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Case Report | International Journal of Medical Case Reports

# Mitral Valve Prolapse: Notching Up The Diagnosis

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## ABSTRACT

**Background**

Mitral valve prolapse affects 2-3% of the general population and 30% of cases are genetic. These syndromes are associated with mutations in transcription factors like NKX2–5, GATA-4, TBX5 and NOTCH signaling pathway that affect the development of the mitral valve.

**Case Report**

This is a case report of a 28-year-old male who presented with hematemesis of one-week duration. He had acromelia of the hands with dysplastic nails and terminal transverse limb defects of feet. On further evaluation he was found to have mitral valve prolapse and portal hypertension. Thus, a syndromic diagnosis was considered. Whole exome sequencing identified a heterozygous pathogenic NOTCH1 gene mutation, leading to a diagnosis of Adams-Oliver Syndrome (AOS).

Adams Oliver Syndrome is a rare genetic disorder characterized by terminal transverse limb defects, cutis aplasia, cardiac defects along with vascular anomalies. Mitral valve prolapse in Adams Oliver Syndrome is however rare. Mutations in NOTCH1 also have a higher incidence of cardiac anomalies as this pathway has a pivotal role in cardiac and vascular development.

**Conclusion**

This highlights the importance of considering genetic syndromes in patients with unexplained congenital anomalies and valvular disease as early recognition and a multidisciplinary approach are essential for optimal management.

***Keywords: Mitral Valve Prolapse, Notch1, Adams Oliver Syndrome, Acromelia***

## INTRODUCTION

Mitral valve prolapse (MVP) is a common condition affecting two to three percent of the general population. As per the Framingham study it is the leading cause of mitral regurgitation in developed countries and its prevalence in the Sudden Cardiac Death victims is 2.4%.[1]

In developed countries, genetic factors contributing to myxomatous degeneration are the predominant risk factors, while rheumatic heart disease is common in developing countries like India.[2] Other causes include ischemic cardiomyopathy, papillary muscle rupture due to infective endocarditis and trauma.

Genetic MVP can be syndromic or non-syndromic. MVP results from gene mutations affecting the growth and development of the mitral valve. Genes encoding transcription factors like NK2 Homeobox5 (NKX2–5), GATA binding protein 4 (GATA-4) and T-box transcription factor 5 (TBX5) are among the earliest ones expressed in the developing heart and their dysregulation has been associated with mitral valve prolapse. The NOTCH signalling pathway, TGF-β signalling pathway, Bone Morphogenetic protein (BMPs), SOX9 and matrix metalloproteinases (MMPs) also play an important role in extracellular matrix remodeling and development of the mitral valve. Dysregulation of these genes has been reported to cause MVP.[3]

Presence of additional skeletal and vascular abnormalities such as high arched palate, disproportionate upper segment lower segment ratio, hernia and vascular abnormalities such as aneurysms and telangiectasias with multisystem involvement point towards syndromic mitral valve prolapse. Syndromes like Down syndrome, Marfan syndrome, Loeys-Dietz syndrome, Juvenile polyposis syndrome, Aneurysms-osteoarthritis syndrome, Ehlers-Danlos syndrome and Osteogenesis imperfecta are associated with MVP.[4,5]

We are reporting a case of a young male patient who presented with hematemesis and was incidentally found to have MVP with skeletal abnormalities but with no significant family history of cardiac disease whose evaluation led to a rare genetic syndrome.



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## CASE REPORT

A 28-year-old male presented with a history of hematemesis of one-week duration. He had a history of a similar episode six months back which was not evaluated. On examination his vitals were stable. He had limb defects in the form of acromelia of the hands with dysplastic nails and terminal transverse limb defects of feet.since birth (Figure 1, Figure 2).

