Article published online: 2024-06-03

Case Report of Recurrent Popliteal Pterygium Syndrome

Komal Rangholiya[1] Pruthviben K. Ponkiya[1] Purvi Desai[2] Binodini Chauhan[1] Shimolee Patel[3]

[1] Department of Fetal Medicine, Government Medical College, New Civil Hospital, Surat, Gujarat, India
[2] Department of Radiodiagnosis, Government Medical College, New Civil Hospital, Surat, Gujarat, India
[3] Surat Municipal Institute of Medical Education and Research, Surat, Gujarat, India

Address for correspondence Pruthviben K. Ponkiya, DGO, Department of Fetal Medicine, Government Medical College, New Civil Hospital, 11, Shantinagar-1 Society, Sarthana Jakatnaka, Surat 395006, India (e-mail: pruthviponkiya@gmail.com).

J Fetal Med

Abstract

A 23 week pregnant woman with a history of a child with facial and limb malformations underwent a fetal ultrasound revealing similar abnormalities in the current fetus. Genetic testing confirmed a new IRF6 gene mutation consistent with popliteal pterygium syndrome type 1. This case highlights the potential for recurrence and the role of genetic testing in prenatal diagnosis.

Keywords

- cleft lip and palate
- popliteal pterygium syndrome
- popliteal webbing
- prenatal diagnosis
- recurrent popliteal pterygium

Case

A 23 year old, G2P1L1, presented at 23 weeks of gestation for a fetal anomaly scan. The patient had a six year live male child with bilateral cleft lip and palate, unilateral popliteal web, cryptorchidism, and syndactyly in both feet (►**Fig. 1**). Ultrasound (US) examination (on Voluson E8 with 2 to 4 MHz curvilinear transducers; 3D RAB 6-D probe) showed a single viable fetus with abnormalities as shown in ►**Fig. 2**. (Defect of the lip on the left side with defect of the alveolar ridge, and hard palate with symptoms of left cleft lip and palate. Midfacial hypoplasia and frontomaxillary flattening with upturned lips consistent with Binder's face. Both lower limbs showed persistent partial flexion at the knee joint and abnormal genitalia). All biometric centiles of the fetus were normal range. Since findings were similar to the couple's previous child, a provisional diagnosis of popliteal pterygium syndrome (PPS) was made.

The amniotic fluid of the fetus and blood sample of the index case and both parents were sent for genetic testing. Because of the severe abnormalities, the couple decided to terminate the pregnancy. Postabortal examination confirmed the prenatal sonographic findings (►**Fig. 3**). Whole-exome sequencing revealed a heterozygous pathogenic variant in *IRF6* (NM_006147.4; c.251G > A; p.Arg84His), consistent with a diagnosis of PPS type 1. Target mutation analysis on Sanger sequencing for the same genetic defect as seen in the fetus was done in the index case and in the sample of both parents. The index case was positive for the same mutation as seen in the fetus, while both parents were found negative.

DOI https://doi.org/10.1055/s-0044-1787057.
ISSN 2348-1153.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

