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CLINICAL REPORT

De novo nonsense variant in *ASXL3* in a Chinese girl causing Bainbridge–Ropers syndrome: A case report and review of literature

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Abstract

Background: Bainbridge-Ropers syndrome (BRPS, OMIM #615485) was first identified in 2013 by Bainbridge et al. and is a neurodevelopment disorder characterized by failure to thrive, facial dysmorphism and severe developmental delay. BRPS is caused by heterozygous loss-of-function (LOF) variants in the additional sex combs-like 3 (*ASXL3*) gene. Due to the limited specific recognizable features and overlapping symptoms with Bohring–Opitz syndrome (BOS, OMIM #612990), clinical diagnosis of BRPS is challenging.

Methods: In this study, a 2-year-8-month-old Chinese girl was referred for genetic evaluation of severe developmental delay. The reduced fetal movement was found during the antenatal period and bilateral varus deformity of feet was observed at birth. Whole-exome sequencing and Sanger sequencing were used to detect and confirm the variant.

Results: A novel nonsense variant c.1063G>T (p.E355*) in the *ASXL3* gene (NM_030632.3) was identified in the proband and the clinical symptoms were compatible with BRPS. The parents were physical and genetic normal and prenatal diagnosis was requested for her pregnant mother with a negative Sanger sequencing result.

Conclusion: The study revealed a de novo LOF variant in the *ASXL3* gene and expanded the mutation spectrum for this clinical condition. By performing a literature review, we summarized genetic results and the clinical phenotypes of all BPRSs reported so far. More cases study may help to elucidate the function of the *ASXL3* gene may be critical to understand the genetic aetiology of this syndrome and assist in accurate genetic counselling, informed decision making and prenatal diagnosis.

KEYWORDS

ASXL3, Bainbridge-Ropers syndrome, loss-of-function, prenatal diagnosis, whole exome sequencing

1 | INTRODUCTION

Bainbridge-Ropers syndrome (BRPS, OMIM #615485) is a recently identified neurodevelopmental disorder, characterized by the severe developmental delay with feeding problems, hypotonia, ulnar deviation of hands and characteristic facial changes of the prominent forehead, full (everted) lower lip, arched eyebrows, low-set ears, broad nasal tip and anteverted nares (Bainbridge et al., 2013; Dinwiddie et al., 2013). It was first identified in four unrelated probands by Bainbridge et al. (2013) using whole-exome sequencing. Frameshift, truncating or splicing variants in the *ASXL3* gene have been shown to be responsible for the BRPS. De novo truncating mutations in *ASXL1* and *ASXL2*, which belong to the same gene family as *ASXL3*, cause Bohring–Opitz syndrome (BOS, OMIM #612990) and *ASXL2*-related disorder (OMIM #612991), respectively. (Hastings et al., 2011; Shashi et al., 2016). Although BRPS and BOS share some clinical features including severe developmental delay, feeding problems, postnatal growth retardation and sleep disturbance, BRPS patients have not been reported to show the typical BOS posture (defined as having three out of four features: external rotation and/or adduction of shoulders, flexion at elbows, flexion at wrists and ulnar deviation of wrists and/or fingers at the metacarpophalangeal joints).

ASXL3 is mammalian homologs of drosophila *Additional sex combs-like 3* gene. Together with *ASXL1* and *ASXL2*, they consist of ASXL family members and are assumed to be epigenetic regulators that are involved in hereditary neurological disorders, malignancies and congenital heart disease (CHD) (Balasubramanian et al., 2017; Fu et al., 2020; Gelsi-Boyer et al., 2009; Micol & Abdel-Wahab, 2016; Shashi et al., 2016; Shukla et al., 2017; Wei et al., 2018). The ASXL family members share a common domain architecture, namely ASXN and ASXH domains in the N-terminus; ASXM1 and ASXM2 domains in the middle region, and the PHD domain in the C-terminus. *ASXL3* interacts with BAP1 which functions as a component of the Polycomb repressive deubiquitination (PR-DUB) complex, playing a role in chromatin remodelling on transcriptional regulation (Srivastava et al., 2016). Pathogenic genetic variants in *ASXL3* are spread in exon 11 and 12 of *ASXL3*.

