotypical abnormalities, such as arachnodactyly, downslanting palpebral fissures and sparse scalp hair [5].

Likewise, all patients described had been born prematurely and presented with intrauterine growth restriction and, thus, extremely low birth weight [3, 5].

These findings are compatible with the current case and with the genetic findings, although, unlike the cases described above, there was no evidence of diarrhea or bowel disease. However, total enteral nutrition was not achieved until 1 month of age and consisted solely of special preterm formula. Also, the girl in the case described by Alruwaithi and Sherlock did not develop diarrhea until she was 4 years old, unlike the case described by Campbell et al., in which the boy had lifelong diarrhea [3, 5].

Whole exome sequencing has a central role in the challenging diagnosis of this condition.

In the literature, there are no reports of successful therapy, and the longest life expectancy described was 5 years of age [5].

Given the overall bad prognosis associated with this syndrome, the identification of the mutated gene was fundamental in the decisions regarding surgical and medical management.

Conclusions

Homozygous EGFR mutation is associated with neonatal inflammatory skin and bowel disease type 2, which presents with a complex and severe phenotype and overall bad prognosis.

Fragile skin with recurrent skin infections, sparse scalp hair, recurrent respiratory infections, cardiac abnormalities, enlarged kidneys, failure to thrive and chronic diarrhea seem to be the predominant features in these patients.

Directed genetic testing is essential in the diagnosis of this condition.

Neonatologists and pediatricians should consider EGFR mutation in neonates presenting with inflammatory skin disease from birth.

Declaration of interest

The Authors declare that there is no conflict of interest. There are no funding to report for this submission.

References

1. Scaltriti M, Baselga J. The Epidermal Growth Factor Receptor Pathway: A model for targeted therapy. Clin Cancer Res. 2006;12(18):5268-72.
2. https://www.omim.org/entry/616069, last access: 28 December 2018.
3. Campbell P, Morton PE, Takeichi T, Salam A, Roberts N, Proudfoot LE, Mellerio JE, Aminu K, Wellington C, Patil SN, Akiyama M, Liu L, McMillan JR, Aristodemou S, Ishida-Yamamoto A, Abdul-Wahab A, Petrof G, Fong K, Harnchoowong S, Stone KL, Harper JI, Irwin McLean WH, Simpson MA, Parsons M, McGrath JA. Epithelial inflammation resulting from an inherited loss-of-function mutation in EGFR. J Invest Derm. 2014;134(10): 2570-8.
4. Pivnick EK, Angle B, Kaufman RA, Hall BD, Pitukcheewanont P, Hersh JH, Fowlkes JL, Sanders LP, O'Brien JM, Carroll GS, Gunther WM, Morrow HG, Burghen GA, Ward JC. Neonatal Progeroid (Wiedemann-Rautenstrauch) Syndrome: Report of Five. New Cases and Review. Am J Med Genet. 2000;90(2):131-40.
5. Alruwaithi M, Sherlock M. A210 Neonatal Inflammatory Skin and Bowel Disease Caused By a Homozygous EGFR Mutation: A Case Report And Review Of The Medical Literature. J Can Assoc Gastroenterol. 2018;1(Suppl 1):367-8.