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Unilateral polyorchidism with severe male infertility: a case report

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Abstract

Polyorchidism is an uncommon congenital condition often discovered incidentally, which may significantly impact male fertility. We present a case of a 34-year-old man with unilateral polyorchidism and associated severe asthenozoospermia and teratozoospermia. Despite normal hormonal levels and no detected genetic anomalies, the patient's sperm showed mitochondrial damage, and his fertility remained compromised after conservative management and assisted reproductive attempts. This case underscores the intricate relationship between polyorchidism and male infertility, highlighting the need for personalized management strategies and further research into its etiology and impact.

Keywords Polyorchidism, Male infertility, Asthenozoospermia, Teratozoospermia, Mitochondrial damage, Semen analysis

Introduction

Polyorchidism refers to a rare congenital condition characterized by the presence of more than two testes [1]. Specifically, the most frequent manifestation is triorchidism, with an analysis of 41 studies revealing a notable trend: the additional testis is predominantly situated on the left side [2]. Furthermore, although polyorchidism can manifest either unilaterally or bilaterally, cases of unilateral polyorchidism are more commonly reported [3]. The mechanisms and etiology of polyorchidism remain elusive. However, some researchers propose that factors such as incomplete degeneration of the mesonephros or aberrant division/duplication of the genital ridge before 8 weeks of gestation might explain testicular duplications, suggesting aberrations in embryonic development and gonadal differentiation [1, 4]. Polyorchidism often remains asymptomatic, typically detected incidentally during routine physical examinations, imaging studies, or surgical procedures [5]. In some instances, however, patients may exhibit symptoms like palpable supernumerary testes, inguinal or scrotal masses, or associated anomalies, including inguinal hernias, cryptorchidism, or testicular torsion [6].

Male infertility represents another potential complication of polyorchidism, although the precise incidence and relationship between polyorchidism and male infertility remain uncertain. While some studies suggest

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an association between polyorchidism and potentially impaired spermatogenesis or male infertility [7, 8], others report polyorchidism cases in patients with normal semen parameters [9–11].

In this report, we present a rare case of unilateral polyorchidism in a patient with severe asthenozoospermia and teratozoospermia, accompanied by mitochondrial damage in sperm. We discuss the challenges in managing this condition and the therapeutic complexities. This report aims to contribute to the understanding of polyorchidism's potential impact on male fertility and underscore the necessity for comprehensive evaluation and personalized management strategies in such cases.

Case presentation

A 34-year-old male presented to the Urology Department with a chief complaint of infertility for 12 months despite regular unprotected intercourse. He denied any history of diabetes, hypertension, or other chronic diseases, as well as sexual dysfunction or changes in libido.

Physical examination revealed a normal right testis, epididymis, and vas deferens. On the left side, two testes of unequal size were palpated within the scrotum, exhibiting a soft texture. One vas deferens was palpated on the left side, although the epididymis was not clearly palpable for both testes. Ultrasonography demonstrated a right testis measuring 4.0×1.6 cm, and two small testis-like echoes in the left scrotum, measuring 1.9×1.2 cm (upper) and 2.1×1.4 cm (lower), each with its own epididymis but sharing a common vas deferens and spermatic cord (Fig. 1). The lower small testis had an inhomogeneous echo with a low-intensity reticular echo of approximately 0.6×0.5 cm. Additionally, a left testicular hydrocele and bilateral varicocele were noted.

