

CASE REPORT

Successful sperm retrieval and live birth after ICSI in a man with laboratory-reported partial AZFb and complete AZFc microdeletion: a case report

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Abstract

Background: Y-chromosomal azoospermia factor b (AZFb) and AZFbc deletions are associated with near-complete absence of spermatogenesis in their classical forms, and microdissection testicular sperm extraction (micro-TESE) is typically discouraged; non-classical partial patterns may carry a different prognosis. A live birth, however, is not necessarily a healthy one. **Case:** A 36-year-old man with 16 years of primary azoospermia presented with a deletion profile characterised by preservation of proximal AZFb markers (sY105, sY121), loss of the distal AZFb marker sY153, and complete absence of all tested AZFc markers (sY1191, sY1291, sY254, sY255), with a 46,XY karyotype. This sequence-tagged site (STS) profile, generated by standard multiplex polymerase chain reaction (PCR), was laboratory-reported as partial AZFb with complete AZFc deletion. Right-sided micro-TESE demonstrated a mixed-atrophy phenotype with focal residual spermatogenesis (mean Johnsen score 2); a small number of motile spermatozoa were retrieved and cryopreserved. After counselling, the couple declined preimplantation genetic testing (PGT). Intracytoplasmic sperm injection (ICSI) of thawed motile spermatozoa fertilised three of seven oocytes, and a frozen-thawed embryo transfer resulted in a male live birth. The infant carried the same AZF deletion and showed multiple dysmorphic features with high-risk aneuploidy screening (trisomy 21); a confirmatory karyotype was pending. **Conclusions:** Laboratory-reported partial AZFb with complete AZFc deletions may correspond to atypical AZFbc configurations compatible with residual spermatogenesis and successful ICSI. However, a live birth is not synonymous with a healthy child: comprehensive genetic counselling, PGT and prenatal diagnosis are essential, given the obligate transmission of the deletion to male offspring and the increased aneuploidy risk associated with these deletions.

Keywords

AZF microdeletion; Azoospermia; ICSI; Live birth; Micro-TESE; Preimplantation genetic testing; Aneuploidy; Y chromosome

Recuperación exitosa de espermatozoides y nacimiento vivo tras ICSI en un varón con microdelección parcial de AZFb y completa de AZFc informada por el laboratorio: reporte de un caso

Resumen

Antecedentes: Las deleciones de las regiones del factor azoospermico b (AZFb) y AZFbc del cromosoma Y se asocian con ausencia casi completa de espermatogénesis en sus formas clásicas, y la extracción de espermatozoides testiculares por microdissección (micro-TESE) generalmente está desaconsejada. Sin embargo, los patrones de delección parcial no clásicos pueden presentar un pronóstico sustancialmente diferente. **Caso clínico:** Un hombre de 36 años con 16 años de azoospermia primaria presentó un perfil de delección caracterizado por preservación de los marcadores AZFb proximales (sY105, sY121), pérdida del marcador AZFb distal sY153 y ausencia completa de todos los marcadores AZFc analizados (sY1191, sY1291, sY254, sY255), con cariotipo 46,XY. Este perfil de sitios de secuencia etiquetada (STS), obtenido mediante reacción en cadena de la polimerasa (PCR) múltiple estándar, fue informado por el laboratorio como delección parcial de AZFb con delección completa de AZFc. La micro-TESE del lado derecho demostró un fenotipo de atrofia mixta con espermatogénesis residual focal (puntuación media de Johnsen: 2); se recuperaron y criopreservaron un pequeño número de espermatozoides móviles. Tras el asesoramiento, la pareja rechazó el diagnóstico genético preimplantacional (DGP). La inyección intracitoplasmática de espermatozoides (ICSI) con espermatozoides móviles descongelados fecundó tres de siete ovocitos y una transferencia de embriones descongelados resultó en el nacimiento de un varón. El recién nacido portaba la misma delección AZF y presentaba múltiples rasgos dismórficos con cribado de aneuploidía de alto riesgo (trisomía 21); el cariotipo confirmatorio estaba pendiente. **Conclusiones:** Las deleciones de AZFb parcial con AZFc completo informadas por el laboratorio pueden corresponder a configuraciones AZFbc atípicas compatibles con espermatogénesis residual e ICSI exitoso. Sin embargo, un nacimiento vivo no es sinónimo de un hijo sano: el asesoramiento genético integral, el DGP y el diagnóstico prenatal son esenciales, dada la transmisión obligada de la delección a la descendencia masculina y el mayor riesgo de aneuploidía en estas parejas.

