Received: 10 June 2023 | Revised: 18 September 2023 | Accepted: 27 September 2023

DOI: 10.1002/ccr3.8028

CASE REPORT

Clinical Case Reports Open Access WILEY

Esophageal stenosis in an adult Mexican patient with diastrophic dysplasia: Case report

Tamara N. Kimball[1] | **Pamela Rivero-García**[1] | **Bernardo Pérez González**[2] | **Alfredo Adolfo Reza-Albarrán**[1,3]

[1]División de Estudios de Posgrado de la Facultad de Medicina, Universidad Nacional Autónoma de México/Departamento de Genética, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

[2]División de Estudios de Posgrado de la Facultad de Medicina, Universidad Nacional Autónoma de México/Departamento de Endoscopia Gastrointestinal, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

[3]Departamento de Endocrinología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Correspondence
Alfredo Adolfo Reza-Albarrán, Departamento de Endocrinología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. Vasco de Quiroga 15, Belisario Domínguez, Sección XVI, Delegación Tlalpan, 14080, Mexico City, Mexico.
Email: alfredo.rezaa@incmnsz.mx

Funding information
Universidad Nacional Autónoma de México

Key Clinical Message

Diastrophic dysplasia (DTD) is caused by biallelic pathogenic variants in the *SLC26A2* gene. We report the case of a 49-year-old female with DTD and esophageal stenosis. This broadens the phenotypic spectrum in adult patients with DTD and raises awareness of extra-skeletal manifestations that could develop in later stages of life.

KEYWORDS

diastrophic dysplasia, esophageal stenosis, skeletal dysplasia, *SLC26A2*

1 | INTRODUCTION

Diastrophic dysplasia (DTD, OMIM #222600) is an autosomal recessive disorder caused by biallelic pathogenic variants (PVs) in the *SLC26A2* gene (OMIM #606718), located at 5q32.[1] It was first described by Lamy and Maroteaux in 1960.[2] Worldwide prevalence is currently unknown; however, it has a high frequency in the Finnish population, estimated at 1/33,000.[3]

SLC26A2 codes for a solute carrier family 26-member 2 transporter, which is known to have a role in endochondral bone formation. Mutations in this gene can also lead to Achondrogenesis Ib, atelosteogenesis type II, De la Chapelle dysplasia, and multiple epiphyseal dysplasia (MED) type 4, all with an autosomal recessive mode of inheritance.[1] The phenotype correlates with the *SLC26A2* specific mutations and relies on the residual solute transporter activity. Diverse studies have observed that *SLC26A2* is expressed in many tissues (cartilage, colon, placenta, sweat glands, pancreas, and liver); however, the reported phenotypic characteristics of DTD have been limited to bone and joints.

DTD is characterized by limb shortening, spinal deformities, large joint contractures, ulnar deviation of fingers, sandal gap, bilateral clubfoot, and abduction of the thumbs (also known as "Hitchhiker's thumbs"). The latter is considered a hallmark of DTD, but the absence does not rule out the disease.[4,5] In addition, hearing loss has been reported in 66% of the cases.[6]

Most long-term follow-up of patients with DTD has focused on bone complications, such as an earlier

presentation of osteoarthritis and progressive spinal deformity.[4] However, there are no previous studies that document gastrointestinal manifestations in patients with DTD. Therefore, we present the case of a 49-year-old female patient with DTD and molecular confirmatory test who presented with esophageal stenosis to expand the phenotype of adult patients with this syndrome and raise awareness of extra-skeletal manifestations that could develop in later stages of life.

2 | CASE REPORT

We present the case of a 49-year-old Mexican woman, born to non-consanguineous parents. She was referred to the genetics consult under the clinical suspicion of bone dysplasia. Her weight, height, and head circumference were under the third percentile (24 kg, 85 cm, and 48 cm, respectively), adapted from Mexican Ramos Galvan growth charts, but her body mass index was in the obesity range (33.2 kg/m^2). On physical exam, she exhibited a short, narrow thorax with pectus carinatum, intercalary shortening of upper limbs, with a limited extension due to multiple joint contractions, hands with Hitchhiker thumbs, and camptodactyly of the first four fingers, bilaterally. Short, hypotrophic lower limbs with bilateral clubfoot and sandal gap were observed. Bone radiographs are described in Figure 1.