To our knowledge, 54 cases with *ASXL3* LOF variants and one splicing mutation have been reported including 12 Chinese patients (Bacrot et al., 2018; Bainbridge et al., 2013; Balasubramanian et al., 2017; Chinen et al., 2018; Dad et al., 2017; Dinwiddie et al., 2013; Duan et al., 2021; C. Fu et al., 2019; Gou et al., 2019; Hori et al., 2016; Koboldt et al., 2018; Kuechler et al., 2017; Li et al., 2020; Lyu et al., 2020; Myers et al., 2018; Qiao et al., 2019; Schirwani et al., 2020; Srivastava et al., 2016; Verhoeven et al., 2018; Wayhelova et al., 2019; Yang et al., 2020; Yu et al., 2021; Zhang et al., 2018; Zheng et al., 2021). The studies demonstrate clinical heterogeneity exists in the affected subjects and the correlation between the position of variants and the severity of the phenotype is uncertain (Balasubramanian et al., 2017; Wayhelova et al., 2019; Yu et al., 2021). Nonsense variants found in phenotypically normal individuals, germline and postzygotic mosaicism were also reported (Fu et al., 2019; Schirwani et al., 2020; Yu et al., 2021).

In this study, we present a de novo nonsense variant c.1063G>T (p.E355*) in the *ASXL3* gene (NM_030632.3) in a Chinese patient and summarized the clinical phenotypes of BRPS. Prenatal diagnosis was made for her pregnant mother with a negative Sanger sequencing result. The proband's phenotypic features were consistent with BRPS and molecular result expands the genetic spectrum. More cases study may help to elucidate the function of the *ASXL3* gene that may be critical to understand the genetic aetiology of this syndrome and assist in accurate genetic counselling, informed decision making and prenatal diagnosis.

2 | CASE REPORT

2.1 | Clinical phenotype

A 2-year-8-month-old Chinese girl was referred for genetic evaluation of developmental and speech delay at the genetic counselling clinic in Shenzhen Maternal and Child Healthcare Hospital (Figure 1a). Physical examination showed her weight was 10.9 kg at 10th percentile, her height was 88 cm at 10th percentile and her head circumference was 47 cm at 10-25th percentile. The couple performed genetic counselling for the next pregnancy. Blood samples were collected from the patient and their parents. Detailed clinical information was obtained by the clinicians examining the patient. The present study was approved by the hospital's Institutional Review Board (LLYJ2021-150-083) and written informed consent for publication of their clinical details and/or clinical images was obtained from the parents.

The patient was the first child of a non-consanguineous Chinese couple with unremarkable family history and her mother was pregnant for the genetic counselling. The girl was born at the 39th gestational week by Cesarean section with decreased fetal movement during the antenatal period. At birth, she was found to have bilateral varus deformity of feet and the internal rotation of the femur. She was able to hold her head up by 6 months and sat without support at 10 months. She stood by herself at 12 months and walked freehand at 20 months. His feeding problem was also complicated with gastroesophageal reflux at 12 months old. She was able to say baba and

