CASE REPORT

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Holt-Oram Syndrome in a Patient with Crohn's Disease: a Rare Case Report and Literature Review

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ABSTRACT

Introduction: Holt-Oram syndrome (HOS) is an uncommon autosomal dominant disorder defined by congenital cardiac defects, some anatomical deformities in the upper limb and conduction abnormalities. Sequence alteration of TBX5 gene located on chromosome 12 has associated with HOS. **Case report:** We present the case of a 26-year-old female with known upper limb alteration and ventricular septal defect who later in life developed Crohn's disease. **Conclusion:** To the best of our knowledge association of Holt-Oram syndrome with Crohn's disease has not been reported in literature before. Therefore, a possible genetic connection between Holt-Oram syndrome and Crohn's disease remains to be determined.

Keywords: Holt-Oram syndrome, Crohn's disease, Cardiac-limb syndrome.

1. INTRODUCTION

Holt-Omer syndrome (HOS) known as well as the cardiac-limb syndrome or as heart -hand syndrome type 1 is autosomal dominant multiple malformation disorder characterized by anatomical deformities of the upper limb and congenital heart defects.

The prevalence of Holt- Oram syndrome is regarded to be 0,95/100000 births. TBX5 gene mutation of T-box family transcription factors has been associated with reduction or complete loss of TBX5 protein. Holt-Oram syndrome is defined by the clinical criteria deformity in upper limb and the congenital heart defect and or conduction defect (1, 2).

2. CASE PRESENTATION

In February 2017, a 26-year-old female presented in our surgical department with fever, abdominal pain, diarrhea, weight loss and high output enterocutaneous fistula. Her medical history revealed congenital bilateral upper limb defect, bilateral thumb aplasia, which had been repaired surgically in 1995, an operation for the restoration of ventricular septal defects in 1998 and Crohn's disease (CD) diagnosed in 2008. The patient had been treated with varying doses of 5-aminosalicylates (5-ASA), azathioprine, and anti-tumor necrosis factors (anti-TNF) between 2008 and 2017, with no course of steroid treatment needed during this time frame. In 2008, the patient underwent ileocolectomy for stricturing CD of the terminal ileum and ileocecal valve and in 2010 a right total hip replacement after a motorcycle accident.

During her admission in our department, the patient was clinically diagnosed with HOS due to heart and upper limb abnormalities. After obtaining the consent of the patient, blood sample was collected, and high-purity DNA was extracted (QIAamp DNA blood mini kit; Qiagen) following the manufacturer's protocol. The Nextera-based protocol (Nextera DNA Library Preparation Kit; Illumina) was used to convert genomic DNA into adapter-tagged libraries starting from 50 ng DNA input, according to manufacturer's instructions. The sample sequenced with a mean target region coverage depth of 376.8 X and 99.9 % of the target area covered at a minimum depth of 20 X. In detail, all exons (100%) of TBX5, TBX3, and SALL4 genes covered at the lowest depth of 30 X. The analysis of the variant calling file of the sample revealed no variants in the exonic and exonic-flanking regions of TBX5 and TBX3 genes while in the SALL4 gene the two variants that were detected: NM_020436.4:c.1860A>G (rs6021437) and NM_020436.4

Figure 1. Morphological abnormalities of the upper limb

:c.1520T>G (rs6126344) were characterized as benign according to ACMG criteria due to minor allele frequency of >5% in all three databases (1000 Genomes: http://www.1000genomes.org, Exome Variant Server: http://evs.gs.washington.edu/EVS and ExAC: http://exac.broadinstitute.org).

The patient during her hospitalization underwent a computerized-tomography scan which revealed intra-abdominal abscess, enterocutaneous fistula, as well as signs of small bowel obstruction. Therefore, a laparotomy was performed, during which further ileal resection was conducted, with concommitant jejunal Heineke-Mikulicz strictureplasty, abscess drainage, and right salpingo-oophorectomy (solid adhesions were developed between right fallopian tube, ovary and the inflamed ileum).

