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CASE REPORT

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Infertility case presentation in Zinner syndrome: Can a long-lasting seminal tract obstruction cause secretory testicular injury?

Gianmartin Cito[1] | Simone Sforza[1] | Luca Gemma[1] | Andrea Cocci[1] | Fabrizio Di Maida[1] | Sara Dabizzi[2] | Alessandro Natali[1] | Andrea Minervini[1] | Marco Carini[1] | Lorenzo Masieri[1]

[1]Department of Urology, Careggi Hospital, University of Florence, Florence, Italy

[2]Sexual Medicine and Andrology Unit, Department of Experimental and Clinical Biomedical Sciences, Careggi Hospital, University of Florence, Florence, Italy

Correspondence
Gianmartin Cito, Department of Urology, Careggi Hospital, University of Florence, Largo Brambilla, 3, 50134 Florence, Italy.
Email: gianmartin.cito@gmail.com

Abstract

Zinner syndrome (ZS) could represent an uncommon cause of male infertility, as result of the ejaculatory duct block, which typically leads to low seminal volume and azoospermia. A 27-year-old Caucasian man reported persistent events of scrotal-perineal pain and dysuria during the past 6 months. The andrological examination showed testicular volume of 10 ml bilaterally. Follicle-stimulating hormone was 32.0 IU/L, luteinising hormone was 16.3 IU/L, total testosterone was 9.0 nmol/L, and 17-beta-oestradiol was 0.12 nmol/L. The semen analysis revealed absolute azoospermia, semen volume of 0.6 ml and semen pH of 7.6. The abdominal contrast-enhanced computed tomography showed (a) left kidney agenesis; (b) an ovaliform hypodense mass of 65 × 46 millimetres with fluid content, which was shaping the bladder and the left paramedian prostatic region, compatible with a left seminal vesicle pseudocyst; and (c) an enlargement of the right seminal vesicle. The patient was diagnosed with ZS, and he was scheduled for robot-assisted laparoscopic left vesiculectomy. Subsequently, testis biopsy was characterised by complete germ cell aplasia. The onset symptomatology is often blurred and difficult to detect. It is important to diagnose and manage early this condition, because a long-lasting seminal tract obstruction could determine an irreversible secretory testicular injury.

KEYWORDS

azoospermia, infertility, Zinner syndrome

1 | INTRODUCTION

The seminal vesicle cysts can be classified as both acquired and congenital. The acquired cysts are generally associated with other developmental abnormalities regarding the genitourinary tract. Usually, they are unilateral and related to inflammatory processes or seminal vesicles/ejaculatory ducts obstruction, often resulting from a retrograde urinary infection. Moreover, it has been shown that there is a link between the acquired cysts and the benign prostatic hyperplasia, as well as with previous urological interventions and cancers. Otherwise, the cystic congenital lesions are almost always solitary (Patel, Gujral, Jefferson, Evans, & Persad, 2002).

The relationship between seminal vesicle cysts and ipsilateral renal agenesis was originally explained in 1914 by Zinner, who highlighted the connection of these lesions with other abnormalities, such as adult polycystic kidney disease, hemi-vertebra, male fertility

disorders, seminal tract alterations and ipsilateral testicular agenesis (Zinner, 1914). Nowadays, about 200 cases have been reported in literature (Pereira et al., 2009).

The defective development of the final tract of the mesonephric duct—also known as Wolffian duct—could determine the ejaculatory duct obstruction, causing a congenital cyst formation. The urological anomalies, such as renal dysplasia, hypoplasia or agenesis, do occur as a result of the failing differentiation of the metanephric blastemal at the beginning of the metanephrogenic diverticulum (Williams & Sandlow, 1998).

Usually, small seminal vesicle cysts appear without symptoms. Equally, greater cysts can have no symptoms and can infrequently be a casual detection on rectal examination, as a floating corpus between the bladder and rectum, and this way allowing a premature diagnosis (Slaoui et al., 2016).