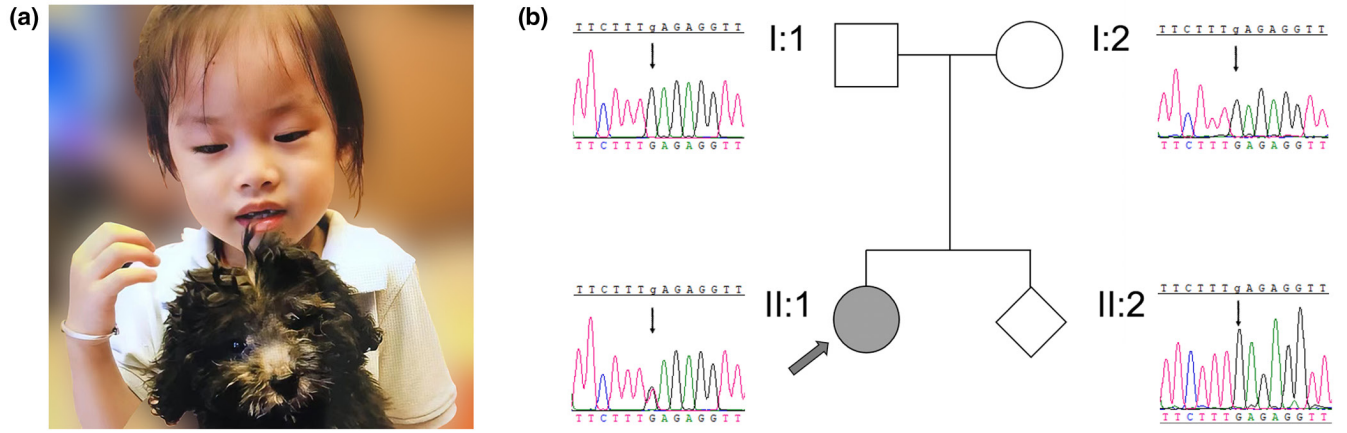

FIGURE 1 Facial appearance of the proband and pedigree of the proband and Sanger sequencing of a family member at position c.1063G>T (p.E355*) in the *ASXL3* gene (NM_030632.3, GRCh38/hg38). (a) Facial appearance of the proband with arched eyebrows, prominent forehead, low-set cupped ears, broad nasal tip, anteverted nostril, hypertelorism and everted lower lip. (b) Family tree of the proband shows the affected patient (II:1) born from non-consanguineous parents. Sanger sequencing validates the exome sequencing variant of c.1063G>T (p.E355*) in the *ASXL3* gene (NM_030632.3) in the proband (II:1). The father (I:1), mother (I:2) and the fetal (II:2) were variant negative

mama at 2 years old. The girl had tapering fingers and CT, MRI, hearing test were normal. Sleeping disturbance was observed from infancy. Mild craniofacial features were arched eyebrows, prominent forehead, low-set cupped ears, broad nasal tip, anteverted nostril, hypertelorism and everted lower lip. The parents planned to enrol her on special child care kindergarten for special training.

2.2 | Genetic analysis

We performed whole-exome sequencing on proband. The genomic DNA was extracted from peripheral blood. The mean read depth of the protein-coding regions was 56.2x and an average of 92.3% of coding sequences (CDS) were sequenced by 20 or more reads. We found a pathogenic variant c.1063G>T (p.E355*) in the *ASXL3* gene (NM_030632.3, GRCh38/hg38) with a dominant inheritance pattern, causing Bainbridge-Ropers syndrome (BRPS) and matching the proband clinically. Besides the primary variant, three secondary findings were revealed, including c.625C>T (p.R209*) in the *EDN1* gene (NM_001955.5), c.343C>T (p.R115*) in the *SCNN1A* gene (NM_001159576.2) and c.1476delG (p.M492fs) in the *CYP26C1* gene (NM_183374.3). The secondary findings were excluded for not matching the clinical features of the proband. We then sequenced the parent's DNA to perform trio analysis. The result confirmed the patient carried a de novo dominant nonsense variant of c.1063G>T (p.E355*) in the *ASXL3* gene and the parents were absent from the variant. The proband's mother had amniocentesis at 20th gestational week and the Sanger sequencing result of c.1063G>T was negative (Figure 1b). Primers used to amplify the mutant sequence were *ASXL3*-1063-F (5′TCTGTGCCTTGTGATTTA3′) and *ASXL3*-1063-R (5′TGCTTTCAGGGTTAGTTC3′).

3 | DISCUSSION

In the present study, whole-exome sequencing detected a novel heterozygous nonsense variant c.1063G>T (p.E355*) in the *ASXL3* gene (NM_030632.3) in a Chinese girl with BRPS. Sanger sequencing confirmed the wildtype in parents and fetal which revealed the dominant de novo pattern. In silico prediction analysis demonstrated this variant had damaging or disease-causing effects (PVS1 + PM1 + PM2) according to ACMG guidelines (Richards et al., 2015). *ASXL3* c.1063G>T (p.E355*), located in exon 11, is also a truncating variant as reported variants. The loss-of-function variants in the *ASXL3* gene generate stop codons and were predicted, in silico, to lead to a truncated *ASXL3*. The proband presented in this study exhibit most of the typical clinical manifestations of BRPS including feeding difficulties, hypotonia, absent speech, intellectual disability and facial dysmorphism. Our study reports a novel variant in *ASXL3* which enriches the genetic spectrum and further emphasizes the dominant inheritance of BRPS.