She presented with profound sensorineural hearing loss, apparently since birth, therefore she did not develop language. Audiometry was performed, showing descending curves corresponding to severe, sensorial hearing loss and tympanometry with abnormal flat curves bilaterally. DTD was suspected, therefore next-generation sequencing was conducted. Two variants in the *SLC26A2* gene in compound heterozygous state were found: c.835C>T (p.Arg279Trp), classified as a pathogenic variant according to the American College of Medical Genetics and Genomics (ACMG) and c.1153G>T (p.Asp385Tyr), classified as a probably pathogenic variant, which confirmed the diagnosis of DTD.

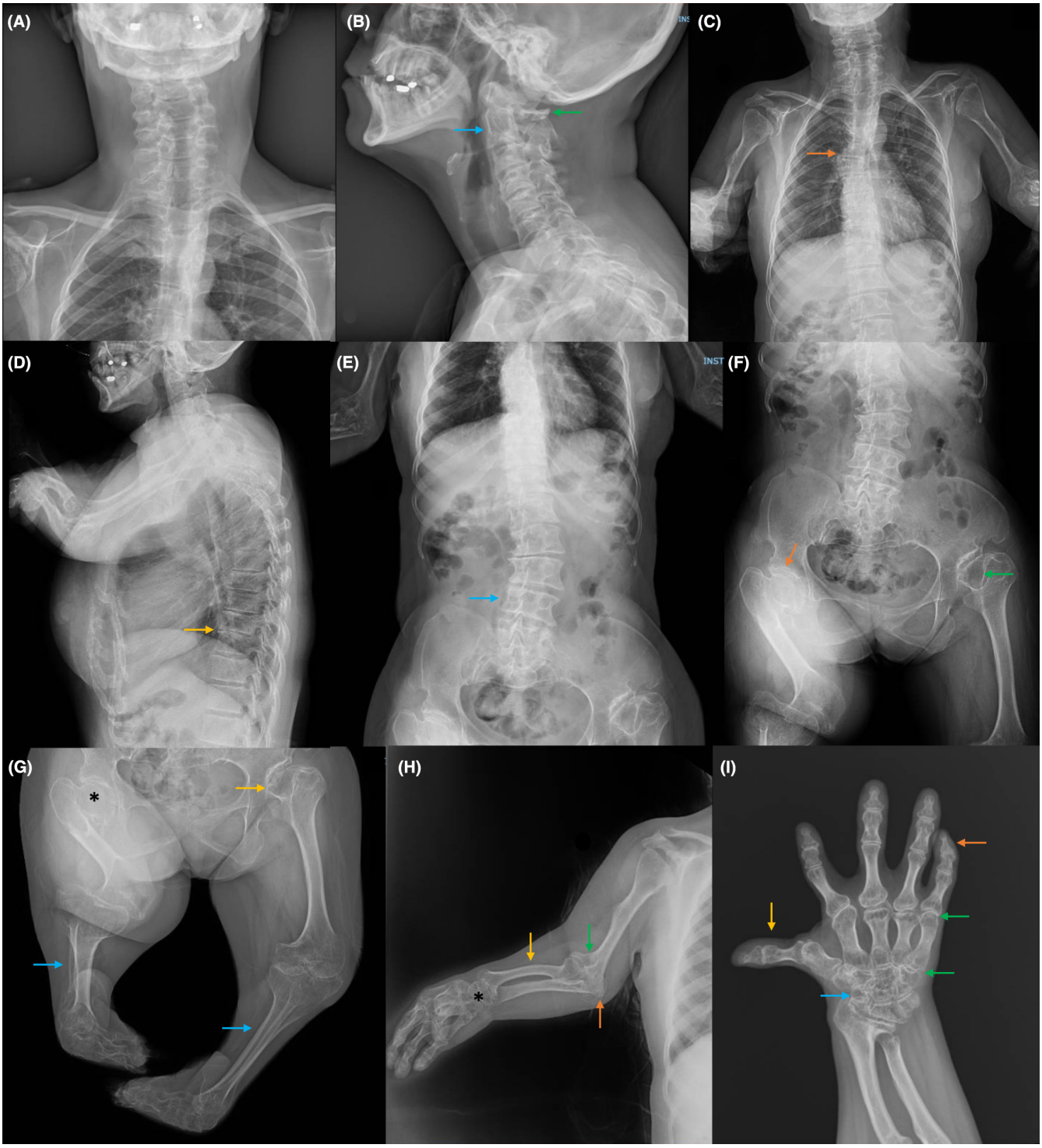
She presented with progressive dysphagia of 3 years of evolution. This caused 7 kg weight loss and hypochromic microcytic anemia secondary to iron deficiency, which required blood transfusions. Also, she presented with episodes of oropharyngeal candidiasis and oral and buccal herpes on multiple occasions. A thorax computer tomography revealed a type 1 hiatal hernia.

