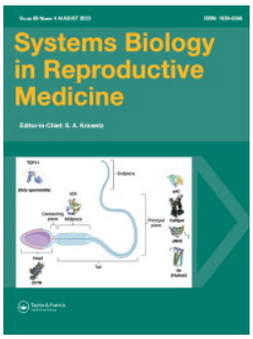

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A rare ring chromosome 21 abnormality is associated with azoospermia in two different phenotypically normal cases

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CLINICAL: CASE REPORT

A rare ring chromosome 21 abnormality is associated with azoospermia in two different phenotypically normal cases

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ABSTRACT

Azoospermia can be diagnosed with spermiogram analysis, and karyotyping is the golden standard to explain the etiology. In this study, we investigated two male cases with azoospermia and male infertility for chromosomal abnormalities. Their phenotypes and physical and hormonal examinations were both normal. In karyotyping G-banding and NOR staining, a rare ring chromosome 21 abnormality was detected in the cases and no microdeletion in chromosome Y. Ring abnormality, deletion size, and deleted regions were shown with subtelomeric FISH (.ish r(21)(p13q22.3?)(D21S1446-)) and array CGH analyses. Due to the findings, bioinformatics, protein, and pathway analyses were done to detect a candidate gene through common genes in two cases' deleted regions or ring chromosome 21.

Abbreviations: AZF: Azoospermia factor; CGH: Comparative genomic hybridization; DISC1: Disrupted in schizophrenia 1; FISH: Fluorescence in situ hybridization; GRCh: Genome reference Consortium human; NCBI: National center for biotechnology ınformation; NEK2: NIMA-related kinase 2; PCBP3: Poly(RC) Binding Protein 3; PCM: pericentriolar material; PCNT: pericentrin; PCR: Polymerase chain reaction; r: ring; SPATC1L: Spermatogenesis And Centriole Associated 1 Like; UK: United Kingdom; ZFY: Zinc Finger protein Y-Linked

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KEYWORDS
Ring chromosome 21; azoospermia; *PCNT*; male infertility

Introduction

One of the well-known genetic abnormalities that lead to infertility in both genders is chromosomal; they are classified as structural/numerical; and, according to their effects on the phenotype, as balanced/unbalanced. Sex chromosome anomalies, especially numerical abnormalities (for example, 47,XXY anomaly in the presence of azoospermia in males), are frequently detected in both female and male infertility. Autosomal structural chromosomal abnormalities are more noticeable in male cases with oligoasthenoteratozoospermia. Ring chromosomes are one of the structural chromosomal abnormalities rare in eukaryotes (1/50,000) (Pristyazhnyuk and Menzorov 2018). They mainly occur due to the end-joining repair mechanism of double-strand DNA breaks, inverted duplication associated with terminal deletion reorganization in meiosis, and mitosis or telomeric and subtelomeric fusion (Burssed et al. 2022, Li et al. 2022).

In this article, we report a rare ring chromosome 21 (46, XY.ish r(21)(p13q22.3?)(D21S1446-)) in two different cases that are phenotypically normal with azoospermia. Few publications in the literature show that this chromosomal anomaly can cause only azoospermia and male infertility without causing congenital anomalies or cognitive deficits (Huret et al. 1985; Dallapiccola et al. 1986; Hammoud et al. 2009; Cetin et al. 2015). Also, we report a candidate gene, *PCNT*, to explain the etiology and examine for male infertility.

Results

The cases of pubertal developments, physical and hormonal examinations were both normal. They were not taking any medication, had no allergic history, and had no positive findings in the families. They were both thirty-two years old and married. They were both consulted due to male infertility and unsuccessful assisted reproductive techniques trials. Analyses of the patients' semen revealed azoospermia. Y chromosome microdeletion analyses were performed to rule out the presence of any genomic deletions in the azoospermic factor a, b, and c regions on the long arm of

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chromosome Y, and no deletion was detected. 46,XY.ishr(21)(p13q22.3?) (D21S1446-) (Aquarius-Cytocell, Cambridge, UK) chromosomal structures both identified *via* subtelomeric FISH analyses in these two different phenotypically normal but azoospermia cases. Parental cytogenetic studies were performed to investigate the ring chromosome's origin and detected it as normal. Associated with these results, ring chromosome 21 formations were interpreted as *de novo*. The karyotype examination (G banding and NOR banding) and FISH analysis results of the cases are shown in Figures 1, 2.