To date, there are 56 BRPS patients with a wide age range from 4 months to 47 years including our study. The mutation spectrum of *ASXL3* and the number of patients were listed in Table 1. Forty-six different pathogenic mutations in *ASXL3* were summarized with 23 patients in exon 11 and 33 patients in exon 12. All described mutations are nonsense or frameshift variants

TABLE 1 Mutation spectrum of *ASXL3* reported in the literature and our study

No.	Variant	Patient no.	Reference
Exon 11			
1	c.1063G>T (p.Glu355*)	1	★
2	c.1074T>A (p.Tyr358*)	1	Balasubramanian et al. (2017)
3	c.1082dup (p.Leu362AlafsTer23)	1	Balasubramanian et al. (2017)
4	c.1201del (p.Ala401GlnfsTer8)	1	Balasubramanian et al. (2017)
5	g.31318578C>T (p.Gln404*)	1	Bainbridge et al. (2013)
6	c.1219delA (p.Ser407AlafsTer2)	1	Kuechler et al. (2017)
7	c.1314_1316delinsA (p. Ser439Argfs*7)	1	Dad et al. (2017)
8	c.1318dup (p.Glu440Glyfs*7)	1	Bacrot et al. (2018)
9	c.1369G4T (p.Glu457Ter)	1	Kuechler et al. (2017)
10	c.1377_1378del (p.Glu459fs*)	1	Yu et al. (2021)
11	g.31318764C>T (p.Gln466*)	1	Bainbridge et al. (2013)
12	g.31318789_insT (p.Pro474fs)	1	Bainbridge et al. (2013)
13	c.1421_1422ins (p.Leu483*)	1	Zheng et al. (2021)
14	c.1448dupT (p.Thr484AsnfsTer5)	1	Srivastava et al. (2016)
15	c.1484insTGAA (p.Asp497*)	1	Balasubramanian et al. (2017)
16	c.1491dup (p.Asn498*)	1	Balasubramanian et al. (2017)
17	c.1632-1637delins31 (p.Pro545LeufsTer10)	1	Schirwani et al. (2020)
18	c.1783C>T p.(Gln595*)	1	Balasubramanian et al. (2017)
19	c.1795G>T (p.Glu599*)	1	Li et al. (2020)
20	c.1897_1898delCA (p.Gln633ValfsTer13)	1	Dinwiddie et al. (2013)
21	g.31319343_31319346delACAG (p.Thr659fsTer41)	1	Bainbridge et al. (2013)
22	c.3006delT (p.Arg1004Glufs*21)	1	Wayhelova et al. (2019)
23	c.3028delC (p.Pro1010Leufs*14)	1	Chinen et al. (2018)
Exon 12			
24	c.3039 + 1G>A	2	Myers et al. (2018) Hori et al. (2016)
25	c.3106C>T (p.Arg1036*)	6	Koboldt et al. (2018) Kuechler et al. (2017) Myers et al. (2018) Gou et al. (2019) Duan et al. (2021)
26	c. 3127_3128dup (p.Gly1045Valfs*99)	1	Balasubramanian et al. (2017)
27	c.3178dup (p.Arg1060Profs*50)	1	Balasubramanian et al. (2017)
28	c.3284_3288del (p.Thr1096AsnfsTer12)	2	Schirwani et al. (2020)
29	c.3307A>T (p.Lys1103*)	1	Yu et al. (2021)
30	c.3313_3316delCAGA (p.Thr1106ArgfsTer36)	1	Myers et al. (2018)
31	c.3349C>T (p.Arg1117*)	1	Zhang et al. (2018)
32	c.3355dup (p.His1119Profs*7)	1	Balasubramanian et al. (2017)
33	c.3364C>T (p.Gln1122*)	1	Srivastava et al. (2016)
34	c.3464C>A (p.Ser1155*)	1	Qiao et al. (2019)
35	c.3493_3494delTG (p. Cys1165Ter)	1	Yang et al. (2020)
36	c.3494_3495delGT (p.Cys1165Ter)	1	Kuechler et al. (2017)

TABLE 1 (Continued)