Palabras Clave

Delección AZFbc; Azoospermia; ICSI; Nacimiento vivo; Micro-TESE; Diagnóstico genético preimplantacional; Aneuploidía; Cromosoma Y

1. Introduction

Y-chromosomal microdeletions are among the most frequently identified genetic causes of non-obstructive azoospermia (NOA) [1]. They are detected in approximately 5–10% of men with azoospermia or severe oligozoospermia and represent the most common molecularly defined cause of primary spermatogenic failure after Klinefelter syndrome; their prevalence rises with the severity of the spermatogenic defect [2]. Three contiguous spermatogenesis loci (AZFa, AZFb and AZFc) occupy the long arm of the Y chromosome at Yq11. In their 2023 best-practice guideline, the European Academy of Andrology (EAA) and the European Molecular Genetics Quality Network (EMQN) organise clinically meaningful microdeletions according to the recombination events that generate them: complete AZFb arises from P5/proximal-P1 exchange, complete AZFc from b2/b4 exchange, and AZFbc from either P5/distal-P1 or P4/distal-P1 exchange. Patterns falling outside these archetypes (whether non-classical, atypical or partial) may carry a more favourable prognosis than the classical P5/proximal-P1 AZFb deletion, because a portion of the AZFb gene content can remain intact [1, 3].

Aggregated clinical experience indicates that microdissection testicular sperm extraction (micro-TESE) recovers spermatozoa in roughly two-thirds of men with isolated AZFc deletions, whereas the corresponding yield falls close to zero when the deletion involves the entirety of AZFa, AZFb or

AZFbc [4]. This pessimistic outlook, however, should not be applied without nuance to partial or atypical AZFb/AZFbc patterns. In the pooled analysis by Kleiman *et al.* [5], sperm cells were identified far more often in partial AZFb and partial AZFbc deletions than in their complete counterparts, with reported frequencies of 57% and 43% versus 7% and 3%, respectively. We here describe a man carrying a laboratory-reported partial AZFb with complete AZFc deletion (best characterised as distal AZFb/AZFc involvement compatible with atypical AZFbc deletion), in whom micro-TESE followed by intracytoplasmic sperm injection (ICSI) ultimately resulted in a live birth. We report, with equal emphasis, that the live-born infant was not healthy—a course that underscores the central importance of genetic counselling, preimplantation genetic testing (PGT) and prenatal diagnosis in these couples.

2. Case presentation

A 36-year-old man was referred for assessment of primary infertility of 16 years' duration. His past medical history was unremarkable, with no history of cryptorchidism, orchitis, testicular trauma, chemotherapy, or radiotherapy. Clinical examination demonstrated bilaterally reduced testicular volume (right 10.6 cc and left 10.0 cc on scrotal ultrasonography); the epididymides and vasa deferentia appeared normal, and no varicocele was identified.

Hormonal work-up yielded a serum follicle-stimulating hormone (FSH) of 7.5 IU/L, luteinising hormone (LH) of 4.2

IU/L and total testosterone of 2.7 ng/mL, a pattern compatible with compensated primary testicular failure. Non-obstructive azoospermia was confirmed on three centrifuged semen analyses performed at intervals of at least two weeks.

All genetic analyses were performed at the Department of Medical Genetics, Trakya University Hospital, Edirne, Türkiye. Y-chromosomal microdeletion analysis was conducted by multiplex polymerase chain reaction (PCR) with microsatellite analysis of peripheral blood-derived DNA, using the zinc finger protein X-linked/Y-linked (ZFX/Y) and sY14 as internal reaction controls to verify DNA integrity and successful amplification. Karyotyping was performed by short-term lymphocyte culture with G-bands by trypsin using Giemsa (GTG banding); twenty metaphases were analysed at a resolution of 450–500 bands. Cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation screening was carried out by next-generation sequencing using the QIAseq Targeted DNA Panel (QIAGEN) on an Illumina NextSeq550 platform (Illumina, Inc., San Diego, CA, USA), with data analysis performed using QIAGEN Clinical Insight (QCI) Interpret (<https://digitalinsights.qiagen.com/products-overview/clinical-insights-portfolio/qiagen-clinical-insight/qci-interpret/>, QIAGEN Digital Insights, Redwood City, CA, USA) and the Integrative Genomics Viewer (IGV 2.3.8).