In 2022, the Department of Gastrointestinal Endoscopy conducted two sequential dilatation procedures that were 5 months apart. The initial procedure used a front-view Olympus H180 videoendoscope which revealed an area of stenosis obstructing the endoscope's passage about 10 cm from the dental arch. Septotomy was performed using a MicroKnife XL Triple-Lumen Needle Knife 5.5F (1.8 mm). This area displayed clear scar changes, which prompted a CRE balloon dilation to address the issue.

First, a hydrophilic guide was advanced beyond the stenosis with the help of fluoroscopic guidance. Once the correct placement was confirmed, the dilation was executed at a steady pressure of 12 mmHg for 60 s. The examination of the gastric chamber revealed a hyaline pool and mucosal atrophy was observed in the gastric fundus and body (Figure 2). Furthermore, biopsies were taken from the esophagus, which indicated mild chronic esophagitis.

The second procedure utilized a Front-view endoscope Fuji 600 VPP 4450, which revealed that the esophagus exhibited an altered shape and decreased distensibility due to two stenotic areas located at 10 cm and the esophagogastric junction, posing challenges for endoscope passage. The esophagogastric junction was located 32 cm from the dental arch, and a diaphragmatic constriction was

FIGURE 1 X-rays of a Mexican patient with diastrophic dysplasia. (A, B) Anteroposterior (AP) and lateral x-ray of the cervical spine with widening of the vertebral bodies and decreased intersomatic spaces, C1 with hypotrophy of the posterior tubercle (green arrow) and discrepancy of C2 height in comparison to other vertebral bodies (blue arrow). (C, D) AP and lateral x-ray of the thoracic spine with decreased intersomatic spaces, vertex of scoliosis at T5–T6 (orange arrow), effacement of the costovertebral joints and T8 with subchondral sclerosis and osteophytes (yellow arrow). (E) AP x-ray of the lumbar spine with morphological abnormalities from L2 to L5, L4 with decreased height (blue arrow). (F) AP x-ray of the pelvis showing multiple morphological abnormalities at iliac crest, predominantly left, with verticalization of the left acetabulum and loss of its concavity (green arrow), the right acetabule with subchondral sclerosis and multiple osteophytes (orange arrow). (G) Bipodalic mechanical axis. Right leg with evidence of coxa valga and abnormal femoral head (black asterisk); decreased bone density. Left leg with subluxation of the femoral head due to verticalization of the acetabulum (yellow arrow), subchondral sclerosis, and varus attitude. Bilateral tibial and fibular hypoplasia (blue arrows). (H) AP x-ray of the right arm. Humerus with widening of distal metaphysis (green arrow). Ulna with morphological alterations at the level of the proximal metaphysis (orange arrow). Widening of the radial dome and valgus deformity (yellow arrow). Abundant subchondral sclerosis and decreased joint spaces. Lack of distinction of carpal bones (black asterisk). (I) AP x-ray of the left hand. Decreases in the intra-articular spaces at the level of the carpus (blue arrow). Metacarpals with widening in proximal and distal metaphyses and abundant subchondral sclerosis (green arrows). The characteristic “Hitchhiker's thumb” is observed (abnormally abducted) (yellow arrow). Fifth finger with a deviation of the distal phalange towards medial (orange arrow).