3. DISCUSSION

Initially reported in 1960 by Holt and Oram, HOS is known to be a rare autosomal dominant condition with genetic heterogeneity. Clinical presentation includes different upper limb anomalies, congenital heart defects and conduction abnormalities (1). Even though in most patients there is a familial transmission, the recent literature describes de novo mutations in 30%-40% of cases (2, 3). The most common mutation located on chromosome 12 (12q 24.1) in the TBX5 gene of the T-box complex that is of most importance for the embryonic development of both upper limbs and heart. TBX5 pathogenic variants are detected at approximately 50-70% of clinically diagnosed individuals with Holt-Oram syndrome that have a family history of structural or conductive cardiovascular disease (4). However, lower pathogenic variant detection rates are expected when the patient does not meet the strict diagnostic criteria of the syndrome or does not present a family history.

The HOS is rarely diagnosed prenatally since intrauterine growth and development are not affected by the syndrome. The distribution among the genders is equal and upper limb anomalies are present. The usual clinical manifestation of the upper extremity due to the defective development of the embryonic radial axis include absence of thumbs, triphalangeal/digital thumbs and phocomelia. Such deformities may present bilaterally or unilaterally and asymmetrically (5). Congenital heart defect is among the clinical criteria of the syndrome, with ostium secundum type Atrial Septal Defect and Ventricular Septal Defect being the most common. Additionally, patent ductus arteriosus, heart blocks and Wolff-Parkisson-White syndrome are described (6, 7).

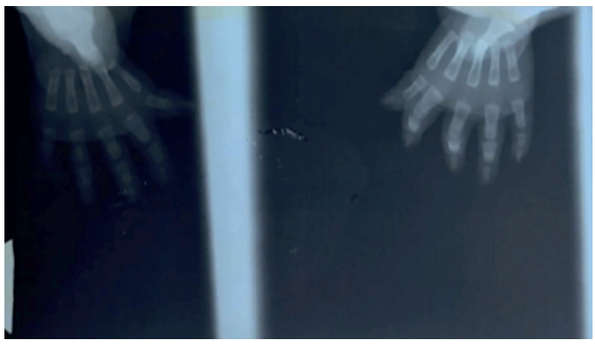

Figure 2. Posteroanterior radiograph of the hands of the patient. The distal phalanx of both thumbs is hypoplastic. In association with congenital heart disease, the upper limb deformities are suggestive of Holt-Oram syndrome.

The differential diagnosis includes SALL-4 anomalies such as Townes- Brocks syndrome and VACTREL/VATER association because such conditions share same skeletal disorders with Holter-Omer syndrome. Additionally, the differential diagnosis includes Tabatzink hand-heart syndrome type 2 and type 3(Spanish) together with other similar upper extremity disorders such as thrombocytopenia-absent radius syndrome, Fanconi Anemia, Kaufmann McKusick syndrome, Okihiro syndrome, Nanger syndrome and teratogenic embryopathies (8, 9).

Such anomalies can easily be excluded with proper clinical examination and diagnostic evaluation. In the present case, the patient had obvious skeletal abnormalities affecting the upper limb (Figure 1, 2), ventricular septal defect repaired surgically and histologic diagnosis of Crohn's disease. Moreover, her family history was negative for skeletal upper extremities anomalies, cardiac defects or inflammatory bowel disease. Despite all the difficulties the patient has encountered, a satisfactory social activity level was declared.

4. CONCLUSION

To the best of our knowledge association of Holt-Oram syndrome with Crohn's disease has not been reported in literature before. Therefore, a possible genetic connection between Holt-Oram syndrome and Crohn's disease remains to be determined.

- **Author's contribution:** All authors equally participated in preparing this case report presentation. Final proof reading made by the first author.
- **Conflict of interest:** None declared.
- **Declaration of patient consent:** Authors certify that they have obtained patient consent form.

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