Peripheral blood karyotype was 46,XY. Y-chromosomal microdeletion analysis by multiplex PCR showed preservation of

the control markers ZFX/Y and sY14, of every AZFa marker tested (sY82, sY83, sY1065 and sY88), and of the proximal AZFb markers sY105 and sY121. By contrast, the distal AZFb marker sY153 and all examined AZFc markers (sY1191, sY1291, sY254 and sY255) were undetectable (Table 1, Ref. [1]). The original laboratory report classified this profile as a partial AZFb deletion combined with a complete AZFc deletion. The full 2023 EAA/EMQN AZFb/AZFbc extension marker set (sY127, sY134, sY1192, sY116 and sY1224) was not included in the laboratory's panel; the interpretive and mechanistic implications of this profile are considered in the Discussion. *CFTR* sequencing returned a negative result. The couple received detailed genetic counselling before treatment, which addressed the obligate transmission of the Y-chromosomal deletion to all male offspring conceived with the patient's own spermatozoa, the expectation of a similar spermatogenic phenotype in sons, and the availability of PGT and of donor sperm. PGT was specifically recommended; the couple declined it in a signed, witnessed statement acknowledging that they accepted the associated reproductive and genetic risks, and elected to proceed with autologous ICSI without PGT and provided written informed consent. Reproductive options, including discontinuation of treatment, adoption, donor sperm, ICSI with PGT, and ICSI without PGT followed by prenatal diagnosis, were discussed. After non-directive counselling, the couple elected to proceed with autologous ICSI without PGT.

TABLE 1. Sequence-tagged site (STS) markers tested in this case and their results, with notation of EAA/EMQN 2023 recommended extension markers.

STS Marker	AZF Region	Result	EAA/EMQN 2023 Recommended Panel
ZFX/Y	Control	Present (+)	Yes (mandatory control marker)
sY14	Control	Present (+)	Yes (mandatory control marker)
sY82	AZFa	Present (+)	No
sY83	AZFa	Present (+)	No
sY1065	AZFa	Present (+)	No
sY88	AZFa	Present (+)	No
sY105	AZFb (proximal)	Present (+)	No
sY121	AZFb (proximal)	Present (+)	No
sY127	AZFb (distal)	Not tested ¹	Yes—required for partial AZFb/AZFbc classification
sY134	AZFb (distal)	Not tested ¹	Yes—required for partial AZFb/AZFbc classification
sY153	AZFb (distal)	Absent (–)	Yes (standard panel)
sY1191	AZFb/AZFc	Absent (–)	No
sY1291	AZFc	Absent (–)	No
sY1192	AZFc	Not tested ¹	Yes—required for AZFbc breakpoint mapping
sY116	AZFb/AZFc boundary	Not tested ¹	Yes—required for AZFbc breakpoint mapping
sY1224	AZFc	Not tested ¹	Yes—required for AZFbc breakpoint mapping
sY254	AZFc	Absent (–)	Yes (standard panel)
sY255	AZFc	Absent (–)	Yes (standard panel)

¹Not included in the laboratory's multiplex PCR panel; these markers are required for precise breakpoint characterisation of partial AZFb and atypical AZFbc deletions under the 2023 EAA/EMQN best-practice guideline [1]. EAA, European Academy of Andrology; EMQN, European Molecular Genetics Quality Network; STS, sequence-tagged site; AZF, azoospermia factor; ZFX/Y, zinc finger protein X-linked/Y-linked.

Because of the low-normal serum testosterone, empirical clomiphene citrate (25 mg daily) was administered for six months before surgery in an attempt to optimise intratesticular androgen exposure. Right-sided micro-TESE was carried out. A small number of dilated seminiferous tubules were identified and sampled, yielding a limited number of motile testicular spermatozoa; overall sperm morphology was poor. The spermatozoa were cryopreserved. Histopathology demonstrated a predominantly Sertoli cell-only pattern (mean Johnsen score 2) with scattered tubules harbouring spermatocytes and early spermatids (Fig. 1), consistent with a mixed-atrophy phenotype, the histological correlate of focal residual spermatogenesis in which micro-TESE outperforms conventional or random biopsy [6].

On the day of ICSI, the cryopreserved specimen was thawed; approximately 20–30 spermatozoa were observed, among which motile spermatozoa were present, and seven motile spermatozoa were selected on the basis of motility and morphology. Because motile spermatozoa were available, a viability test such as the hypo-osmotic swelling test was not required. Seven metaphase-II oocytes underwent ICSI, and three fertilised normally (fertilisation rate 42.9%). On day 3, three embryos were available (an 8-cell grade 1, an 8-cell grade 2, and a 6-cell grade 2); the two 8-cell embryos were cryopreserved. In a subsequent frozen-thawed embryo transfer cycle, the two thawed embryos were transferred, and a singleton intrauterine pregnancy with fetal cardiac activity was documented.