In the a-CGH examination performed to detect the broken regions of the detected ring chromosome, a deletion of 2,578 Mb was found in case 1 and 1,522 Mb in case 2. The results are listed in Table 1 and shown in Figure 3. Genes in the deleted regions were analyzed based on their functions *via* databases of UniProt, OMIM, the Human Protein Atlas, and Pubmed to identify the candidate gene for the etiology and detailed in Table 2. The *PCNT* gene was determined as the strongest candidate by considering the functions, tissues in which they are expressed, and associated phenotypes.

Discussion

When male infertility is considered, 4.9% 47,XXY Klinefelter syndrome, 3.5% autosomal anomalies, 1.8% sex chromosome anomalies, and 3.5% Y microdeletions are detected. Ring chromosomes also influence this phenotype by causing sperm formation defects. Ring 21 chromosomal anomaly, reported in very few cases, is said to be associated with azoospermia in phenotypically normal male individuals.

The basic mechanism in the formation of ring chromosomes is two double-chain breaks in a chromosome and fusion at these break sites, and they are classified as telomeric or subtelomeric in the chromosome arm according to the locations of the breaks (Burssed et al. 2022). The features affecting the phenotype in cases with ring chromosomes are the location of the fractures that occur during ring chromosome formation, aneuploidies associated with ring chromosomes, and the accelerated cell death of changing metabolic activities. Ring chromosome formation can be seen between 5 and 9% in D/G group chromosomes (13, 14, 15, 21, and 22), and 88% of ring chromosomes diagnosed after birth due to mild phenotypes compatible with life occur de novo (Li