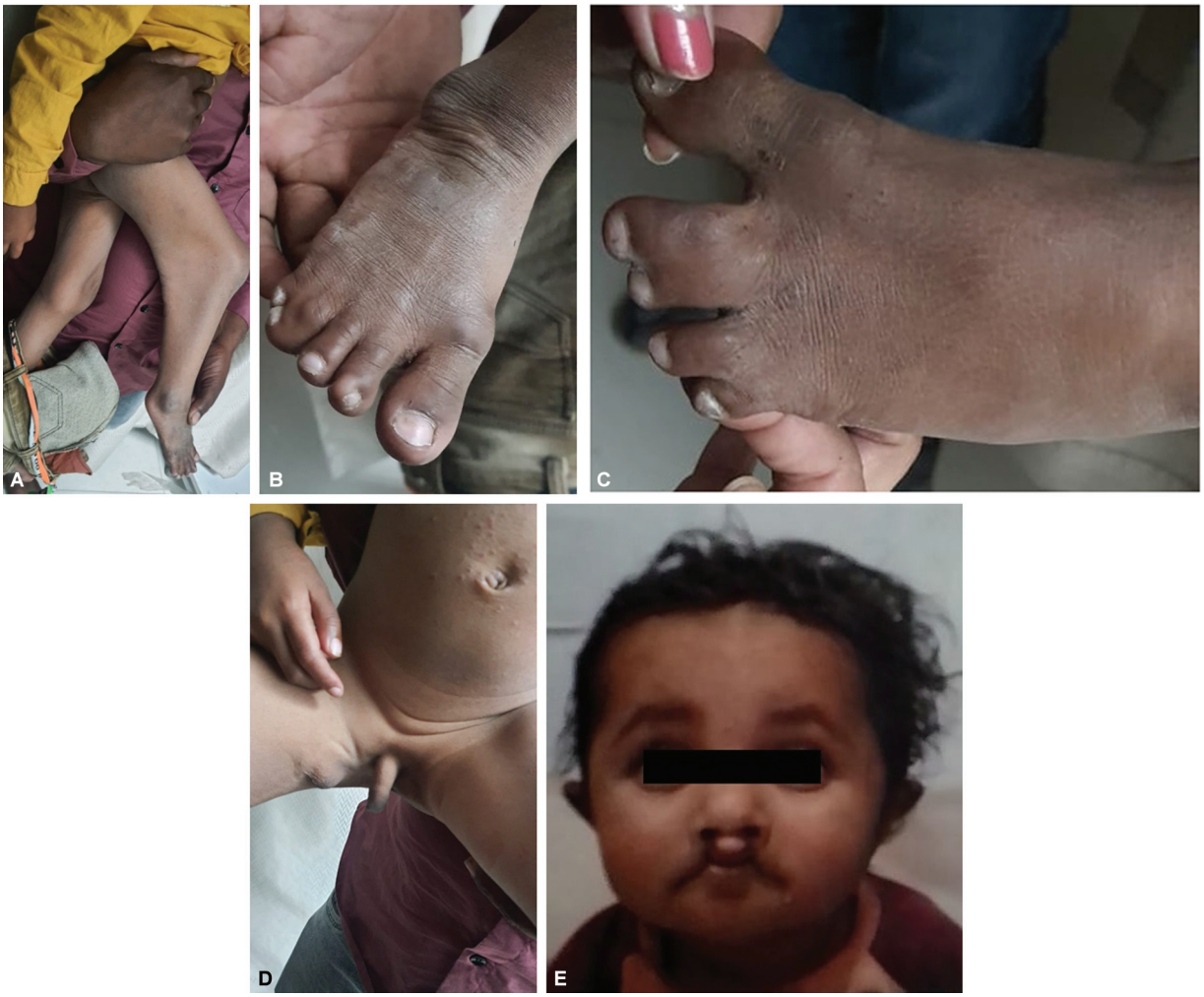

Fig. 1 Images of the index case. (**A**) Index case with popliteal webbing. (**B**,**C**) Index case with lower limb shows syndactyly. (**D**) Cryptorchidism of the index case. (**E**) Bilateral cleft lip and palate of the index case.

Hence, we can conclude that the pathogenic variant in the affected case occurred due to confined gonadal mosaicism.

Discussion

PPS is an extremely rare, autosomal dominant condition associated with a mutation of the *IRF6* gene, localized to chromosome 1q32.2.[1,2] The prevalence is estimated to be approximately 1 in 300,000 live births.[3,4] The minimal diagnostic criteria for PPS are cleft lip/palate, popliteal pterygium (webbing of the skin extending from the ischial tuberosity to the heels, resulting in severe malposition of the lower limbs), paramedian lower lip sinuses, genital anomalies (particularly bifid scrotum and cryptorchidism in males and hypoplasia of the labia majora and uterus in females), and toe nail abnormalities, especially syndactyly.[5] However, in our case, there is a difference in structural findings of PPS between the current pregnancy and the index case, as shown in ►**Table 1**. The molecular diagnosis of both the current fetus and the index case was the same. On US, an abnormal posture of the lower limbs including clubfeet (equinovarus) and restriction of lower limb movement are the first clues to suspicion of PPS. The well-defined popliteal pterygia can be missed if the sections are not exactly midsagittal and there is no previous history.