The pregnancy was followed as high-risk. First-trimester

combined screening and second-trimester triple screening both returned a high risk for trisomy 21 (adjusted risks of the order of 1/112–1/411), an expanded cell-free DNA non-invasive prenatal testing (NIPT) panel flagged a rare autosomal trisomy (trisomy 7), and detailed ultrasonography showed grade 1 echogenic bowel; invasive prenatal testing (amniocentesis or chorionic villus sampling) was declined. A male infant was delivered by caesarean section at 38 weeks and 4 days, with a birth weight of 2750 g (appropriate for gestational age) and Apgar scores of 9 and 10 at 1 and 5 minutes, respectively.

Neonatal examination was not that of a healthy infant: multiple dysmorphic features were noted, including low-set ears with a preauricular skin tag, a depressed nasal bridge, bilateral single transverse (simian) palmar creases and a sacral dimple. The neonatal course was further complicated by early-onset sepsis (raised C-reactive protein and thrombocytopenia), for which the infant was admitted to the neonatal intensive care unit and treated with antibiotics. On the basis of the dysmorphic features and the prenatal screening, the neonatology team raised a clinical suspicion of Down syndrome. Y-chromosomal microdeletion analysis performed in the infant confirmed transmission of the same AZF deletion (absence of sY153, sY1191, sY1291, sY254 and sY255). A confirmatory constitutional karyotype was requested; the result was still pending at the time of submission of this revised manuscript. The dysmorphic features were descriptive clinical findings that prompted further genetic evaluation and should not be interpreted as attributable to the inherited Y-chromosomal AZF microdeletion itself.