identified at 35 cm. Within the distal third of the esophagus, two non-confluent linear erosions larger than 5 mm, separated by folds, were observed. No abnormalities were detected in the gastric chamber and duodenum. Furthermore, as a follow-up measure, a Savary dilator guide was utilized to expand the narrow section of the passage, resulting in an expansion of up to 11 mm. For both procedures, controlled tearing was observed, and no perforations were encountered.

3 | DISCUSSION

SLC26A2 gene codes for a Na^+-independent sulfate/chloride antiporter. It has 14 transmembrane domains and intracellular amino and carboxyl ends, the latter with an anti-sigma factor antagonist domain.[7] In optimal conditions, it regulates the uptake of inorganic sulfate, necessary for cartilage proteoglycan sulfation. However, *SLC26A2* gene mutations in homozygous or compound

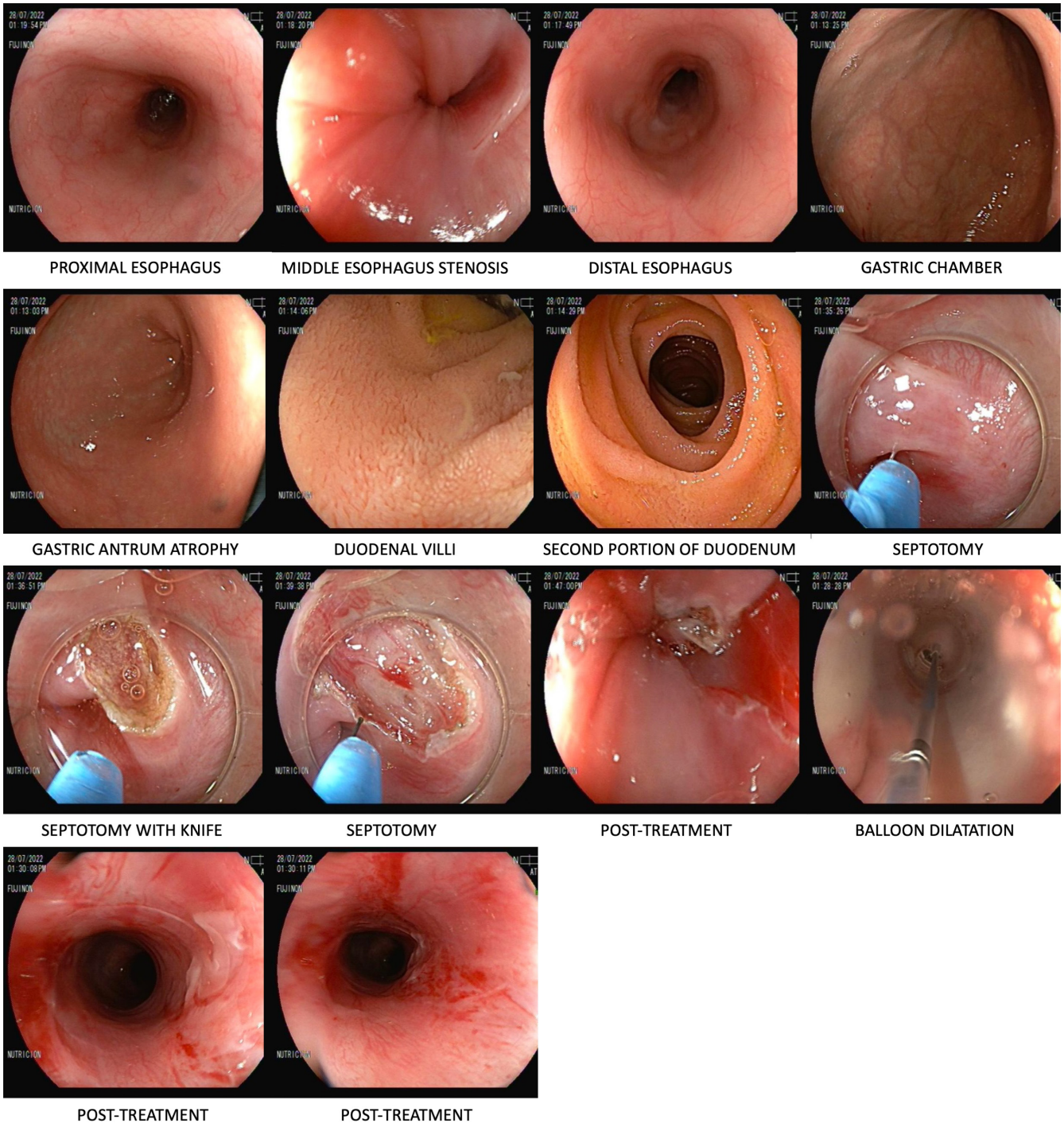


FIGURE 2 Endoscopic images of a patient with diastrophic dysplasia and esophageal stenosis, which required septotomy and balloon dilatation.

heterozygous state lead to chondrodysplasias, a heterogeneous group of genetic disorders. The proposed underlying pathophysiological mechanism is impaired sulfate transportation through cell membranes, intracellular sulfate depletion, and insufficiently sulfated proteoglycans, leading to cartilage immaturity and bone deformity.[8,9]

Although in vivo *SLC26A2* protein expression has been documented in many different cells other than chondrocytes, the phenotype of DTD has been essentially confined to chondrocyte-dependent tissues. A possible explanation is the compensatory activity of other transporters which is insufficient in chondrocytes.[9]

Contrary to other skeletal dysplasias, which are hard to differentiate one from another, DTD has distinctive ultrasonographic skeletal findings that can be detected as early as 11 weeks of gestation, even though most of the prenatal