The hormonal profile showed normal levels of luteinizing hormone, follicle-stimulating hormone, prolactin, and estradiol. Testosterone level was 3.61 ng/ml

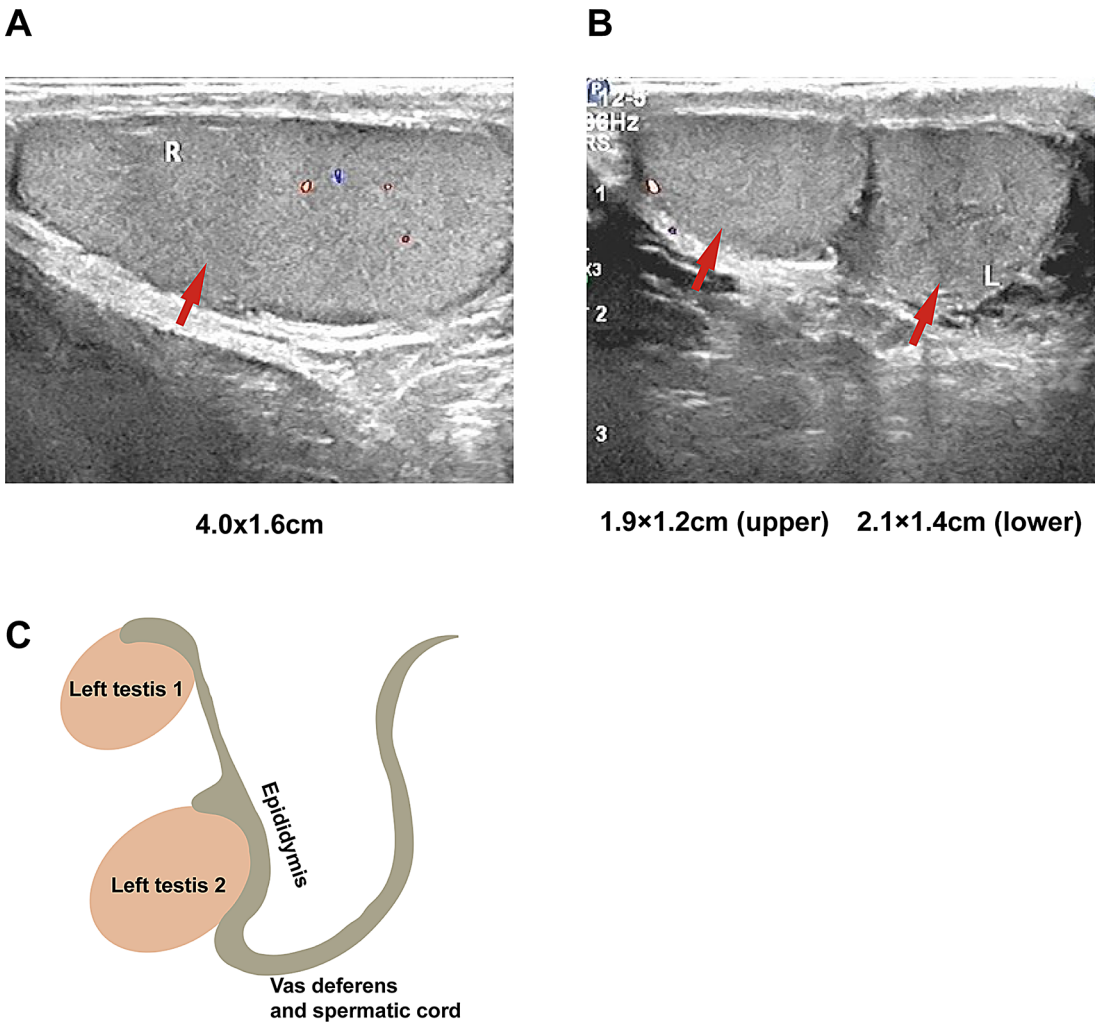

Fig. 1 Testicular color Doppler ultrasound images and schematic representation. **(A)** Right testicle. **(B)** Left testicle with two small testicles. **(C)** Schematic representation of the left spermatic path

(reference range: 2.8-8.0 ng/ml), which was within the normal range but on the lower end. Eugenics antibodies and anti-sperm antibodies were negative. However, semen analysis revealed impaired sperm parameters, including progressive motility of 0.69% (normal≥32%), sperm viability of 29% (normal≥59%), and normal morphology of 1.49% (normal≥4%). Moreover, transmission electron microscopy of the patient's sperm revealed decreased mitochondrial quantity, disorganized mitochondrial arrangement, and mitochondrial cristae expansion and swelling, which may contribute to the observed poor sperm motility (Fig. 2).