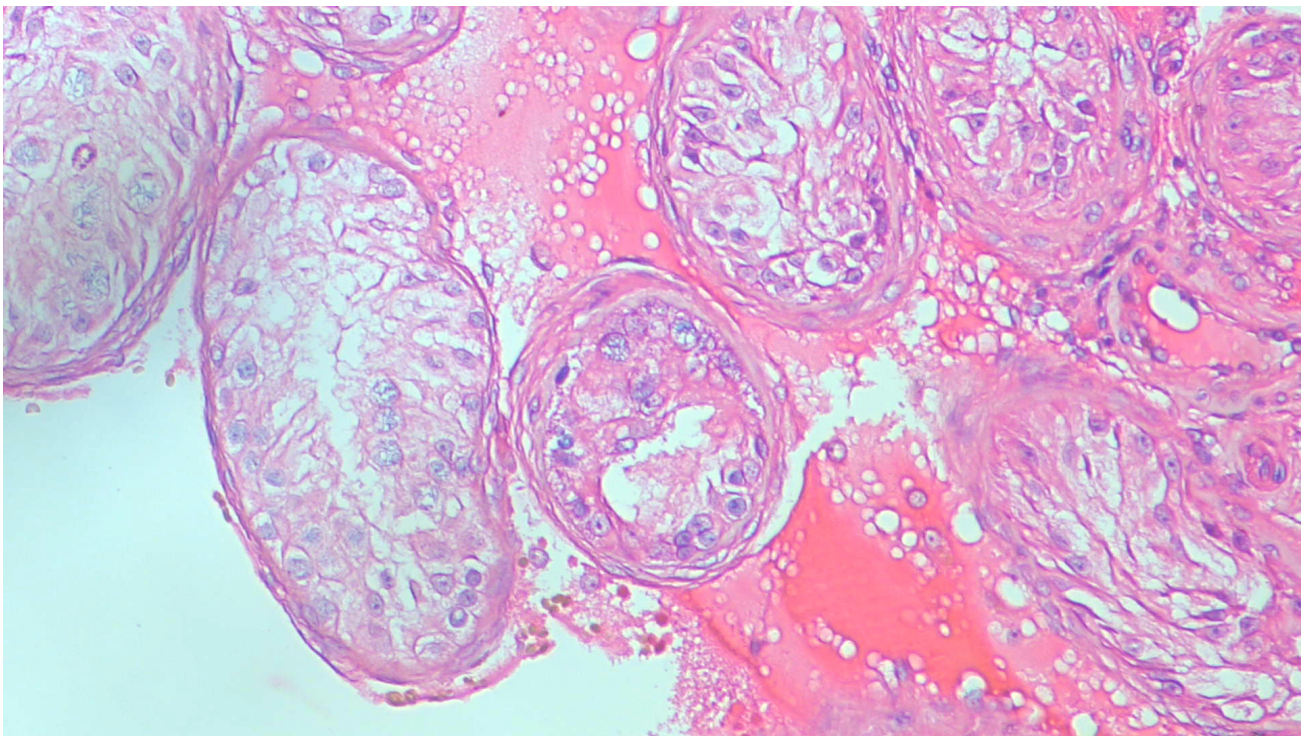


FIGURE 1. Testicular histopathology obtained at right-sided micro-TESE. The majority of seminiferous tubules show a Sertoli cell-only pattern with reduced tubular diameter and absence of germ cells (mean Johnsen score 2); a minority of focally dilated tubules contain spermatocytes and early spermatids, consistent with focal residual spermatogenesis and representing the intraoperative target of microdissection. This mixed-atrophy pattern is compatible with partial preservation of the proximal AZFb region (sY105 and sY121 retained). Haematoxylin and eosin; original magnification $\times 200$.

3. Discussion

The STS profile (retention of the proximal AZFb markers sY105 and sY121 alongside loss of the distal AZFb marker sY153 and of all tested AZFc markers) does not match either a classical complete AZFb deletion or an isolated complete AZFc deletion. In particular, the combination of retained sY121 with absent sY153 weighs against a typical classical P5/proximal-P1 AZFb configuration; conversely, the preservation of sY105 alone is not sufficient to exclude classical AZFb, since sY105 can be retained in the canonical P5/proximal-P1 deletion [1]. Overall, the pattern is most compatible with distal AZFb/AZFc involvement of the atypical AZFbc type, although precise breakpoint mapping remains a matter of inference because key EAA/EMQN extension markers (sY127, sY134, sY1192, sY116 and sY1224) were not available [1, 3]. The 2023 EAA/EMQN guideline identifies two principal palindromic recombination events generating AZFbc deletions: P5/distal-P1, which spans the entirety of AZFb and AZFc, and P4/distal-P1, which spares part of the proximal AZFb gene content; the retention of sY105 and sY121 is more consistent with a P4/distal-P1 or alternative atypical breakpoint [1, 3].

Set against the well-documented near-zero retrieval rate observed in classic complete AZFb and AZFbc deletions [4], the outcome in our patient is unusual but not without precedent. As outlined above, the pooled review of Kleiman *et al.* [5] demonstrated that sperm-cell detection occurred substantially more often in partial AZFb and partial AZFbc deletions than in their complete counterparts (Table 2, Ref. [5, 7–10]), reinforcing a meaningful prognostic divide between classical complete deletions on the one hand and partial or atypical configurations on the other. Specifically, mature sperm cells were identified in 57% of partial AZFb and 43% of partial AZFbc deletions, versus only 7% and 3% in their complete counterparts, respectively [5]. Subsequent observations are concordant: men with atypical or partial patterns show heterogeneous phenotypes, ranging from residual spermatogenesis with ejaculated spermatozoa in oligozoospermic men [7, 9] to azoospermia with Sertoli cell-only histology and no retrievable testicular sperm [8], and in 2025 Aoki *et al.* [10] described a man in whom an isolated absence of sY1024 (a proximal AZFb marker in the assay used) was associated with successful sperm retrieval at micro-TESE, although the subsequent ICSI cycle did not result in pregnancy. To our knowledge, the present report stands among the very few documented instances in which a distal AZFb/AZFc deletion compatible with atypical AZFbc involvement has been followed by both successful sperm retrieval and a live birth. The developmental stage of the injected male gamete is a principal determinant of ICSI competence. Fertilising capacity increases across the spermatogenic hierarchy, from secondary spermatocytes and round spermatids to elongating/elongated spermatids and, finally, testicular spermatozoa. Round spermatid injection is technically feasible but yields substantially lower fertilisation, pregnancy and live-birth rates than ICSI with spermatozoa, in part because round spermatids lack a mature oocyte-activating signal and a fully competent centriolar and epigenetic complement [11, 12]. Our patient lay at the favourable end of this

spectrum: motile testicular spermatozoa were recovered, so that viability was assured by motility itself and a viability test such as the hypo-osmotic swelling test—indicated when only immotile spermatozoa are available [13]—was unnecessary. The recovery of motile mature spermatozoa, rather than only spermatocytes or spermatids, is a plausible contributor to the successful fertilisation observed.