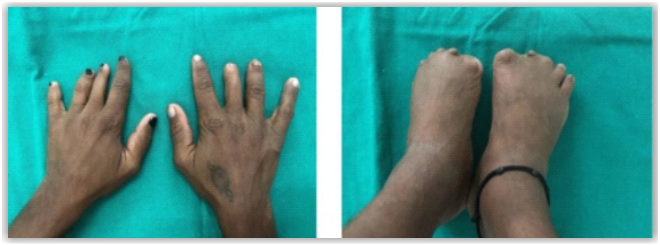

*Figure 1: Clinical photograph showing acromelia of the fingers with terminal transverse limb defects of the feet.*

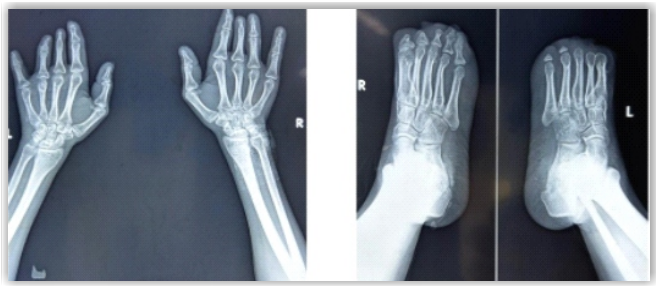


*Figure 2: Plain radiograph showing acromelia involving the hands and feet.*

He also had a high arched palate with umbilical hernia. Abdominal examination revealed hepatomegaly with massive splenomegaly. Cardiac examination revealed an ejection click with a late systolic murmur of grade 4/6 with signs of pulmonary artery hypertension. Clinical examination of the central nervous system and respiratory system examination were normal.

His baseline hemogram showed pancytopenia (hemoglobin: 4.4 g/dl, Total count: 2920 cells/mm$^3$, platelet: 1.03 lakhs/mm3) with a corrected reticulocyte count of 1.61%. Peripheral smear showed shift to the left with metamyelocytes with tear drop cells, micro spherocytes, and giant platelets. Liver function test revealed normal bilirubin (direct and indirect) with hypoalbuminemia and elevated ALT (7.5 times above upper limit). Serum LDH was normal. Chest X-ray was done which showed cardiomegaly (Figure 3). Diffuse liver disease with splenomegaly and mild ascites were noted on ultrasound of abdomen. Contrast enhanced CT abdomen showed cirrhotic liver with splenomegaly with multiple porto-systemic collaterals and umbilical hernia. 2D echo was suggestive of mitral valve prolapse with moderately severe mitral regurgitation, severe tricuspid regurgitation and pulmonary artery hypertension (PASP: 65mmHg) with normal ejection fraction (58%). Upper gastrointestinal endoscopy showed large esophageal varices.

As a part of pancytopenia workup, bone marrow aspiration and biopsy were performed which showed active hypercellular marrow with no abnormal cells suggestive of hypersplenism. Serology showed positive anti HCV antibody titers, though the HCV RNA load was low. HIV serology was positive with a CD4 count of 426 with no evidence of opportunistic infections.

The patient was managed with blood transfusions and diuretics following which his ascites reduced and anemia improved. He was also started on beta blockers for esophageal varices. After ruling out opportunistic infections, antiretroviral therapy was started with Tenofovir, lamivudine and Dolutegravir as per national guidelines.

In view of his transverse limb defect, MVP and umbilical hernia, a syndromic diagnosis was considered. However, there was no family history of the same. With a possibility of a syndromic diagnosis a Whole exome sequencing was done after obtaining informed consent. Whole exome sequencing showed a heterozygous mutation, a likely pathogenic c.6026 deletion in Exon 32 coding for the NOTCH1 gene with another mutation of uncertain significance causing Alanine to Glutamine substitution in Exon 33 at c.6118. A combined genetic and phenotypic diagnosis of Adams-Oliver Syndrome was made. Although aplasia cutis congenita was absent, the presence of terminal transverse limb defects together with a likely pathogenic NOTCH1 mutation was considered sufficient to establish the diagnosis of Adams–Oliver syndrome, consistent with the known phenotypic variability of the disorder.