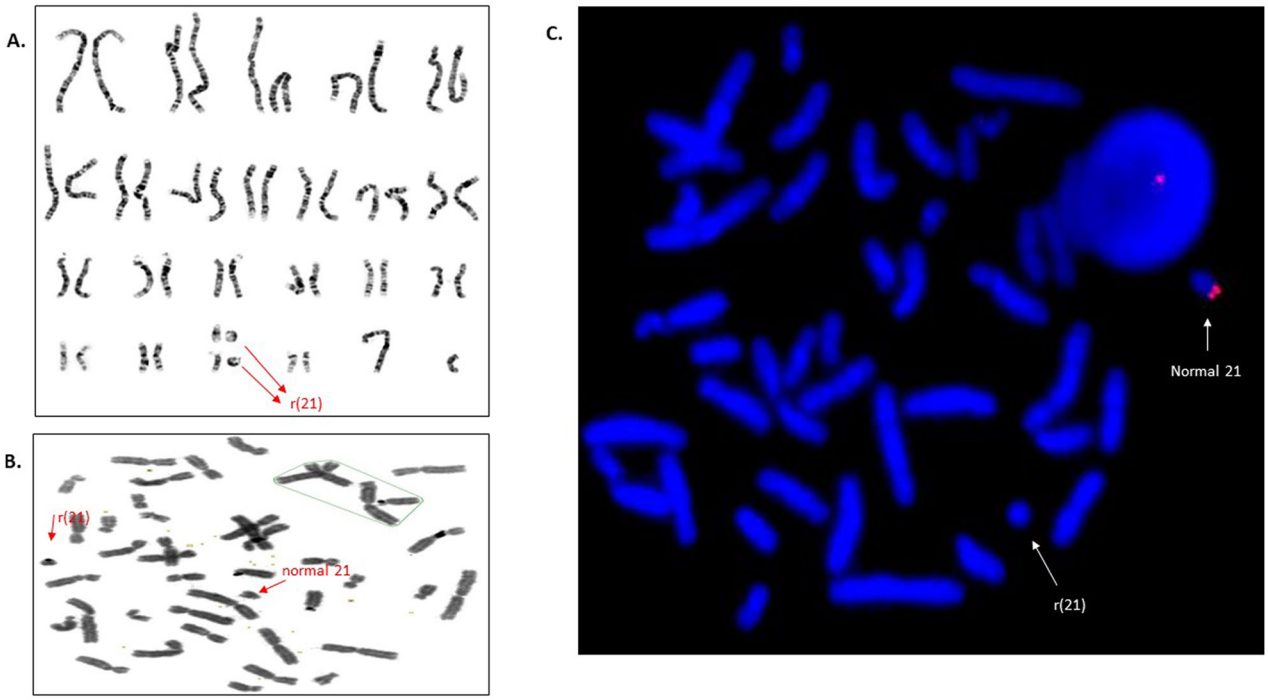

Figure 1. Karyotyping and FISH images of Case-1. Normal chromosome 21 and ring chromosome 21 are indicated with arrows. **A.** Metaphase images detected by G-banding; ring 21 and normal chromosome 21 from two separate metaphases of Case-1. **B.** NOR staining of Case-1, which Ag-NOR staining is specific for human chromosomes 13, 14, 15, 21, and 22. Ring chromosome 21 interpreted NOR positive. **C.** Subtelomeric FISH image for D21S1446 probe of Case-1. Two signals were detected in normal 21 (red), but none in the ring chromosome 21. (G: Giemsa; NOR: nucleolar organization region).

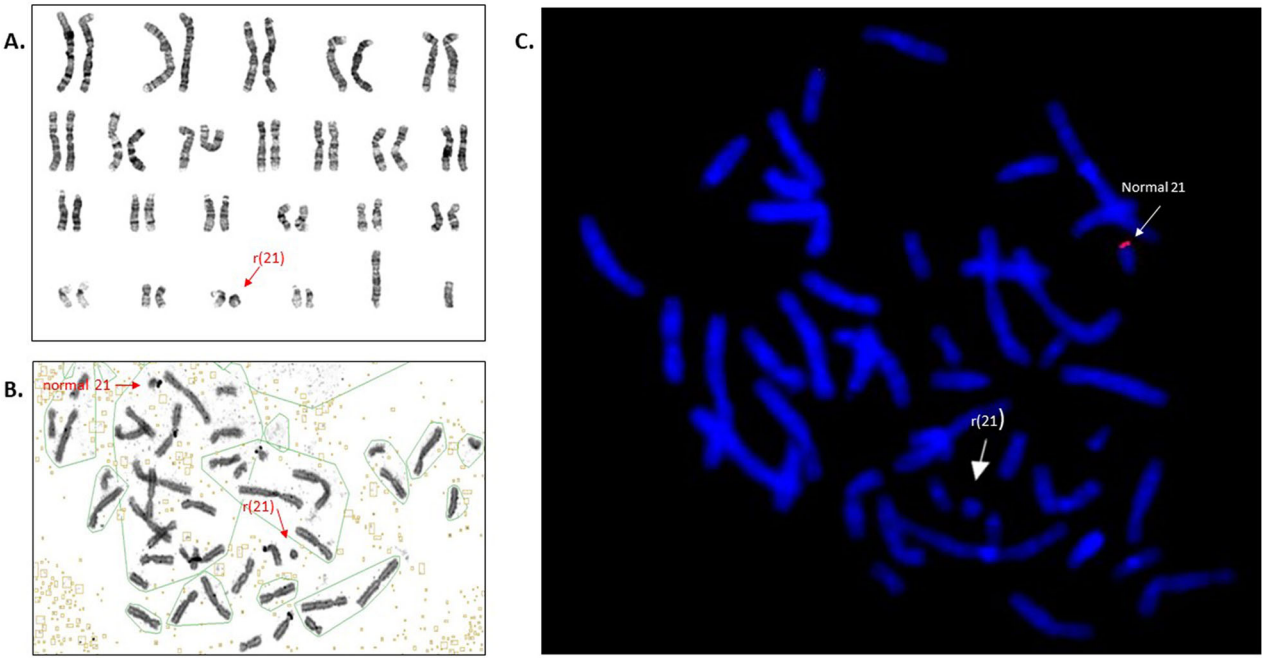

Figure 2. Karyotyping and FISH images of Case-2. Normal chromosome 21 and ring chromosome 21 are indicated with arrows. **A.** Metaphase images detected by G-banding of Case-2. **B.** NOR staining of Case-2, which Ag-NOR staining is specific for human chromosomes 13, 14, 15, 21, and 22. NOR negative in ring chromosome 21 of the case. **C.** Subtelomeric FISH image for D21S1446 probe of Case-2. Two signals were detected in normal 21 (red), but none in the ring chromosome 21. (G: Giemsa; NOR: nucleolar organization region).