Three clinical implications follow. First, men with non-classical, atypical or partial distal AZFb/AZFbc deletion patterns should not be counselled reflexively as having no chance of sperm retrieval; this message, however, must not be transposed onto patients with classical complete P5/proximal-P1 AZFb or complete AZFbc deletions, whose prognosis remains very poor. The probability of recovering such cells may be optimised by micro-TESE performed by an experienced surgeon, which outperforms conventional or random biopsy in focal spermatogenesis, together with wide sampling of dilated tubules [6, 14, 15]. The role of hormonal optimisation before surgical sperm retrieval in NOA remains uncertain. In our patient, clomiphene citrate was prescribed empirically for six months because of low-normal testosterone and preserved gonadotropin secretion, to increase endogenous testosterone before micro-TESE. As there was no evidence of hypogonadotropic hypogonadism, human chorionic gonadotropin/human menopausal gonadotropin (hCG/hMG) therapy was not selected. Follow-up FSH, LH, oestradiol, and testosterone levels were unavailable, preventing assessment of the endocrine response and representing a limitation of this case. Current evidence does not support routine hormonal therapy before sperm retrieval in NOA [16]. Second, diagnostic algorithms should be aligned with the 2023 EAA/EMQN recommendations and should incorporate the relevant AZFb/AZFbc extension markers (sY127, sY134, sY1192, sY116 and sY1224) so that classical complete, partial and atypical configurations can be distinguished as accurately as possible at the initial testing stage [1]. Third, genetic counselling is an indispensable component of the clinical pathway for men with AZFb/AZFbc deletions. Counselling must address the obligatory transmission of the Y-chromosomal deletion to all male offspring conceived with the patient's own spermatozoa, the absence of somatic phenotype in carrier males, and the uncertainty surrounding long-term fertility outcomes when precise breakpoint data are unavailable. In the present case, these points were discussed prior to the micro-TESE procedure, in accordance with EAA/EMQN recommendations [1]. Reproductive options presented to the couple comprised ICSI with autologous testicular spermatozoa with or without PGT for embryo sex selection, and the use of donor sperm; after full counselling the couple elected autologous ICSI without PGT. This case therefore reinforces the importance of comprehensive genetic characterisation (including the full EAA/EMQN extension marker panel) before initiating assisted reproduction in men with atypical deletion profiles, so that counselling on retrieval prognosis, transmission risk, and the relative merits of available reproductive strategies rests on the most accurate deletion map achievable.

TABLE 2. Published reports relevant to residual spermatogenesis in non-classical, atypical, or partial AZFb/AZFbc deletion patterns.

Report	Year	N	Deletion pattern (STS/breakpoint)	Semen/histology	TESE outcome	ICSI/pregnancy
Kleiman <i>et al.</i> [5] (systematic review 1994–2010 + 6 new cases)	2011	21	Pooled dataset comprising heterogeneous partial AZFb (n = 14) and partial AZFbc (n = 7) STS profiles, benchmarked against complete AZFb (n = 28) and complete AZFbc (n = 71) reference groups.	Across the aggregated cohort, semen and histology findings were heterogeneous and ranged from azoospermia and hypospermatogenesis to residual spermatogenesis and a Sertoli cell-only pattern.	Sperm-cell detection (testicular cytology/histology): partial AZFb 57% (8/14), partial AZFbc 43% (3/7), complete AZFb 7% (2/28), complete AZFbc 3% (2/71).	At the date of publication, neither chemical nor clinical pregnancies after ICSI had been documented in the complete AZFb or complete AZFbc subsets; outcome data for the partial-deletion subgroup were not consistently reported across the source cohorts.
Shi <i>et al.</i> [7]	2011	1	De novo partial AZFb deletion of approximately 5.25 Mb that spared the <i>RBMY</i> gene family, combined with a concurrent inherited duplication of about 2.4 Mb within Yp11.2; both breakpoints fell outside palindromic regions, arguing against a non-allelic homologous recombination mechanism.	Severe oligoasthenoteratozoospermia (sperm concentration $\sim 5 \times 10^6/\text{mL}$) with normal serum FSH, LH, testosterone and oestradiol and a 46,XY karyotype; testicular histology was not reported.	Not applicable; ejaculated spermatozoa were available.	Ejaculated sperm were used for ICSI, yielding two twin pregnancies.
Soares <i>et al.</i> [8]	2012	4	Three AZFb/AZFbc-related breakpoint configurations were identified: IR4/distal-P2 (n = 1), P5/proximal-P1 (n = 2) and P5/distal-P1/AZFbc (n = 1).	The clinical phenotype comprised severe oligozoospermia in two patients and non-obstructive azoospermia in the remaining two, the latter exhibiting Sertoli cell-only morphology at testicular biopsy.	TESE outcomes varied with the deletion subtype; in the azoospermic patients displaying Sertoli cell-only histology, no testicular spermatozoa adequate for autologous assisted reproduction were obtained.	Autologous pregnancy after ICSI was not achieved in the azoospermic Sertoli cell-only cases.
Stouffs <i>et al.</i> [9]	2017	2	Basic multiplex PCR initially suggested an AZFb deletion because the primary markers sY127 and sY134 were absent; subsequent extension analysis using additional EAA/EMQN markers revealed an aberrant, non-classical AZFb deletion pattern rather than a canonical complete P5/proximal-P1 AZFb deletion.	Residual ejaculated sperm production was demonstrated in both patients—an unexpected finding for classical complete AZFb; testicular histology was not reported.	Not applicable; ejaculated spermatozoa were available.	Ejaculated sperm were used for ICSI; an ongoing pregnancy was achieved in one of the two patients.