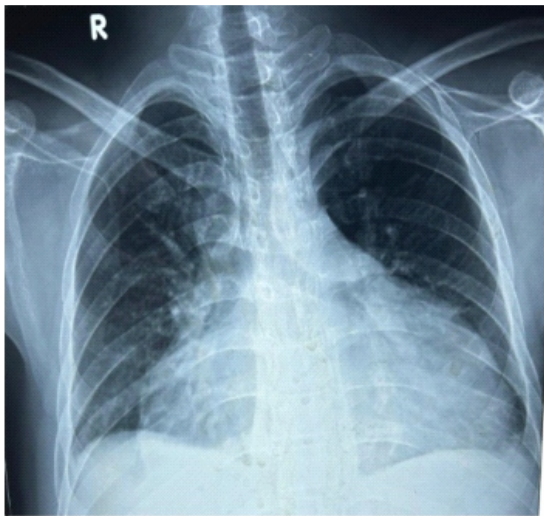


*Figure 3: Chest Xray PA view showing cardiomegaly*

## DISCUSSION

In 1945, Adams and Oliver described congenital transverse limb defects associated with aplasia cutis congenita in three-generation kindred with typical autosomal dominant inheritance and intrafamilial variable expressivity.[6] There have also been reports of autosomal recessive inheritance pattern as described by Sybert et al[7] and Tekin et al.[8]

Congenital heart defects have been estimated in 20% of patients with Adams-Oliver syndrome. Reported malformations include ventricular septal defects, anomalies of the great arteries and their valves, and Tetralogy of Fallot.[9] In addition, vascular anomalies like cutis marmorata, pulmonary hypertension, portal hypertension and retinal vascular abnormalities may be seen. In the present case, pulmonary hypertension was likely multifactorial, related to severe mitral regurgitation, portal hypertension and underlying chronic liver disease. Mutations in *ARHGAP31, DLL4, DOCK6, EOGT, NOTCH1* and *RBPJ* genes have been implicated in this condition.[10] Mitral valve prolapse is an uncommon cardiac manifestation of Adams–Oliver syndrome, making the present case clinically noteworthy.

Our patient presented with symptoms due to portal hypertension. However, as the patient was HCV positive, the cause of portal hypertension may be multifactorial. Given the presence of HCV-related cirrhosis, portal hypertension in our patient is more likely attributable to chronic liver disease rather than directly to Adams–Oliver syndrome. The transverse limb defects, umbilical hernia and mitral valve prolapse have been described in Adams-Oliver syndrome because of NOTCH1 mutation which was seen in our patient. The NOTCH signaling pathway is known to regulate

communication between neighboring cells that has important functions in skeletal and cardiovascular development. A study done by Stittrich et al showed that the majority of patients with Adams-Oliver syndrome carrying the NOTCH1 variant show cardiac or vascular defects. In addition to these observations, NOTCH1 loss-of-function or gain-of-function mutations in mice were found to cause major vascular defects.

Several hereditary cardiovascular disorders have unveiled the pivotal role that NOTCH signaling plays in cardiovascular development and homeostasis (Table 1). NOTCH1 also plays a role in vasculo-genesis and vascular obstruction by thromboses during embryonic development and thus was suggested as a cause of terminal transverse limb defects.[11,12]