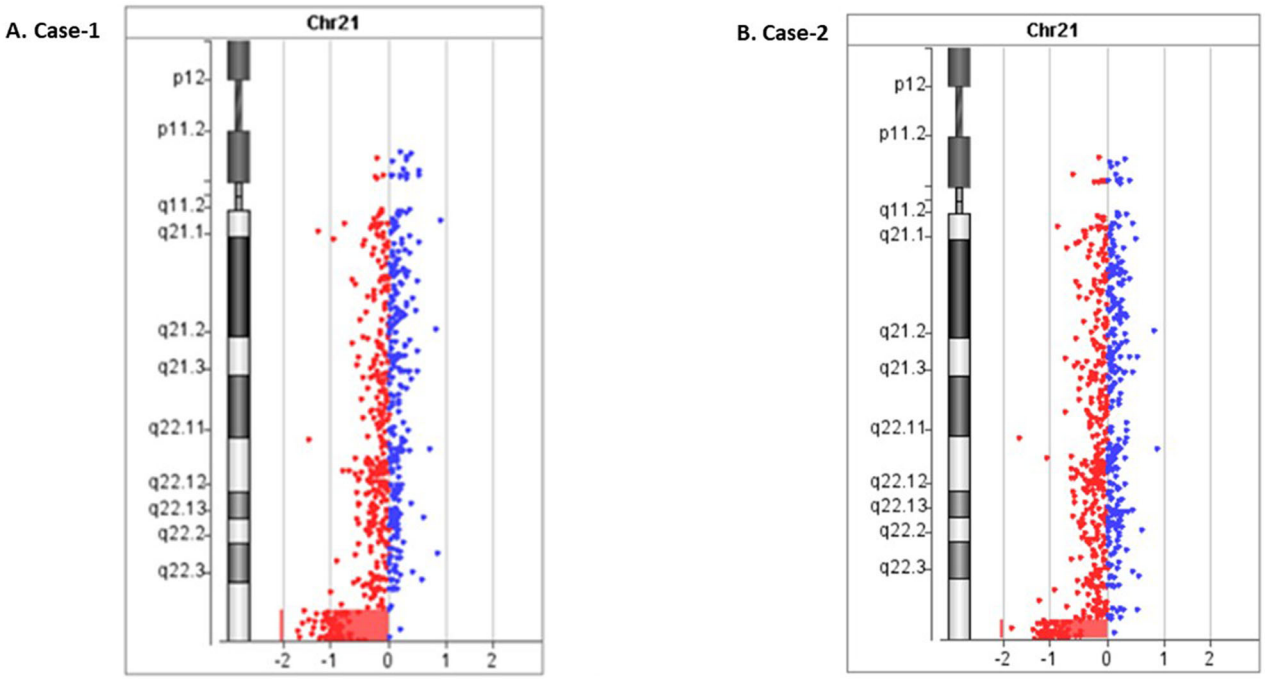

Figure 3. a-CGH analysis reports of chromosome 21 of the cases. Agilent SurePint CGH + SNP 8x60K platform with at least three probes and Cytogenomics v5.1.2.1 analysis software were used. The minimum log ratio was +/- 0.5. Array based CGH technique provides increased resolution for changes in copy number of the genome and detailed examination for the chromosomes. **A.** 2,578 Mb deletion in 21q22.3 region (44082065_46661014) detected in Case-1. **B.** 1,522 Mb deletion in 21q22.3 region (45138321_46661014) detected in Case-2. (Mb: Megabase).

Table 1. Molecular cytogenetics analyses results of the cases.

Results	Case-1	Case-2
FISH	46,XY,r(21)(p13q22.3)	46,XY,r(21)(p13q22.3)
a-CGH	.arr[GRCh38]21q22.3(44082065_46661014)x1	.arr[GRCh38]21q22.3(45138321_46661014)x1
Deletion region	44082065_46661014	45138321_46661014
Deletion size	2,578 Mb	1,522 Mb
Deleted genes	*TRAPPC10, PWP2, GATD3A, ICOSLG, DNMT3L, AIRE, PFKL, CFAP410, TRPM2, LRRC3, TSPEAR, UBE2G2, SUMO3, PTTG1IP, ITGB2, LINC00163, PICSAR, ADARB1, POFUT2, COL18A1, SLC19A1, PCBP3, COL6A1, COL6A2, FTCD, SPATC1L, LSS, MCM3AP, YBEY, PCNT, DIP2A, S100B, PRMT2*	*ADARB1, POFUT2, COL18A1, SLC19A1, PCBP3, COL6A1, COL6A2, FTCD, SPATC1L, LSS, MCM3AP, YBEY, PCNT, DIP2A, S100B, PRMT2*