TABLE 2. Continued.

Report	Year	N	Deletion pattern (STS/breakpoint)	Semen/histology	TESE outcome	ICSI/pregnancy
Aoki <i>et al.</i> [10]	2025	1	Single-marker loss restricted to sY1024—a sequence-tagged site mapped within the proximal AZFb segment of the assay employed—while every remaining tested marker across AZFa, AZFb and AZFc was retained; 46,XY karyotype.	Cryptozoospermia in the setting of normal-volume testes and unremarkable testosterone and FSH values; histologically, individual seminiferous tubules contained spermatocytes and spermatozoa, with the Johnsen score varying between 4 and 8.	At micro-TESE, a number of immotile spermatozoa with marked morphological abnormalities were recovered and frozen for later use.	Cryopreserved-thawed testicular spermatozoa were thawed for ICSI; progression to a good-quality blastocyst was uncommon, and neither of the two subsequent frozen embryo transfers achieved conception.
Present case	2026	1	Proximal AZFb markers sY105 and sY121 retained; distal AZFb marker sY153 and the tested AZFc markers sY1191, sY1291, sY254 and sY255 absent. The profile is compatible with a distal AZFb/AZFc deletion and atypical AZFbc involvement; precise breakpoint assignment remains inferential because the full EAA/EMQN AZFb/AZFbc extension marker panel was unavailable.	Non-obstructive azoospermia on three serial semen analyses; histology showed a predominantly Sertoli cell-only pattern with focal tubules containing spermatocytes and early spermatids, consistent with mixed atrophy; mean Johnsen score 2.	Right-sided micro-TESE: a small number of motile testicular spermatozoa were retrieved and cryopreserved.	Following ICSI with thawed motile testicular spermatozoa, two frozen-thawed embryos were transferred, resulting in a male live birth. The infant carried the same AZF deletion and had dysmorphic features with high-risk trisomy-21 screening (karyotype pending).

The table draws together cases and series in which AZFb involvement diverged from the canonical complete P5/proximal-P1 AZFb deletion, encompassing partial AZFb deletions, atypical AZFb configurations and AZFbc deletions with variable proximal breakpoints. The 2011 work of Kleiman et al. [5] is treated as a systematic review of AZFb and AZFbc deletions reported up to 2010, while subsequent reports are tabulated separately. Data were extracted from the cited publications, with terminology aligned where feasible to the 2023 EAA/EMQN guideline. The present case represents distal AZFb/AZFc involvement suggestive of an atypical AZFbc configuration and, to our knowledge, one of the very few instances in which sperm retrieval has been followed by clinical pregnancy, with the caveat that exact breakpoint assignment remains inferential owing to the unavailability of the complete EAA/EMQN extension marker panel. AZF, azoospermia factor; EAA, European Academy of Andrology; EMQN, European Molecular Genetics Quality Network; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IR4, inverted repeat 4; LH, luteinising hormone; PCR, polymerase chain reaction; RBMY, RNA-binding motif protein, Y-linked; STS, sequence-tagged site; TESE, testicular sperm extraction.