| Author(s) & Year | Patient Details | Cardiovascular anomaly |
|---|---|---|
| **Sybert et al. (1989)**[7] | Male patient with aplasia cutis congenita (ACC) | Ventricular septal defect (VSD), mother with Adam Oliver syndrome |
| **Tincopa et al. (1986)**[13] | Male patient with ACC and transverse limb defects | Ventricular septal defect (VSD) |
| **Torrelio et al. (1986)** [14] | Male patient with family history of mother with cutis marmorata | Pulmonary venous stenosis and Pulmonary artery hypertension |
| **Kuster et al. (1988)**[15] | Male patient with ACC and characteristic limb defects | Tetralogy of Fallot |
| **Santos et al. (1989)** [16] | Female patient with scalp ACC | Coarctation of the aorta, VSD |
| **Der Kaloustian et al. (1991)** [17] | Male patient with ACC phenotype | Atrial septal defect (ASD) |
| **Ishikiriyama et al. (1992)** [18] | Male patient with classical Adam Oliver phenotype | Pulmonary Atresia |
| **Bamforth et al. (1994)** [19] | Female patient in a family of four affected | Tetralogy of Fallot |
| **Zapata HH et al. (1995)**[20] | First patient: 9.5-year-old female with ACC and limb defects, Second patient: 4.5-year-old female with parachute mitral valve | Aortic and subaortic stenosis (First patient), Parachute mitral valve (Second patient) |
| **Stittrich et al. (2014)** [11] | Family of five with classic phenotype | Mitral annular hypoplasia, multiperforated PFO (fourth proband in family) |

*Table 1: The varied cardiovascular anomalies in AOS reported over the years.*

## CONCLUSION

Adams-Oliver syndrome is a complex syndrome with multiple phenotypes. Cutaneous defects and vascular abnormalities are well recognized manifestations of the disease. While congenital cardiac defects are recognized manifestations of Adams–Oliver syndrome, mitral valve prolapse remains a rare and underreported association which can be attributed to myxomatous changes due to NOTCH1 signaling defect. This multisystem syndrome affects the quality of life and can be fatal if internal organs are affected. Therefore, these patients require a continuous and comprehensive multidisciplinary monitoring starting from birth. Further cases with precise phenotype-genotype correlations are required for better understanding of this rare syndrome.

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**Consent: Obtained From Patient**

## REFERENCES

1. Narayanan K, Uy-Evanado A, Teodorescu C, et al. Mitral valve prolapse and sudden cardiac arrest in the community. Heart Rhythm 2016; 13:498-503. 10.1016/j.hrthm.2015.09.026
2. Guy TS, Hill AC. Mitral valve prolapse. Annu Rev Med. 2012;63:277-92. doi: 10.1146/annurev-med-022811-091602.
3. Opris CE, Suciu H, Flamand S, Opris CI, Hamida AH, Gurzu S. Update on the genetic profile of mitral valve development and prolapse. Pathol Res Pract. 2024 Oct;262:155535. doi: 10.1016/j.prp.2024.155535.
4. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF. Braunwald's heart disease: A textbook of cardiovascular medicine, 2-volume set. 11th ed. Philadelphia, PA: Elsevier - Health Sciences Division; 2018. https://onesearch.nihlibrary.ors.nih.gov/discovery/fulldisplay/alma991001193429704686/01NIH_INST:NIH
5. Delwarde C, Capoulade R, Mérot J, Le Scouarnec S, Bouatia-Naji N, Yu M, Huttin O, Selton-Suty C, Sellal JM, Piriou N, Schott JJ, Dina C, Le Tourneau T. Genetics and pathophysiology of mitral valve prolapse. Front Cardiovasc Med. 2023 Feb 16;10:1077788. doi: 10.3389/fcvm.2023.1077788.
6. Chen, H. (2017). Adams-Oliver Syndrome. In: Atlas of Genetic Diagnosis and Counseling. Springer, New York, NY. https://doi.org/10.1007/978-1-4939-2401-1_4
7. Sybert VP. Congenital scalp defects with distal limb anomalies (Adams-Oliver syndrome-McKusick 10030): further suggestion of autosomal recessive inheritance. Am J Med Genet. 1989 Feb;32(2):266-7. doi: 10.1002/ajmg.1320320230.
8. Tekin M, Bodurtha J, Ciftçi E, Arsan S. Further family with possible autosomal recessive inheritance of Adams-Oliver syndrome. Am J Med Genet. 1999 Sep 3;86(1):90-1. doi: 10.1002/(sici)1096-8628(19990903)86:1<90::aid-ajmg20>3.0.co;2-9.