et al. 2022). Rare ring chromosome 21 abnormalities (r(21)(p13q22.3 and r(21)(p11q22.3)) were published in cases that are phenotypically normal with azoospermia. These publications declared that this chromosomal abnormality could cause only azoospermia or cryptozoospermia and male infertility without causing congenital anomalies or cognitive deficits (Huret et al. 1985; Dallapiccola et al. 1986; Hammoud et al. 2009; Cetin et al. 2015). A gene that may change the function during ring formation in the q telomere region of chromosome 21 and affect spermatogenesis has yet to be identified. We examined the genes in the deleted areas bioinformatically, and due to the high expression levels in the testis and the effect on spermatogenesis, *PCBP3*, *PCNT*, and *SPATC1L* were examined in detail.

PCBP3 gene product poly(rC)-binding protein-3 play essential roles in post-transcriptional activities and RNA-binding proteome member in the elongation of round spermatids (Chapman et al. 2013). In the Human Protein Atlas database, expressed RNA is explicitly mentioned for the brain and retina, also detected in many and not specificity mentioned for protein expression. SPATC1L is known for high expression levels in the testis and localized in the neck. Biallelic mutations of *SPATC1L* were reported for a rare teratozoospermia, acephalic spermatozoa syndrome (Li et al. 2022). Also, homozygous and heterozygous gene loss led to defects in head-to-tail junction, and headless sperm were observed in mice (Kim et al. 2018). In light of these findings, the predominant expression of *PCBP3* in the human retina and the association of *SPATC1L* with acephalic spermatozoa were not considered in the foreground due to the absence of these findings in our cases.

Pericentrin, the product of *PCNT* gene, is a protein found in the structure of centrosomes and interacts with gamma-tubulin (Flory et al. 2000). Biallelic pathogenic *PCNT* variants have been associated with Microcephalic osteodysplastic primordial dwarfism type-II (MIM #210720), while hypospadias and precocious puberty have also been reported in male cases.

PCNT is essential in ciliogenesis and is one of the genes associated with ciliopathy and coding pericentrin protein with 3336 amino acids. Pericentrin protein is a centrosome and pericentriolar material (PCM) component, forming the microtubule arrays in mitosis and meiosis. It is involved in microtubule network formation together with DISC1. It is also thought to effectively prevent early centrosome division in interphase by inhibiting NEK2 kinase activity in the centrosome (Matsuo et al. 2010). As a result of the studies in mice, it is actively expressed in the retina, brain, and skeletal system (Falk et al. 2018). In a study conducted with mouse oocytes to determine their functions in the reproductive system, it was found that the silencing of the gene disrupted the alignment of chromosomes during meiosis (Ma and Viveiros 2014). There are no studies on sperm and the male reproductive system with the *PCNT* gene. But, the relationship between ciliopathies with spermatogenesis and male infertility is well-known (Sironen et al. 2020). When the tissue expressions of this gene are examined through the Human Protein Atlas database, it is seen that one of the tissues with the most expression after skeletal muscles is the testis in humans (Uhlén et al. 2015). This finding is a strong indicator of the gene's association with infertility. Both cases can contribute to the clarification of this relationship.

As a result, we detected a new candidate gene to explain azoospermia cases etiology. This article is the first one that declares *PCNT* gene loss might be associated with male infertility and azoospermia. These results need to be supported with functional studies, and monoallelic *PCNT* mutations and function loss should be studied in male infertility cases.

Materials and methods

Two patients were referred to Istanbul University Medical Faculty Medical Genetics Department for chromosomal karyotyping. This study was approved by the Istanbul Medical Faculty Clinical Research

Table 2. Common genes in two deletions, associated pathways, their functions, and possible effects.