In high risk cases, only one abnormality should warrant genetic confirmation, while in de novo cases, US findings relatively specific for PPS may be needed for molecular genetic testing.

Reports of prenatal diagnosis of PPS are rare. To the best of our knowledge, there are only two prenatal cases reported to date. The first case was reported in 2000 with prenatal diagnosis by Perrotin et al.[6] In 2014, Posey et al[7] reported a prenatal diagnosis of PPS with US cleft lip and cleft palate (CLCP) and magnetic resonance imaging (MRI; popliteal web). The summary of these prenatal cases is presented in ►**Table 2**. The main differential diagnoses include Van der Woude syndrome (VWS), a disorder caused by deletions and mutations in the same gene (*IRF6*) and is the most common generic form of syndromic orofacial cleft.[8] The underlying

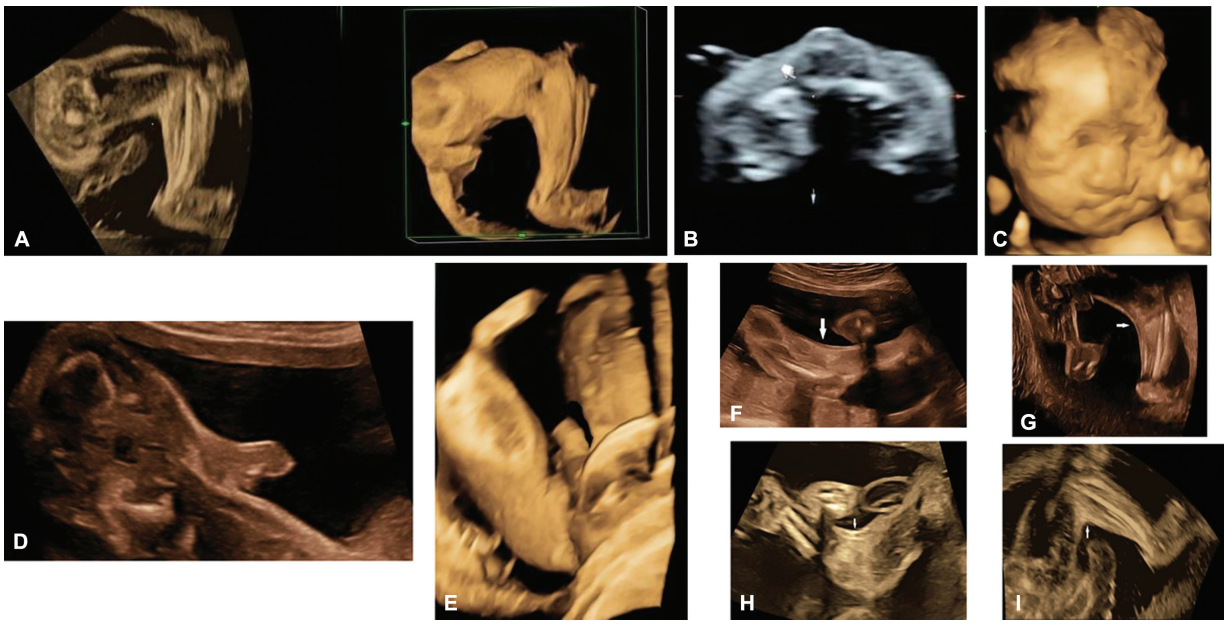

Fig. 2 Ultrasound finding of the fetus. (**A**) 2D and 3D images of webbing from the posterior aspect of the thigh extending to the heels. (**B**) 2D axial view of unilateral cleft lip and palate. (**C**) 3D reconstructed image of cleft lip and palate. (**D,E**) 2D and 3D (respectively) images of genitalia with only the penis and scrotal sac not seen (cryptorchidism). (**F–I**) 2D images of webbing from the posterior aspect of the thigh extending to the heels.