9 Jarjanazi L, Kebbeh S, Alam E, Saado Q, Jarjanazi M, Alkadi L, Etr A, Aswad TG, Nawfal H. Adams-Oliver syndrome: an unusual congenital disorder. Oxf Med Case Reports. 2025 Sep 28;2025(9):omaf176. doi: 10.1093/omcr/omaf176. PMID: 41025031; PMCID: PMC12476548.A
10. Zhu VZ, Hansen-Kiss E, Hecht JT, Payne PE. Adams-Oliver Syndrome: Vestigial Tail and Genetics Update. Arch Plast Surg. 2022 Jul 30;49(4):517-522. doi: 10.1055/s-0042-1751107.
11. Stittrich AB, Lehman A, Bodian DL, Ashworth J, Zong Z, Li H, Lam P, Khromykh A, Iyer RK, Vockley JG, Baveja R, Silva ES, Dixon J, Leon EL, Solomon BD, Glusman G, Niederhuber JE, Roach JC, Patel MS. Mutations in NOTCH1 cause Adams-Oliver syndrome. Am J Hum Genet. 2014 Sep 4;95(3):275-84. doi: 10.1016/j.ajhg.2014.07.011. Epub 2014 Aug 14.
12. Hoyme H.E., Jones K.L., Van Allen M.I., Saunders B.S., Benirschke K. Vascular pathogenesis of transverse limb reduction defects. J. Pediatr. 1982;101:839–843. doi: 10.1016/s0022-3476(82)80343-0.
13. Tincopa Wong O, Pelaez Gutierrez R, Melendez Guevara G, Paoli Razuri C, Sanchez Aznaran N. Aplasia cutis congénita. Relato de dos casos [Aplasia cutis congenita. Report of 2 cases]. Med Cutan Ibero Lat Am. 1986;14(3):199-204. Spanish. https://sisbib.unmsm.edu.pe/bvrevistas/dermatologia/v22_n2/pdf/a03v22n2.pdf
14. Toriello HV, Higgins JV, Waterman DF. Autosomal-recessive aplasia cutis congenita--report of two affected sibs. Am J Med Genet. 1983 May;15(1):153-6. doi: 10.1002/ajmg.1320150122.
15. Küster W, Lenz W, Kääriäinen H, Majewski F. Congenital scalp defects with distal limb anomalies (Adams-Oliver syndrome): report of ten cases and review of the literature. Am J Med Genet. 1988 Sep;31(1):99-115. doi: 10.1002/ajmg.1320310112.
16. Santos H, Cordeiro I, Menezes I. Aplasia cutis congenita associated with congenital heart defect, not a coincidence? Am J Med Genet. 1989 Dec;34(4):614-5. doi: 10.1002/ajmg.1320340437.
17. Der Kaloustian VM, Hoyme HE, Hogg H, Entin MA, Guttmacher AE. Possible common pathogenetic mechanisms for Poland sequence and Adams-Oliver syndrome. Am J Med Genet. 1991 Jan;38(1):69-73. doi: 10.1002/ajmg.1320380116.
18. Ishikiriyama S, Kaou B, Udagawa A, Niwa K. Congenital heart defect in a Japanese girl with Adams-Oliver syndrome: one of the most important complications. Am J Med Genet. 1992 Jul 15;43(5):900-1. doi: 10.1002/ajmg.1320430533.
19. Bamforth JS, Kaurah P, Byrne J, Ferreira P. Adams Oliver syndrome: a family with extreme variability in clinical expression. Am J Med Genet. 1994 Feb 15;49(4):393-6. doi: 10.1002/ajmg.1320490408.
20. Zapata HH, Sletten LJ, Pierpont ME. Congenital cardiac malformations in Adams-Oliver syndrome. Clin Genet. 1995 Feb;47(2):80-4. doi: 10.1111/j.1399-0004.1995.tb03928. x.

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