Asymptomatic or mild cases are usually treated conservatively, although sometimes percutaneous drainage, trans-rectal or transurethral aspiration may be considered. In case of more severe symptomatic cases, an excision by laparoscopic or an open surgery of the cystic lesions may be necessary. Moreover, the fertility status should always be investigated in patients with Zinner syndrome (ZS), since it has been reported a relationship with infertility up to 45% of cases (Pereira et al., 2009). This can be considered as a consequence of the ejaculatory duct stenosis, which determines low seminal volume and azoospermia.

2 | CASE DESCRIPTION

2.1 | Case

A 27-year-old Caucasian man showed up to our Department of Urology reporting persistent events of scrotal-perineal discomfort and dysuria during the past 6 months. He did not have any reported history of trauma, haemospermia or haematuria. In his past medical history, cryptorchidism or delayed pubertal development was excluded. The patient did not report any previous surgery nor ongoing pathologies. The physical andrological examination revealed testicular volume of about 10 ml bilaterally, estimated with the Prader testicle orchidometer. No sign of varicocele was found bilaterally. On digital rectal examination, a cystic palpable swelling above the prostate mostly on the left side was appreciated. Some serum blood samples were taken from the patient in order to determine the endocrinal and oncological assessment. Follicle-stimulating hormone was 32.0 IU/L, luteinising hormone (LH) was 16.3 IU/L, total testosterone was 9.0 nmol/L, and 17-beta-oestradiol was 0.12 nmol/L. Tumour marker dosage, including alpha-fetoprotein (α-FP), beta-human chorionic gonadotropin (β-HCG) and lactate dehydrogenase (LDH), was reported to be in the normal range (Table 1). Further reasons of primary hypogonadism were excluded through a genetic assessment, including karyotype, analysis of microdeletions for Y chromosome and mutations of cystic fibrosis transmembrane conductance regulator (CFTR) genes, resulting in no abnormalities. Both urine and semen culture were performed to rule out the presence of infections, showing no alterations. Semen analysis, repeated at least in two different occasions, showed an absolute azoospermia, even after centrifugation step at high speed, in accordance with the 2010 World Health Organization (WHO) guidelines (Figure 1). The semen volume was 0.6 ml and the semen pH 7.6.

2.2 | Diagnostic assessment

The transabdominal ultrasounds (US) revealed the absence of left kidney, replaced by a hypertrophic vicariant right kidney, and the presence of ipsilateral anechogenic formation, with a tick wall, of approximately 67 × 35 mm at the distal end of the left ureter. The diagnostic investigation followed with the execution of abdominal contrast-enhanced CT scan, which confirmed (a) left kidney agenesis; (b) ovaliform hypodense mass of 65 × 46 mm with fluid content, that shapes the bladder and the left paramedian prostatic region, compatible with a left seminal vesicle (SV) pseudocyst; and (c) enlargement of the right seminal vesicle (Figure 2). Thus, the patient was diagnosed for ZS.

TABLE 1 Baseline serum parameters

Parameter	Value	Normal range
FSH (IU/L)	32.0	1.7–8.0
LH (IU/L)	16.3	0.6–7.0
TT (nmol/L)	9.0	10.4–34.6
E2 (nmol/L)	0.12	<0.20
AFP	1.1	0.0–5.8
B-hCG (IU/L)	<1	<1
LDH (IU/L)	186.0	84.0–246.0

Abbreviations: AFP, alpha-fetoprotein; B-hCG, beta-human chorionic gonadotropin; E2, oestradiol; FSH, follicle-stimulating hormone; LDH, lactic acid dehydrogenase; LH, luteinising hormone; TT, total testosterone.