No.	Variant	Patient no.	Reference
37	c.3613G4T (p.Glu1205Ter)	1	Kuechler et al. (2017)
38	c.3635T>G (p.Leu1212*)	1	Balasubramanian et al. (2017)
39	c.4072_4073delGT (p.Val1358LeufsTer8)	1	Kuechler et al. (2017)
40	c.4090G>T (p.Gly1364*)	1	Lyu et al. (2020)
41	c.4144C>T (p.Gln1382*)	1	Balasubramanian et al. (2017)
42	c.4330C>T (p.Arg1444*)	3	Balasubramanian et al. (2017) Srivastava et al. (2016) Fu et al. (2019)
43	c.4399C>T (p.Arg1467*)	1	Yu et al. (2021)
44	c.4509_4513dup (p.Val1505AspfsTer3)	2	Schirwani et al. (2020)
45	c.5455C>T (p.Gln1819*)	1	Yu et al. (2021)
46	c.6697_6710dup (p.Ser2238fs)	1	Verhoeven et al. (2018)

Note: ★ Represents variant in this study. (*ASXL3* gene NM_030632.3, GRCh38/hg38).

except one splice site mutation carried by two separate patients. In addition to the splice site mutation, variant c.3106C>T (p.Arg1036*) was detected in six patients and c.4330C>T (p.Arg1444*) was detected in three patients, which suggested they are likely mutational hotspots. We summarized the main clinical features of 56 BRPS patients and sort the phenotype in decreased order in Table 2, which is basically consistent with the reported study (Balasubramanian et al., 2017; Yu et al., 2021). The core clinical features of BRPS like delay of speech, intellectual disability, hypotonia and feeding problems have a high-penetrant per cent of 80% to 94.6%. Some less penetrant phenotypes like sleeping disturbances, brain MRI abnormality and seizures have a positive rate of about 30% or less. The prediction that phenotype severity decreases as the variants occur further away from the 5′-end of exon 11 and towards the 3′-end needs to be further confirmed (Wayhelova et al., 2019). Many of mRNAs containing nonsense variants within ~50-55 bp upstream of 3′-most exon-exon junction escape from nonsense-mediated decay (NMD) and are predicted to potentially not abrogate protein production (55-bp rule) (Jagannathan & Bradley, 2016). The regulation of mRNA initiation and termination is yet incompletely understood. More patients should be collected to study the genotype–phenotype correlation in this severe atypical neurodevelopmental disorder.

In our study, the proband was diagnosed as BRPS and the parents were phenotypic and genetic normal. Considering the recurrence risk, the pregnant mother still had a prenatal diagnosis and the negative result excluded the gonadal mosaicism of the couple. The prenatal diagnosis of BRPS was challenging owing to its limited ultrasonography findings. Polyhydramonios decreased fetal movements in late pregnancy and arthrogryposis on ultrasound were observed on the separate foetus (Bacrot et al., 2018; Balasubramanian et al., 2017; Schirwani et al., 2020; Srivastava et al., 2016). In our study, the reduced fetal movement was found during pregnancy and bilateral varus deformity of feet was observed at birth, which was consistent with the reported fetal cases (Bacrot et al., 2018). The positive rate of pregnancy problems in reported BRPS patients is 33.9% (Table 2) and three main prenatal features are intrauterine growth retardation, decreased fetal movement and the abnormal amniotic fluid content. The limited prenatal cases revealed that reduced fetal movements and arthrogryposis on ultrasound maybe the clinical features of the BRPS foetus. Prenatal imaging results combined with molecular genetic analysis would help a clear diagnosis. In previous studies, three families had sibling recurrent variants and one family had mosaicism variant in the proband. Germline mosaicism in one of the parents seems to be a more likely explanation (Koboldt et al., 2018; Schirwani et al., 2020). Within the families, behavioural phenotype diversity and differences in intellectual development amongst siblings with consistent variants have demonstrated the heterogeneity of this clinical condition (Schirwani et al., 2020). A nonsense *ASXL3* mutation carried by a patient with developmental delay and hypotonia was inherited from the clinically unaffected father, which suggests incomplete penetrance (C. Fu et al., 2019; Ropers & Wienker, 2015). Accurate genetic counselling should be carefully performed in families of a child with a dominant genetic condition caused by a de novo pathogenic variant.