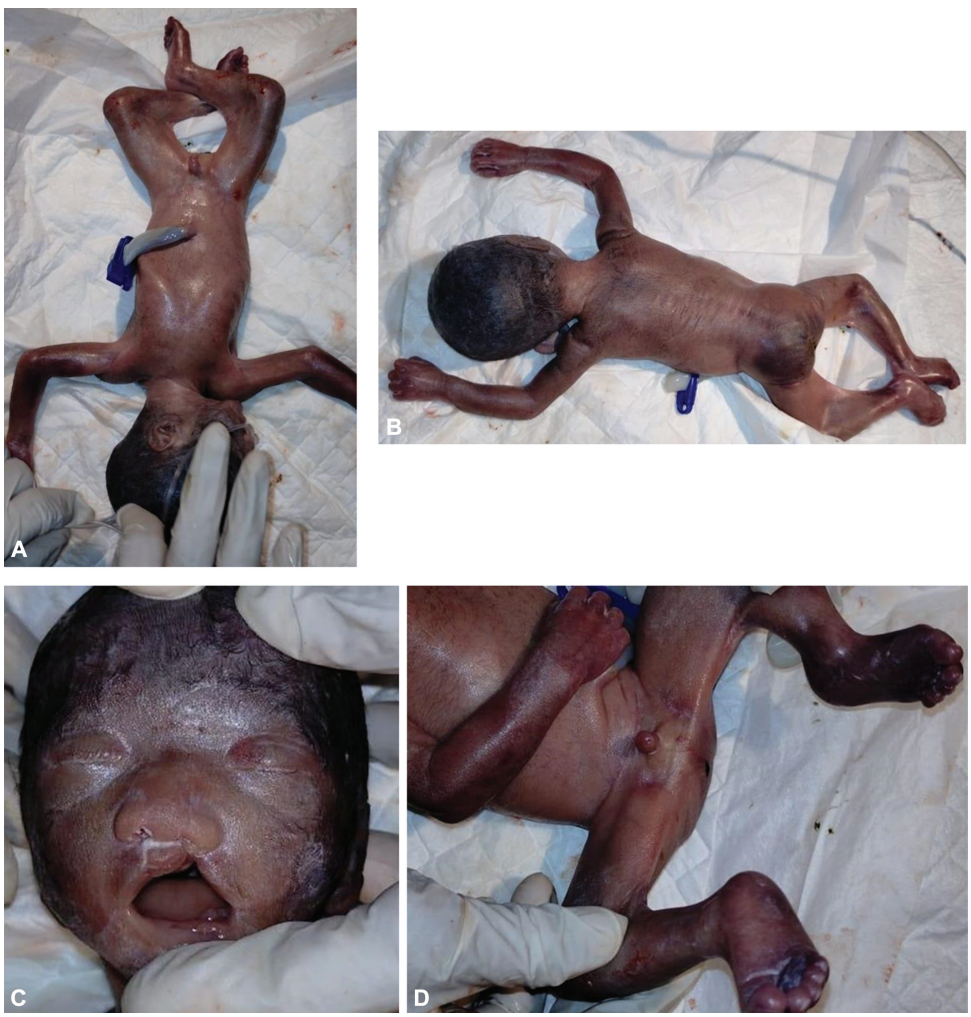

Fig. 3 Postabortal images of our case. (**A,B**) Postabortal images of popliteal webbings. (**C**) Cleft in the upper lip and palate. (**D**) Cryptorchidism.

Table 1 Comparisons of postabortal findings of current pregnancy (this fetus) and previous affected live child (index case)

Postabortal findings of current pregnancy	Previous live child (index case) findings
Bilateral popliteal pterygia	Unilateral popliteal pterygia
Unilateral cleft lip and palate	Bilateral cleft lip and palate
Cryptorchidism	Cryptorchidism
No syndactyly	Syndactyly in both lower limbs

genetic mechanism that results in a different effect of IRF6 function is hypothesized (haploinsufficiency for VWS, missense mutation for PPS).

The recurrence risk of PPS as an autosomal dominant disorder is 50%. Growth and mental development of the affected child are expected to be normal. However, the prognosis for physical disabilities depends on the severity of the pterygium, genital abnormalities, and orofacial defects. Accordingly, the options of pregnancy termination in cases of early detection may be offered.