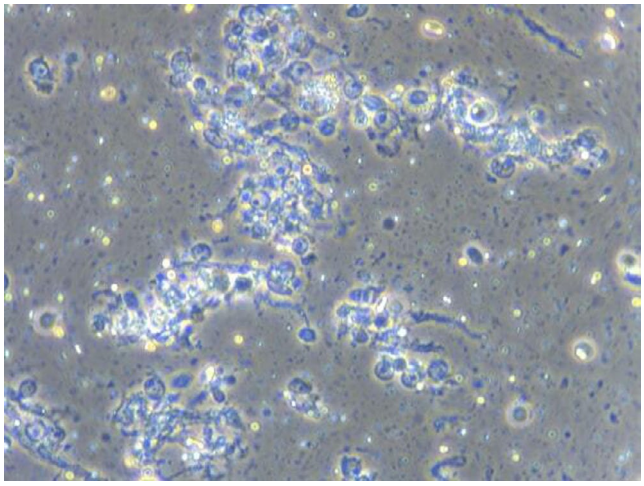

FIGURE 1 Semen analysis showed the absence of mature spermatozoa, consistent with absolute azoospermia

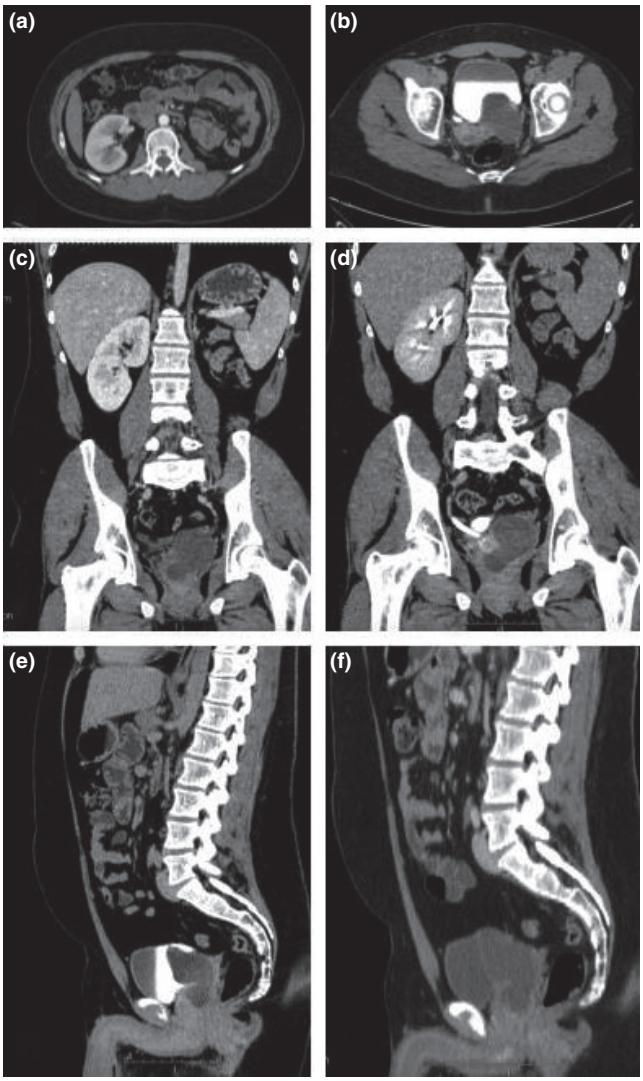

FIGURE 2 Abdominal contrast-enhanced CT: (a) left kidney agenesis; (b) left seminal vesicle that compress bladder and enlargement of the right seminal vesicle; (c, d) coronal CT scans showed ovalar hypodense mass of 65 × 46 millimetres with fluid content, that shapes the bladder and the left paramedian prostatic region, compatible with a left seminal vesicle pseudocyst; (e, f) sagittal CT images confirmed the left seminal vesicle pseudocyst and ipsilateral kidney agenesis