To further investigate the etiology of the two testes on the left side, genetic testing using NGS high-throughput sequencing on the Illumina platform was performed. The genetic testing did not detect any known pathogenic gene variations or Y chromosome AZF microdeletions directly related to the patient's clinical presentation (Fig. 3). The patient's karyotype was 46, XY, indicating no gross chromosomal abnormalities.

In addition to genetic testing, the patient underwent several other investigations. Eugenics antibodies and anti-sperm antibodies were both negative. Infectious disease screening, including hepatitis B, HIV, and syphilis, were all normal. Sperm DNA fragmentation testing revealed a high DNA fragmentation index (DFI) of 53.6%.

Management and outcome

Given the potential adverse impact of surgical removal of supernumerary testes on androgen production [12], conservative management was recommended for the patient. However, it is important to note that preserving the supernumerary testis may carry a risk of malignant transformation [13]. Careful monitoring and regular follow-up are essential in such cases. He underwent a year-long conservative treatment regimen that included 0.3 g of alpha-lipoic acid administered twice daily to reduce lipid oxidation in neural tissues, inhibit protein glycation, and suppress aldose reductase. Additionally, 10 ml (1 g) of levocarnitine was given twice daily to enhance lipid metabolism, and 25 mg of clomiphene citrate was prescribed once daily to facilitate competitive binding at estrogen receptors in the hypothalamus. These interventions aimed to improve sperm quality. Unfortunately,