diagnosis is made in the second trimester. Some of the frequently reported are micromelia, congenital talipes equinovarus, and Hitchhiker's thumbs,[10] observed in our patient's physical examination (Figure 1). Based on the conservation of the external anatomy of the ear, it can be assumed that she did not have cystic ear swelling during infancy. Although it is considered a pathognomonic characteristic of the disease, it is absent in one-third of the individuals with DTD.

Our patient presented with a combination of *SLC26A2* variants in compound heterozygous state that has not been previously reported. The first, c.835C>T (p.Arg279Trp), is the most common PVs found in non-Finnish populations, corresponding to 45% of the alleles.[11] It is a missense variant located at exon 3, affecting an extracellular loop. Previous authors have determined genotype–phenotype associations depending on the location of the variants at the *SLC26A* gene. PVs located at the extracellular loops, regulatory 5′ flanking region, or cytoplasmic tail of the protein are associated with milder phenotypes in comparison to PV located at the transmembrane domain.[7,8] In a functional study by Karniski et al., they evaluated the expression of sulfate transport in 11 mutations of mammalian cells located in the *SLC26A2* gene. The p.Arg279Trp variant was found to have a partial residual activity, at a rate of 32% in comparison with the wild type. The authors concluded that patients with DTD typically have a partial function on one allele and a loss of function in the other.[12] Likewise, Barbosa et al. reported that patients with this variant in a homozygous state present mostly with the MED-phenotype, contrary to compound heterozygous state which usually present with DTD or atelosteogenesis phenotype.[7]

The second variant identified, *SLC26A2* c.1153G>T (p.Asp385Tyr), is a novel variant, also located at exon 3. It was classified as a likely pathogenic variant since it meets the following ACMG[13] criteria: based on *in-silico* predictions for a missense variant in this gene supporting a deleterious effect (PP3, aggregated prediction score 0.873), extremely low frequency in gnomAD population databases (PM2, allele frequency 0.288%) and patients phenotype is highly specific for the disease (PP4).