Our case is extremely unique as the diagnosis was made antenatally with genetic confirmation both by next-generation sequencing (NGS) and Sanger sequencing. The accuracy of NGS is 99.2%, while Sanger is 99.99% accurate.[9] There was a recurrence of the same mutation in two consecutive pregnancies. Thus, we can conclude that, in our case, the recurrence was due to confined gonadal mosaicism.

What's Already Known about This Topic?

Prenatal diagnosis of PPS is very rarely reported. To the best of our knowledge, only two prenatal cases have been reported to date. The first case was reported in 2000 with prenatal diagnosis by Perrotin et al.[6] In 2014, Posey et al[7] reported a prenatal diagnosis of PPS with US (CLCP) and MRI (popliteal web).

What Does This Study Add?

The recurrence risk of PPS as an autosomal dominant disorder is 50%. Our case is extremely unique as the diagnosis was made antenatally with genetic confirmation and the confined gonadal mosaicism was the cause for recurrence of gene mutation twice in the same family.

Informed Consent

Appropriate written informed was consent taken from the patient for this study.

Funding

None.

Conflict of Interest

None declared.

Table 2 Summary of prenatal diagnosis of popliteal pterygium syndrome (PPS) with postnatal/postabortal associations

Study	GA at prenatal diagnosis	Main USG/MRI findings	Family history	Outcome and postnatal/postabortal findings	Molecular genetic diagnosis
Perrotin et al[6]	18 wk	USG: bilateral cleft lips, equinovarus legs, amyotrophy foot, ambiguous genitalia	Positive (clinical diagnosis in the mother)	Termination of pregnancy at 21 wk. Additional findings: intraoral syngnathia, popliteal pterygia	Not done
Posey et al[7]	24 wk	USG: IUGR, syngnathia, cleft lip MRI: bilateral popliteal pterygia, equinovarus, syndactyly, small scrotum, duplicating renal collecting system	No	CS, 35 wk, weight 1.87 kg Additional finding: ankyloblepharon, genital anomaly, micro-/retrognathia, syngnathia	IRF6 mutation in newborn (parents not done)
Our study 2022	23 wk	USG: bilateral popliteal pterygia, unilateral cleft lip and palate with binder facies, genital anomaly	Sibling affected with the same syndrome	Termination of pregnancy at 23 wk No additional postabortal finding	IRF6 mutation confirmed Same genetic mutation was detected in the previous child

Abbreviations: GA, gestational age; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; USG, ultrasonography; CS, cesarean section.

References

1 Leslie EJ, Mancuso JL, Schutte BC, et al. Search for genetic modifiers of IRF6 and genotype-phenotype correlations in Van der Woude and popliteal pterygium syndromes. Am J Med Genet A 2013;161A(10):2535–2544

2 Schutte BC, Saal HM, Goudy S, Leslie EJ. IRF6-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews. Seattle, WA: University of Washington; 1993

3 Gorlin RJ, Sedano HO, Cervenka J. Popliteal pterygium syndrome. A syndrome comprising cleft lip-palate, popliteal and intercrural pterygia, digital and genital anomalies. Pediatrics 1968;41(02): 503–509

4 Melnick M, Bixler D, Fogh-Andersen P, Conneally PM. Cleft lip+/-cleft palate: an overview of the literature and an analysis of Danish cases born between 1941 and 1968. Am J Med Genet 1980;6(01):83–97

5 Escobar V, Weaver D. Popliteal pterygium syndrome: a phenotypic and genetic analysis. J Med Genet 1978;15(01):35–42

6 Perrotin F, Haddad G, Guichet A, Paillet C, Moraine C, Body G. Prenatal ultrasonographic diagnosis of the popliteal pterygium syndrome. Prenat Diagn 2000;20(06):501–504

7 Posey JE, Dariya V, Edmonds JL, Lee EI, Probst FJ, Premkumar MH. Syngnathia and obstructive apnea in a case of popliteal pterygium syndrome. Eur J Pediatr 2014;173(12):1741–1744

8 Bennun RD, Stefano E, Moggi LE. Van der Woude and popliteal pterygium syndromes. J Craniofac Surg 2018;29(06):1434–1436

9 Cheng C, Fei Z, Xiao P. Methods to improve the accuracy of next-generation sequencing. Front Bioeng Biotechnol 2023;11:982111