2.3 | Management

A robot-assisted laparoscopic left vesiculectomy (RALV) was planned. Under general anaesthesia, a 4-arm trans-peritoneal technique, with a 0° lens, was performed. After a transversal incision of the peritoneum, a large cyst of the left seminal vesicle, strongly adherent to the bladder and the prostate, was found. The retrovesical region was prudently sectioned using monopolar scissors and, if needed, a bipolar Maryland dissector, until the left seminal vesicle had been entirely liberated from the contiguous tissues (Figures 3 and 4). A bladder injury of about 1 cm, promptly repaired, occurred. The piece was then blocked out through the camera port using a retrieval bag and sent for the histological examination. A precise haemostasis was obtained, and both a tube drain and a urinary catheter were inserted. The total surgery time was 133 min, the console time was 108 min, and the estimated blood loss was 150 ml. No intraoperative complications were recorded. The urinary catheter was removed on the fifth postoperative day (POD), and the patient was discharged on the sixth POD with blood tests in the normal range. At sixth months' follow-up visit, the patient had no symptoms and no disorders of continence and potency. Six months after the surgery, the semen analysis confirmed absolute azoospermia. The patient was advised to undertake testicular sperm extraction (TESE), in order to retrieve and cryopreserve spermatozoa for possible assisted reproductive technologies (ART) purpose in future.

The histopathological examination showed a 5.5 × 1.4 × 1.5-cm left seminal vesicle, with nonspecific wall inflammation. The analysis of biological testicular specimens by TESE detected fibrosis and complete germ cell aplasia (SCOS).

3 | DISCUSSION

Zinner syndrome is a rare and uncommon disorder, which is due to Wolffian duct abnormalities (Van den Ouden, Blom, Bangma, &

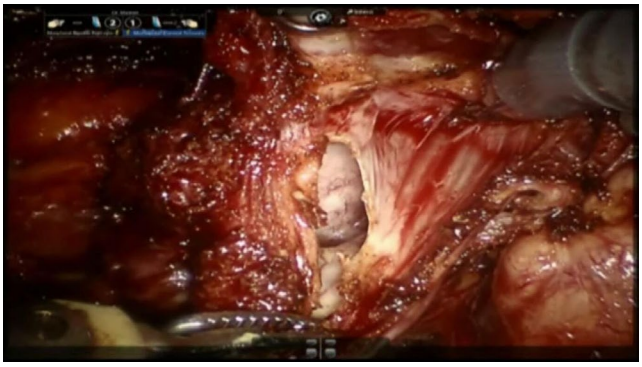

FIGURE 3 Operative image of robot-assisted laparoscopic left vesiculectomy (RALV): the retrovesical region was prudently sectioned using monopolar scissors and, if needed, a bipolar Maryland dissector, until the left seminal vesicle had been entirely liberated from the contiguous tissues

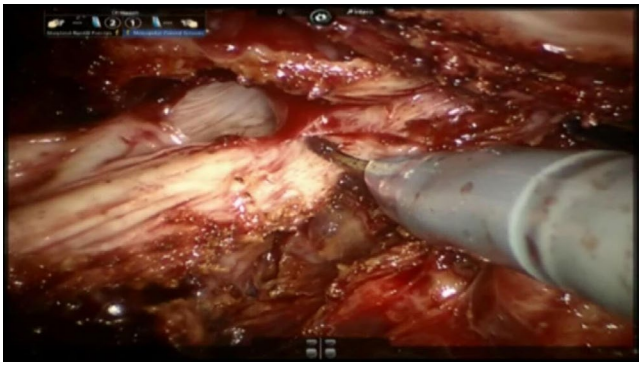

FIGURE 4 The left seminal vesicle had been entirely liberated from the contiguous tissues

Spiegeleer, 1998). This disorder consists of a typical triad of seminal vesical cyst, ipsilateral renal agenesis and male infertility. A feasible embryologic reason for this urologic anomaly is that the anomalous distal mesonephric duct development resulted in faulty ureteral bud fusion with metanephros, as well as atresic ejaculatory ducts and unusual dilatation (Patel et al., 2002).

Different diagnostic methods can be performed in order to detect seminal tract anomalies; trans-rectal ultrasonography (TRUS) or abdominal ultrasounds are the first steps; computed tomography (CT) and magnetic resonance (MR) represent the second lines, very helpful to distinguish cystic lesions from other pelvic formations and to study the pelvis (Pace, Galatioto, Gualà, Ranieri, & Vicentini, 2008).