De novo truncating *ASXL3* mutations are predicted to promote nonsense-mediated decay (NMD) and disrupt the normal activity of the Polycomb repressive deubiquitination (PR-DUB) complex. Transcriptome

TABLE 2 Summary of main clinical information of *ASXL3* patients reported in the literature and our study

	Patient in present study	Total patients (n = 56) +
Speech delay	+	53/56 (94.6%)
Intellectual disability	+	50/56 (89.3%)
Hypotonia	+	50/56 (89.3%)
Feeding difficulties	+	45/56 (80.4%)
Reduced height and weight	+	44/56 (78.6%)
Skeletal problems	Varus deformity of feet & tapering fingers	37/56 (66.1%)
Prominent forehead	+	34/56 (60.7%)
Arched eyebrows	+	31/56 (55.4%)
Failure to thrive	−	29/56 (51.8%)
Microcephaly	−	25/56 (44.6%)
Hypertelorism	+	25/56 (44.6%)
High-arched Palate	−	23/56 (41.1%)
Down-slanting palpebral fissure	−	22/56 (39.3%)
Full (everted) lower lip	+	22/56 (39.3%)
Strabismus	−	21/56 (37.5%)
Autistic features	−	20/56 (35.7%)
Open mouth appearance/little facial expression	+	20/56 (35.7%)
Pregnancy	Deceased fetal movement	19/56 (33.9%)
Sleeping disturbance	+	17/56 (30.4%)
Brain MRI	−	16/56 (28.6%)
Seizures	−	14/56 (25.0%)
Other craniofacial features	Low-set cupped ears	47/56 (83.9%)

Abbreviation: NR, not report.

analysis of *ASXL3* fibroblasts from patients with BRPS resulting in the differentially expressed genes (DEGs) has suggested that *ASXL3* is involved in transcriptional regulation of brain development genes (Srivastava et al., 2016). Besides a causing dominant gene responsible for BRPS phenotype, compound heterozygous variants in *ASXL3* have also been proposed to cause congenital heart disease (CHD) and recurrent mutations in *ASXL3* have been identified in a specific subset of cancer (F. Fu et al., 2020; Micol & Abdel-Wahab, 2016; Wei et al., 2018). Potentially, the underlying mechanism may be that different kinds of variants in *ASXL3* cause various mRNA expression and protein levels across clinical conditions. Compound heterozygous variants in *ASXL3* causing BRPS-like features with primary *IGF1* deficiency proposed the additively or synergistically effect and the complex interaction network of *ASXL3* (Giri et al., 2017). To date, there are three loss-of-function mutations (p.R322*, p.S887Ffs*2, p.P2037Hfs*43) in the *ASXL3* gene within the ExAC (Exome Aggregation Consortium) dataset. These mutations are identified in phenotypically normal individuals and may be presumably explained by escaping from nonsense-mediated RNA decay due to their location. In addition, these mutations probably occurred post-zygotically or late in embryogenesis which is supported by some extent that somatic mutations occur in *ASXL3* in cancers.

In conclusion, our study reports a novel heterozygous nonsense variant in a Chinese patient which expands the mutation spectrum in *ASXL3* and clinical features of BRPS. Insights into the genetic aetiology of BRPS are dependent on the causative gene study and further functional research. More case reports may help to elucidate the function of *ASXL3* that may be critical to understand the aetiology of the disease and facilitate genetic counselling and future prenatal testing.

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CONFLICT OF INTEREST

The authors declare that they have no proprietary, financial, professional or other personal interest of any nature in any product, service and company that could be constructed as influencing the position presented in this manuscript.

AUTHORS' CONTRIBUTIONS

WQ, performed exome sequencing, data analysis, literature review and drafted the manuscript; JMZ, NJ and JXY performed Sanger sequencing analysis and patient record management; JSX, performed genetic counselling; XSZ, organized this study, reviewed clinical and laboratory data and finalized this manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

A statement on ethics approval and consent for this study was approved by the Institutional Ethics Review Board, Shenzhen Maternity and Child Healthcare Hospital (LLYJ2021-150-083). We obtained written, informed consent from the patient's parents for the inclusion of the patient's clinical and imaging details in publications.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

CONSENT TO PUBLISH

The participant has consented to the submission of the case report to the journal.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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