Usually, the phenotype in autosomal recessive diseases with enzyme defects or deficiencies in transporter proteins is associated with residual activity. In the case of DTD, various studies have attributed the severity of the clinical affectation to the residual activity of sulfate transporters.[1,14] However, other studies have observed that the genotype–phenotype associations cannot be entirely attributed to the mutations. Factors such as modifier genes, environmental, and epigenetic have been proposed to interact and activate alternative pathways, which could explain the clinical variability.[1,7,14]

There are multiple complications secondary to bone deformities in DTD that have been reported. During the neonatal period, a short rib cage and instability and collapsibility of the trachea can lead to neonatal respiratory insufficiency. In young adults with DTD, progressive scoliosis and joint contractures are important causes of morbidity.[4,6] To date, treatment in these patients remains symptomatic. Nevertheless, recent studies in mice treated with N-acetylcysteine have shown an increase in the sulfation leading to improvement in the skeletal features.[15,16]

Our patient presented with esophageal stenosis which required several balloon dilatations and a septotomy. This was probably the result of long-term gastroesophageal reflux (GERD) which went undetected as she was unable to communicate symptoms due to her profound hearing loss. Additionally, two factors contributed to the development of GERD in her case: obesity and hiatal hernia. A study by LoTurco et al. found a higher self-reported prevalence of reflux in patients with skeletal dysplasias (predominantly composed of osteogenesis imperfecta cases), which correlated with the number of medications taken.[17]

To our knowledge, this is the oldest patient reported in the literature with DTD, and the second Mexican patient reported in the literature with clinical and molecular confirmation of DTD.[18] Only a few studies have reported the long-term features in adult patients with this disorder, especially involving extra-skeletal manifestations, many of which could be underdiagnosed. This case which presents esophageal stenosis broadens the phenotypic spectrum in adult patients with DTD. More studies are necessary to elucidate the mechanisms underlying DTD and explore their potential involvement in cell types not previously reported.

AUTHOR CONTRIBUTIONS

Tamara N. Kimball: Conceptualization; investigation; writing – original draft. **Pamela Rivero-García:** Conceptualization; investigation; writing – original draft. **Bernardo Pérez González:** Supervision; writing – review and editing. **Alfredo Adolfo Reza-Albarrán:** Supervision; writing – review and editing.

ACKNOWLEDGMENTS

We would like to thank the patient and her family for their participation in this study.

FUNDING INFORMATION

The Universidad Nacional Autónoma de México supported this work by covering the Article Processing Charges.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Tamara N. Kimball https://orcid.org/0000-0002-1107-0771
Pamela Rivero-García https://orcid.org/0000-0003-2189-6523
Bernardo Pérez González https://orcid.org/0000-0003-0128-9574
Alfredo Adolfo Reza-Albarrán https://orcid.org/0000-0002-3732-8726