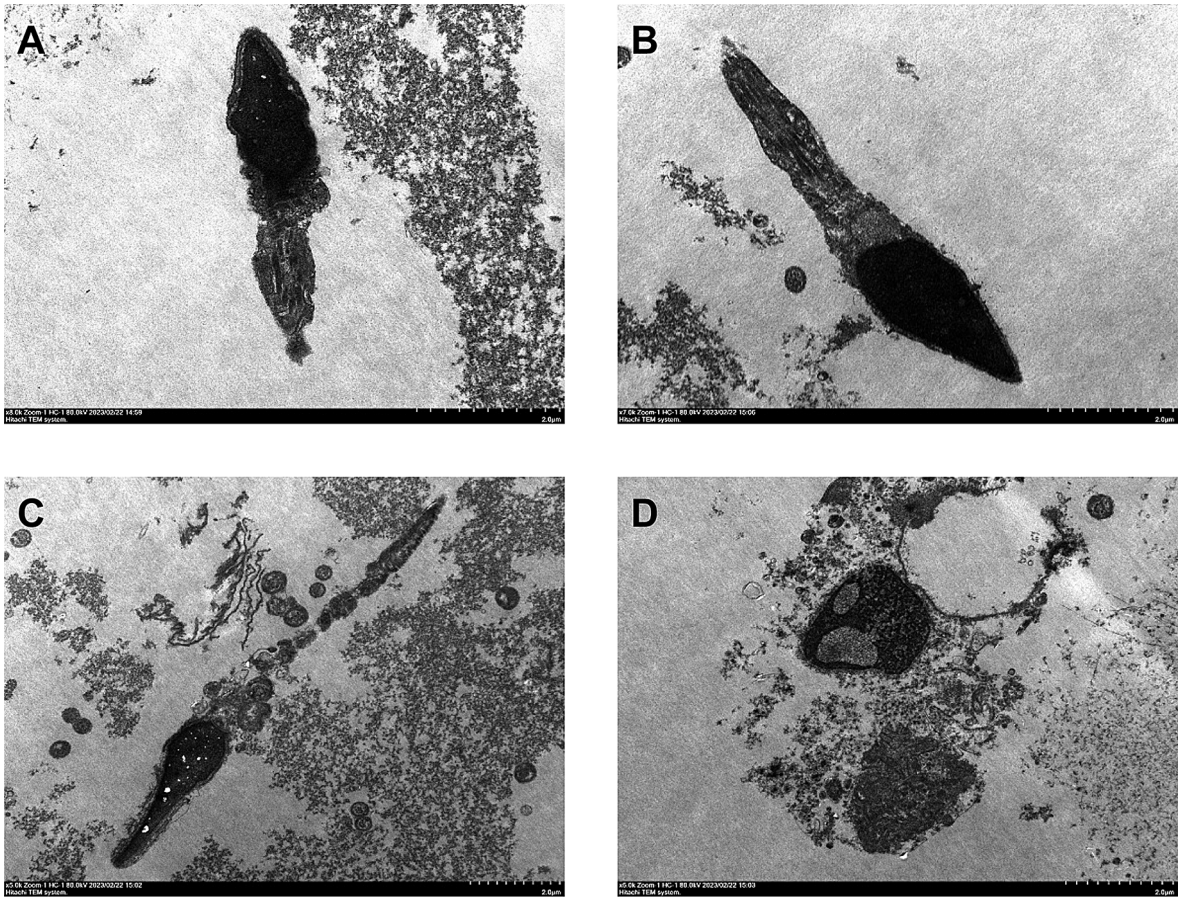

Fig. 2 Transmission electron microscopic observation of sperm ultrastructure. **(A)** Decreased mitochondrial number and disordered arrangement. **(B)** Dissolution of the acrosome; decreased mitochondrial number, disordered arrangement, swollen cristae of the mitochondria. **(C)** Decreased mitochondrial number. **(D)** Granular changes in the sperm nucleus with increased and enlarged nuclear pores