Gene	Biological process	Tissue specificity	Effect on male fertility	Detected phenotype
ADARB1	RNA editing	Brain, heart, placenta, lung, live, kidney	No direct impact on male infertility in knockout mice (Snyder et al. 2017)	Neurodevelopmental disorder with hypotonia, microcephaly, and seizures (AR; MIM #618862)
POFUT2	Carbohydrate metabolism (glycosyltransferase)	Low tissue specificity	N.A.	N.A.
COL18A1	Cell adhesion	Liver, lung, kidney	N.A.	Glaucoma (AD; MIM #61880) Knobloch syndrome, type 1 (AR; MIM #267750)
PCBP3	DNA-binding, RNA-binding	Brain, retina	RNA-binding proteome member in elongation of round spermatids (Chapman et al. 2013)	Frontotemporal dementia (Wang et al. 2010)
COL6A1	Cell adhesion	İntestine fibroblast	N.A.	Bethlem myopathy 1 (AD, AR; MIM #158810), Ullrich congenital muscular dystrophy 1 (AD, AR; MIM #254090)
COL6A2	Cell adhesion	Fibroblast	N.A.	Congenital myosclerosis (AR; MIM #255600), Bethlem myopathy 1 (AD, AR; MIM #158810), Ullrich congenital muscular dystrophy 1 (AD, AR; MIM #254090)
FTCD	Histidine metabolism	Liver, kidney	N.A.	Glutamate formiminotransferase deficiency (AR; 229100)
SPATC1L	Sperm head-to-tail connection	Testis	Teratozoospermia and male infertility (Li et al. 2022)	Acephalic sperm syndrome (Li et al. 2022)
LSS	Steroid biosynthesis	Liver, adipose tissue, hair follicle epithelium	N.A.	Alopecia-intellectual disability syndrome 4 (AR; MIM #618840), Cataract 44 (AR; MIM #616509), Hypotrichosis 14 (AR; MIM #618275)
MCM3AP	Transport, replication	Low tissue specificity	N.A.	Peripheral neuropathy, autosomal recessive, with or without impaired intellectual development (AR; MIM #618124)
YBEY	rRNA maturation	Testis	N.A.	N.A.
PCNT	Microtubule network formation	Skeletal muscle, testis	Cilia formation in spermatocytes (Jurczyk et al. 2004)	Microcephalic osteodysplastic primordial dwarfism, type II (AR; MIM #210720)
DIP2A	Neurogenesis	Low tissue specificity	N.A.	N.A.
S100B	Metal-ion binding	Brain	Sensor for Ca^{2+}-modulated membrane guanylate cyclases (Jankowska et al. 2014)	Neurological Disorders (Langeh and Singh 2020)
PRMT2	Methylation of arginine	Low tissue specificity	N.A.	N.A.

Ethics Committee of Istanbul University (2018-249). The patients both signed detailed consent forms. Peripheral venous blood sampling, karyotyping, FISH and a-CGH techniques were done in Istanbul University Medical Faculty Medical Genetics Laboratory. In karyotyping, the analysis was done by magnifying 250 times with the Metasystem/Cytovision automatic imaging device, with at least 20 metaphases for each case (Hastings et al. 2012). Subtelomeric fluorescence *in situ* hybridization (FISH) analyses were performed on metaphase plates to evaluate the positions of the ring chromosome (Wegner 1999). Multiplex PCR technique and gel electrophoresis studies were done for Y chromosome microdeletion analyses. At least two markers from ZFY, SRY, AZFa, AZFb, and AZFc regions were examined. After that, array-CGH analyses were done to investigate the size and breakpoints of the anomaly detected in the chromosome analysis (Silva et al. 2019). We used Agilent SurePint CGH + SNP 8x60K platform and Cytogenomics v5.1.2.1 analysis software for a-CGH. Array resolution was 60K, and analyses were

performed with the hg19/NCBI Build 38 database. The minimum number of probes was three, and the minimum log ratio was +/- 0.5. The results were reported according to ISCN guideline (McGowan-Jordan et al. 2020). Two cases signed informed consent forms to use their data in academic papers as randomized.

Ethics approval

This study was approved by the Istanbul Medical Faculty Clinical Research Ethics Committee of Istanbul University (2018-249). The patients both signed detailed consent forms.

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This research has not been presented at a scientific meeting has or published in any journals.

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Disclosure statement

The authors declare no competing interests.

Authors' contributions

Planning, acquisition of data and analysis, writing and editing the article: EGB; acquisition of data and analysis, interpretation of data, reporting: BK; conception and design: SB.

Data availability statement

The data will be shared if requested.

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