REFERENCES

1. Rossi A, Superti-Furga A. Mutations in the diastrophic dysplasia sulfate transporter (DTDST) gene (SLC26A2): 22 novel mutations, mutation review, associated skeletal phenotypes, and diagnostic relevance [published correction appears in hum Mutat 2001;18(1):82]. *Hum Mutat*. 2001;17(3):159-171. doi:10.1002/humu.1
2. Maroteaux P, Lamy M, Robert JM. Le nanisme thanatophore [Thanatophoric dwarfism]. *Presse med (1893)*. 1967;75(49):2519-2524.
3. Crowley RL, Haas RE. Total knee arthroplasty in a patient with diastrophic dwarfism. *AANA J*. 2010;78(5):366-368.
4. Silveira C, da Costa SK, Lacarrubba-Flores MD, et al. SLC26A2/DTDST Spectrum: a cohort of 12 patients associated with a comprehensive review of the genotype-phenotype correlation. *Mol Syndromol*. 2023;13(6):485-495. doi:10.1159/000525020
5. de Souza LT, Ferreira BG, Loureiro Souza CW, et al. Prenatal diagnosis of diastrophic dysplasia in the second trimester of pregnancy: two- and three- dimensional ultrasonographic findings. *Turk J Obstet Gynecol*. 2021;18(3):258-263. doi:10.4274/tjod.galenos.2021.35033
6. Tunkel D, Alade Y, Kerbavaz R, Smith B, Rose-Hardison D, Hoover-Fong J. Hearing loss in skeletal dysplasia patients. *Am J med Genet A*. 2012;158A(7):1551-1555. doi:10.1002/ajmg.a.35373
7. Barbosa M, Sousa AB, Medeira A, et al. Clinical and molecular characterization of diastrophic dysplasia in the Portuguese population. *Clin Genet*. 2011;80(6):550-557. doi:10.1111/j.1399-0004.2010.01595.x
8. Superti-Furga A, Rossi A, Steinmann B, Gitzelmann R. A chondrodysplasia family produced by mutations in the diastrophic dysplasia sulfate transporter gene: genotype/phenotype correlations. *Am J med Genet*. 1996;63(1):144-147. doi:10.1002/(SICI)1096-8628(19960503)63:1<144::AID-AJMG25>3.0.CO;2-N
9. Haila S, Hästbacka J, Böhling T, Karjalainen–Lindsberg ML, Kere J, Saarialho–Kere U. SLC26A2 (diastrophic dysplasia sulfate transporter) is expressed in developing and mature cartilage but also in other tissues and cell types. *J Histochem Cytochem*. 2001;49(8):973-982. doi:10.1177/002215540104900805
10. Forlino A, Piazza R, Tiveron C, et al. A diastrophic dysplasia sulfate transporter (SLC26A2) mutant mouse: morphological and biochemical characterization of the resulting chondrodysplasia phenotype. *Hum Mol Genet*. 2005;14(6):859-871. doi:10.1093/hmg/ddi079
11. Superti-Furga A, Neumann L, Riebel T, et al. Recessively inherited multiple epiphyseal dysplasia with normal stature, club foot, and double layered patella caused by a DTDST mutation. *J med Genet*. 1999;36(8):621-624.
12. Karniski LP. Functional expression and cellular distribution of diastrophic dysplasia sulfate transporter (DTDST) gene mutations in HEK cells. *Hum Mol Genet*. 2004;13(19):2165-2171. doi:10.1093/hmg/ddh242
13. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30
14. Syvänen J, Helenius I, Hero M, Mäkitie O, Ignatius J. Recessive MED with auricular swelling due to compound heterozygosity Arg279Tpr/Thr512Lys in the SLC26A2 gene. *Am J med Genet A*. 2013;161A(6):1491-1494. doi:10.1002/ajmg.a.35872
15. Monti L, Paganini C, Lecci S, et al. N-acetylcysteine treatment ameliorates the skeletal phenotype of a mouse model of diastrophic dysplasia. *Hum Mol Genet*. 2015;24(19):5570-5580. doi:10.1093/hmg/ddv289
16. Paganini C, Gramegna Tota C, Monti L, et al. Improvement of the skeletal phenotype in a mouse model of diastrophic dysplasia after postnatal treatment with N-acetylcysteine. *Biochem Pharmacol*. 2021;185:114452. doi:10.1016/j.bcp.2021.114452
17. LoTurco HM, Carter EM, McInerney DE, Raggio CL. Patient-reported prevalence of gastrointestinal issues in the adult skeletal dysplasia population with a concentration on osteogenesis imperfecta. *Am J med Genet A*. 2022;188(5):1435-1442. doi:10.1002/ajmg.a.62658
18. Macías-Gómez NM, Mégarbané A, Leal-Ugarte E, Rodríguez-Rojas LX, Barros-Núñez P. Diastrophic dysplasia and atelosteogenesis type II as expression of compound heterozygosis: first report of a Mexican patient and genotype-phenotype correlation. *Am J med Genet A*. 2004;129A(2):190-192. doi:10.1002/ajmg.a.30149

How to cite this article: Kimball TN, Rivero-García P, Pérez González B, Reza-Albarrán AA. Esophageal stenosis in an adult Mexican patient with diastrophic dysplasia: Case report. *Clin Case Rep*. 2023;11:e8028. doi:10.1002/ccr3.8028