The most important lesson in this case concerns the offspring. A live birth is not synonymous with a healthy live birth. The infant carried the same AZF deletion as his father, confirming the obligate vertical transmission that these men and their partners must understand before treatment [1, 17]; such sons are expected to face the same spermatogenic failure in adulthood. Beyond transmission of the deletion itself, these couples face additional genetic risk: AZFc-deleted Y chromosomes are mitotically unstable and can give rise to 45,X cell lines, so that offspring are at risk of sex-chromosome mosaicism and Turner syndrome [1, 17], and AZFc microdeletion has been associated with a higher rate of embryo aneuploidy [18]. In our patient's child, the dysmorphic features and high-risk screening raised a clinical suspicion of Down syndrome. Trisomy 21 is an autosomal aneuploidy and is not caused by the Y-chromosomal deletion; at a maternal age of 32 years, it is unlikely to reflect advanced maternal age and may be coincidental. Nonetheless, the case is a forceful reminder that PGT for aneuploidy—offered to, but declined by, this couple—together with prenatal diagnosis, is integral to the reproductive care of men with Y-chromosomal microdeletions, and that general reassurance from cohort data on ICSI offspring [19] does not eliminate individual risk. The principal limitation of this report is the incompleteness of the AZFb/AZFbc extension marker panel used; although the issuing laboratory classified the profile as partial AZFb deletion combined with complete AZFc deletion, the markers required for precise breakpoint mapping under the 2023 EAA/EMQN guideline (sY127, sY134, sY1192, sY116 and sY1224) were not assayed. Stored patient DNA was not available for supplementary testing, and paternal DNA was not available, so segregation analysis could not be performed. For this reason, we have characterised the lesion as a distal AZFb/AZFc deletion compatible with atypical AZFbc involvement rather than as a definitively mapped P4/distal-P1 deletion. A further limitation is the single-patient design of this report; selection and publication bias cannot be excluded, as cases with favourable outcomes are more likely to reach publication than those in which micro-TESE fails, and a single live birth does not permit reliable estimation of retrieval or pregnancy rates in this deletion class. In addition, the infant's confirmatory karyotype was pending at submission, no photomicrographs of the retrieved spermatozoa were obtained, and parental consanguinity (a fourth-degree relationship) was present and may contribute independently to genetic risk. The present findings therefore require corroboration in larger, prospectively recruited cohorts before any prognostic generalisation is justified. Future research priorities include the establishment of multicentre registries designed to capture micro-TESE outcomes stratified by STS marker profile in atypical and partial AZFb/AZFbc deletions, and the systematic adoption of high-resolution breakpoint-mapping techniques (such as whole-genome sequencing, chromosomal microarray, or optical genome mapping) that can delineate deletion boundaries with precision beyond the resolving power of multiplex PCR. Such approaches would enable formal testing of the hypothesis that preserved proximal AZFb gene content is the key determinant of residual spermatogenic potential in these atypical configurations.

4. Conclusions

Laboratory-reported partial AZFb with complete AZFc deletions may correspond to atypical AZFbc configurations that retain focal spermatogenesis, so that micro-TESE and ICSI can succeed and should not be withheld reflexively. Complete STS characterisation with the full EAA/EMQN 2023 extension panel is needed to separate these favourable profiles from classical complete deletions, whose prognosis remains very poor. Live birth is not necessarily a healthy one: Given the obligate transmission of the deletion to male offspring and the increased risk of aneuploidy in these couples, comprehensive genetic counselling, preimplantation genetic testing, and prenatal diagnosis remain essential components of care. Accordingly, management should be individualised through informed, non-directive counselling that includes a discussion of all appropriate reproductive options and their implications.

AVAILABILITY OF DATA AND MATERIALS

Owing to patient confidentiality obligations, the underlying clinical, laboratory and molecular genetic data have not been deposited in a public repository; access may be granted on reasonable request directed to the corresponding author, contingent upon the relevant institutional and ethical approvals.

AUTHOR CONTRIBUTIONS

CÖ—Conceptualization; methodology; investigation (surgical management and clinical care of the patient); writing—original draft preparation. GC—Conceptualization; investigation (surgical management); supervision; project administration. MHI—Formal analysis; literature search and preparation of the comparative table of published reports (Table 2). MKB—Visualization; preparation of the histopathological figure and its legend. BBT—Data curation; collection and verification of the clinical records and follow-up data. All authors writing, review and editing. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Because the present work constitutes an isolated, retrospective case description that relies entirely on data generated during routine clinical care, formal review by an institutional ethics committee was not required under our local policy, and exemption was confirmed accordingly. All clinical activities adhered to the ethical principles laid out in the Declaration of Helsinki.

The patient provided written informed consent for the publication of all the clinical, laboratory, genetic, operative, histopathological and reproductive details set out in this report.

Written parental consent was also obtained for the publication of the infant's clinical and genetic data.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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