Symptoms classically raised in the age of highest sexual and reproductive activity, due to the accumulation of seminal fluid in seminal vesicles. The clinical presentation focused predominantly on pain, with the location varying from abdomen, flank, pelvis, scrotum and perineum. Additionally, urinary frequency, dysuria and urgency, as well as inflammation processes, including repeated urinary infections, epididymitis or chronic prostatitis are also likely to happen. Moreover, semen abnormalities until the occurrence of absolute azoospermia may coexist (Pereira et al., 2009).

Nevertheless, since this syndrome has broad-spectrum symptoms, a delayed diagnosis of male infertility could occur. Unfortunately, the few cases of ZS described in literature do not address the fertility issue. Therefore, our attention is focused on the male reproductive health, as this is the first case in which there is reported a clinical presentation of secretory azoospermia.

Indeed, in all cases of ZS described in literature, obstructive azoospermia (OA) was presented. Aghaways I. and Ahmed SM. explained a single case of ZS suffering from OA, who underwent transurethral resection of the ejaculatory duct (TURED). After the surgery, the semen analysis showed a normal sperm count and an acceptable progressive motility, leading to a natural successful pregnancy (Ismaeel & Shyaw, 2016). Equally, other authors have reported a semen quality improvement in 38%–60% of men, with a paternity rate of 22%–31% after TURED (Popken, Wetterauer, Schultze-Seemann, Deckart, & Sommerkamp, 1998; Turek, Magana, & Lipshultz, 1996). In our report, the surgical treatment was directed to solve the urological symptoms, since RALV did not change the seminal panel.

In this scenario, the reason why azoospermia occurs is due to the ejaculatory duct obstruction (EDO), more often diagnosed with TRUS. EDO may be due to congenital abnormalities, genitourinary infections, prior pelvic surgery, indwelling catheters, urethral trauma and prostate diseases (Jarow, 1993). In some cases, Müllerian duct cysts or Wolffian duct anomalies were described as the major cause of EDO by previous authors (Pryor & Hendry, 1991). Partial ejaculatory duct obstruction is a recently noticed entity that is suspected in oligoasthenospermic men with low to normal ejaculate volume and evidence of obstruction on TRUS. Currently, the criteria for EDO on TRUS are seminal vesicle dilatation with a width of more than 1.5 cm, dilated ejaculatory ducts (lumen visible), calcification or calculi inside ejaculatory ducts or verumontanum, Müllerian or Wolffian duct cysts near verumontanum (Jarow, 1993).

Nevertheless, in our case, after the surgical correction of the seminal tract obstruction, the semen analysis at six-month follow-up visit confirmed azoospermia. This probably occurs because other factors play a key role in the pathogenesis of this disorder.

Indeed, even though in most of the cases of OA, the spermatogenesis is preserved, a sperm secretory impairment may be recorded in a variable percentage of patients. It is widely demonstrated that this occurs as a result of the long-lasting obstruction causing injury to the spermatogenic tubules. In fact, the quality of spermatozoa may be changed because the distal epididymis contains high quantities of sperm fragments with macrophages (Schlegel et al., 1994). The number of macrophages gradually reduces towards the proximal epididymis and testis, while the number of motile spermatozoa gradually rises (Schlegel, 2004). Moreover, the overexpression of reactive oxygen species (ROS) in patients with ZS could mediate the reproductive toxicity. In fact, the detrimental effects of ROS on semen quality have been widely demonstrated, due to several reasons (Sharma & Agarwal, 1996). Firstly, the sperm membrane has high levels of polyunsaturated fatty acids, which are extremely vulnerable to peroxidation, leading to a reduction in fertilising ability, motility and viability. Secondly, compared to other cells, spermatozoa are less able to repair damaged structures as a result of their small quantity of cytoplasm and an inactive, highly condensed chromatin. Finally, spermatozoa have a poor defence system against ROS, as catalase is fully absent, and glutathione peroxidase and superoxide dismutase are present in relatively low amounts. Nevertheless, further studies are needed to deepen this topic, in order to evaluate if ROS may actually accelerate the process of germ cell apoptosis, leading to sperm counts decline.