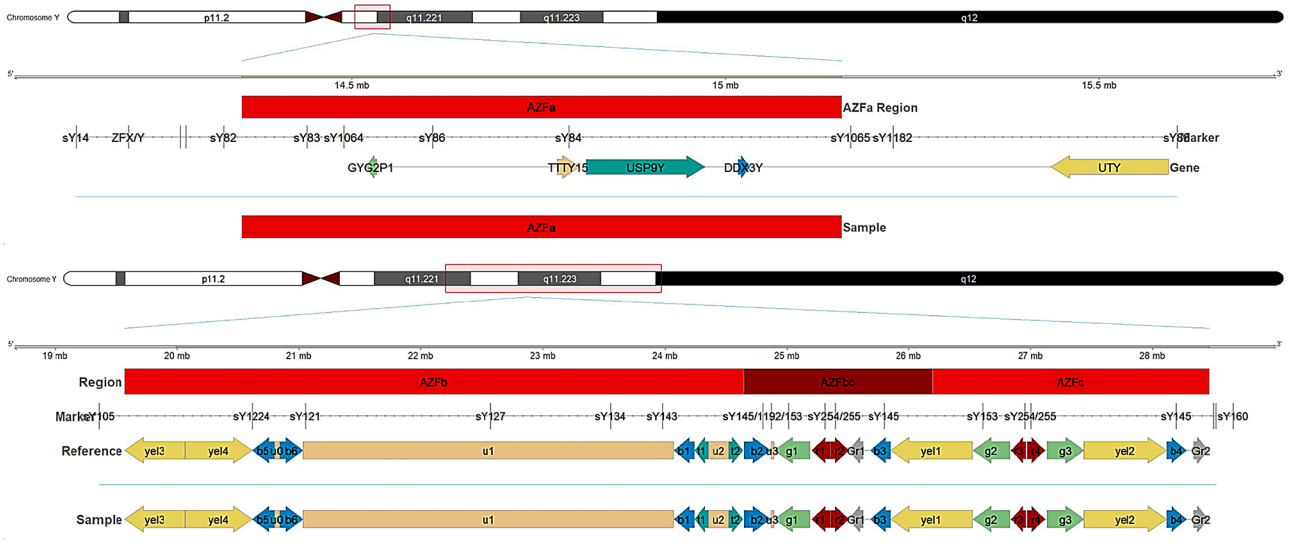

Fig. 3 Illustration of the AZF region on the Y chromosome of Patient Y

despite the comprehensive treatment, sperm motility did not significantly improve. Consequently, the patient opted for assisted reproductive technology (ART) in the form of intracytoplasmic sperm injection due to the severe asthenozoospermia and teratozoospermia. However, the ART attempts did not result in pregnancy due to poor embryo quality. The patient is now contemplating the possibility of continuing with ART, hoping for a successful outcome.

Discussion

The case presented herein highlights the potential association between polyorchidism and male infertility, specifically severe asthenozoospermia and teratozoospermia. Furthermore, transmission electron microscopy provided additional evidence of ultrastructural defects and mitochondrial damage within spermatozoa. Despite medical treatment and failed ART attempts, the lack of significant improvement underscores the challenges in managing polyorchidism with severely impaired spermatogenesis. Consequently, although polyorchidism is a rare condition, its potential impact on male fertility should not be overlooked, as evidenced by this case.

This intricate case thus sets the stage for a deeper investigation into the underlying causes and contributing factors of male infertility in the context of polyorchidism. The etiology of male infertility in patients with polyorchidism remains poorly understood, with various factors potentially contributing to impaired spermatogenesis or sperm quality. Although evidence definitively linking polyorchidism to specific sperm abnormalities has been limited, prior reports have documented associations between polyorchidism and impaired semen parameters, suggesting a predisposition to male infertility in some individuals [7, 8]. To this end, the complexity of factors involved underscores the necessity for extensive research to unravel the multifaceted relationship between polyorchidism and impaired semen parameters.

Among the myriad factors influencing male fertility, mitochondrial function emerges as a critical element. Mitochondria play an indispensable role in sperm motility, providing energy through oxidative phosphorylation [14]. Consequently, mitochondrial dysfunction or damage can lead to impaired sperm motility and additional sperm defects [15, 16]. In this specific case, the patient exhibited mitochondrial damage in sperm, potentially contributing to the observed severe asthenozoospermia. The mechanism underlying these mitochondrial abnormalities remains unclear but is speculated to relate to the potential impact of polyorchidism on the testicular microenvironment and spermatogenesis. This rare finding suggests a potential pathophysiological mechanism, indicating that the presence of additional testes may impair sperm motility through mitochondrial damage, energy depletion, or related apoptotic pathways [17–20]. However, it is important to note that the relationship between polyorchidism and mitochondrial dysfunction cannot be conclusively established based on a single case. Accordingly, further studies are imperative to elucidate whether mitochondrial dysfunction and impaired sperm motility represent common manifestations of polyorchidism.

In addition to mitochondrial damage, the patient's high sperm DFI of 53.6% is noteworthy. While the exact cause of the elevated DFI remains uncertain, the patient's bilateral varicocele may have contributed to the increased DNA fragmentation, as varicocele has been independently associated with higher DFI [21]. This finding

underscores the importance of considering concomitant factors, such as varicocele, when evaluating the impact of polyorchidism on male fertility.

Genetic factors also demand attention for their potential role in the development of polyorchidism and subsequent infertility challenges. While no known pathogenic gene variations or Y chromosome AZF microdeletions were identified in this case, other genetic abnormalities have been documented in polyorchidism patients. Notably, a study by Fiorella Shabtai et al. highlighted a case of a neonate with polyorchidism, revealing the novel discovery of ipsilateral intra-abdominal testes along with a chromosome 21 long arm deletion [22]. Furthermore, cases of polyorchidism associated with chromosomal syndromes [23], and several instances of disorders of sexual differentiation, specifically in individuals with karyotypes of 46,XX [24] and 46,XY DSD [25], have been documented. These findings indicate that genetic factors may contribute to the development of polyorchidism and associated reproductive abnormalities in certain patients.