Furthermore, there is evidence that recurrent urinary tract infections or inflammatory processes in the semen may contribute to the problem, due to the high numbers of activated T lymphocytes producing cytokines (Trofimenko & Hotaling, 2016). All these factors could result in damage of male reproductive health, leading to secretory azoospermia. However, it is unknown whether the spermatogenic injury and subsequent reduced sperm production are sustained and how the balance between obstruction and sperm production is supported over the long term. Currently, there are no available data about how much time should pass so that an obstructive azoospermia can generate a secretory testicular damage. This is usually due to the lack of a seminal routine examination before the diagnosis of ZS. However, considering the patients who undergo a vasectomy, it has been estimated that the damage may be strict one month after surgery (Gupta, Kothari, Dhruva, & Bapna, 1975) and a 20%–40% reduction in the numbers of spermatids may exist at 1–20 years (Raleigh, O'Donnell, Southwick, Kretser, & McLachlan, 2004).

In this setting, it would be of interest to establish how to predict the presence of an irreversible azoospermia and how to perform an early diagnosis of ZS.

Indeed, as showed by previous authors, in patients with EDO, focal hypospermatogenesis or incomplete maturation arrest may coexist (Meacham, Hellerstein, & Lipshultz, 1993).

For that reason, it is crucial to perform testis biopsy in order to show the presence of mature spermatids and spermatozoa in the seminiferous tubules (Schlegel et al., 1994).

However, some predictors of sperm retrieval (SR) can be used in the clinical practice.

At the baseline visit, our patient showed bilateral size testis below the normal range and serum FSH value considerably higher, suggestive of damaged spermatogenesis. Unfortunately, we were not able to assess testicular volume before the diagnosis of ZS, in order to establish for sure whether the long-lasting obstruction could have generated a testicular hypotrophy over time. However, to support our theory, increased FSH value was found, although all the more likely causes of primary hypogonadism were excluded.

Several studies agreed on considering FSH dosage as a predictive factor of spermatogenesis in patients addressed to ART, supporting that high levels of FSH and small testicular volume were significantly related to lower chances of SR (Cito et al., 2018). Moreover, although a smaller testicular volume is associated with the worse possibility of SR, there is no minimum range of size that predicts the presence of spermatozoa (Tsujimura et al., 2004). For all these reasons, our patient was advised to perform TESE, although in the presence of poor predictors of positive sperm recovery. However, unfortunately, we were not able to measure some biomarkers in the blood or in the seminal plasma, predictors of impaired spermatogenesis (Zhuang et al., 2015).

Furthermore, in order to diagnose this syndrome as soon as possible, some assessments should be made. Firstly, prenatal testing with ultrasound scans of the urinary tract could detect renal agenesis and therefore possible embryonic disorders that involve the development of the seminal tracts. Secondly, the andrological prevention with the evaluation of young males in fertile age could be crucial in highlighting any problems inherent to the reproductive health.

4 | CONCLUSION

Zinner syndrome could represent an uncommon cause of male infertility. The onset symptomatology is often blurred and difficult to detect. It is important to diagnose and manage early this condition, since a long-lasting seminal tract obstruction could determine an irreversible secretory testicular damage.

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ORCID

Gianmartin Cito https://orcid.org/0000-0001-7526-4025
Simone Sforza https://orcid.org/0000-0001-8613-3995
Andrea Cocci https://orcid.org/0000-0003-0138-6294
Fabrizio Di Maida https://orcid.org/0000-0003-1885-4808
Alessandro Natali https://orcid.org/0000-0003-4456-7626
Andrea Minervini https://orcid.org/0000-0002-1994-1324
Marco Carini https://orcid.org/0000-0002-2288-3647
Lorenzo Masieri https://orcid.org/0000-0002-2020-3150

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