Understanding the intricate interplay of mitochondrial and genetic factors in polyorchidism lays the groundwork for addressing the significant challenges inherent in its management, particularly in the realm of male infertility. The management of polyorchidism, particularly in the context of male infertility, presents significant challenges. The recommended approaches for managing symptomatic polyorchidism are still a subject of controversy. Some experts advocate for surgical interventions such as orchiopexy or orchiectomy for supernumerary testes with abnormal characteristics, to minimize risks such as torsion, malignancy, or infertility [26]. However, it is important to note that surgical removal can also entail risks, including testosterone deficiency, anti-sperm antibody formation, and ischemic atrophy of the remaining testicular tissue. It is crucial to consider the potential impact of polyorchidism on hormonal regulation and spermatogenesis feedback mechanisms. In this case, the patient's hormonal profiles were within normal ranges, and clomiphene therapy may not have been essential. Considering the patient's fertility aspirations, we recommended a trial of conservative medical therapy. Despite pursuing conservative management and ART, these interventions failed to significantly improve sperm motility, thus not achieving successful conception for this patient. In cases resistant to initial treatments, a more definitive surgical approach, involving the removal of abnormal testicular tissue, may become necessary to achieve pregnancy. Careful patient counseling and the management of expectations play a crucial role in the management of polyorchidism, particularly when semen parameters are profoundly impaired.

While repeated testosterone measurements would have provided a more comprehensive hormonal profile, the patient's decision to pursue assisted reproductive treatment precluded additional testing. Although polyorchidism has been associated with an increased risk of testicular cancer [1], the patient chose to prioritize assisted reproductive treatment. We will advise the patient to undergo oncological marker testing in the future. Reactive oxygen species measurement was not performed on the patient's semen. The lack of improvement with antioxidant therapy suggests that significant oxidative stress may not have been the primary cause of the patient's infertility.

This rare case of polyorchidism, characterized by severe asthenozoospermia, teratozoospermia, and mitochondrial damage in sperm, clearly illustrates the significant impact of this congenital anomaly on male fertility. This necessity for comprehensive evaluation and personalized management strategies in such cases is underscored, emphasizing a tailored approach to treatment. Consequently, further research is crucial to elucidate the mechanisms underlying polyorchidism and its impact on male fertility, and to develop targeted therapeutic strategies aimed at enhancing reproductive outcomes in affected individuals.

Conclusions

This case report highlights the rare yet significant link between polyorchidism and male infertility, characterized by severe asthenozoospermia and teratozoospermia with accompanying sperm mitochondrial damage. Despite comprehensive conservative treatment and the use of assisted reproductive technologies, the difficulties in improving sperm motility and achieving conception underscore the complexity of managing polyorchidism-associated infertility. The case emphasizes the need for detailed evaluation and personalized management strategies, while also pointing towards the importance of further research into the mechanisms of polyorchidism's impact on male fertility.

Abbreviations

ART Assisted reproductive technology

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Author contributions

FY and JYZ conceptualized the research study. YX, MJW, and SYP conducted the investigation. FY and DGC provided the necessary resources for the study. The original draft of the manuscript was written by JYZ and FY. The manuscript was reviewed and edited by XJY, JYZ, SXX, and XYT. The project was supervised by XJY and DGC.

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Data availability
The data and materials utilized in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Per the guidelines of our institution, no formal ethical approval or participant consent is necessary for a single case report if it contains no patient-identifying information. However, informed consent for the publication of this case report and associated images was obtained from the patient, and it can be requested from the corresponding author if needed. The methodologies employed in this study involving human participants align with the ethical norms of our institutional and national research committees and adhere to the principles outlined in the 1964 Helsinki Declaration, its subsequent amendments, or equivalent ethical standards.

Consent for publication
Written informed consent for publication was obtained from the patient.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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