Non-Obstructive Azoospermia with Hypergonadotropic Hypogonadism

Raditya Ibrahim1*, Cennikon Pakpahan1,2, Pety Narulita1,3

1Andrology Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
2Department of Biomedical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
3Andrology Clinic, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Abstract

Around 10% of infertile men and 1% of all males have azoospermia. There are two types of azoospermia which are obstructive and non-obstructive azoospermia. Non-obstructive azoospermia’s main mechanism is because the testes fail to produce the sex hormone and induce spermatogenesis. A patient is 28 years old and has a job as a car paint worker. He came with the chief complaint of infertility two and a half years ago. His wife’s medical history is unremarkable. Physical examination and ultrasound of the testes are normal. The semen analysis in this patient was azoospermia for two different times in 2 weeks with no abnormalities in the accessory gland. Hormonal profiles results are testosterone level 2.32 ng/mL and FSH 15.03 mIU/mL. The patient was suggested to evaluate further (complete hormonal profile, karyotyping analysis, and Y-Chromosome microdeletion) and educate about the possibility to conceive with assisted reproductive technology. Hypergonadotropic hypogonadism is a challenging case that needs a complete assessment such as a full hormonal profile, karyotyping analysis, Y-chromosome microdeletion analysis, and also, in this case, the paint thinner exposure in the workplace is needed to be considered. The chance of normal conception is very small, and an assisted reproductive procedure is necessary for better reproductive healthcare. Some abnormalities are usually present in the physical examination of azoospermia patients. This case convinces us of the importance of thorough history taking and other investigations. Managing this patient will be challenging, with the goal of the therapy being to achieve spermatogenesis to use the spermatozoa available for ICSI.
1. Introduction

Infertility is defined as an inability to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility affects approximately 15% of couples, estimated around 50 million globally. Male infertility contributes to about 20-30% of all infertile couples. Around 10-15% of infertile men and 1 percent of all males have azoospermia. There are two types of azoospermia which are obstructive and non-obstructive azoospermia. Non-Obstructive Azoospermia (NOA) constitutes around 10% of all azoospermia patients. Non-obstructive azoospermia's main mechanism is because the testes fail to produce the sex hormone and induce spermatogenesis (primary testicular failure). Patients with primary testicular failure (PTF) chances of natural conception are very small. Almost all of them have to undergo assisted reproductive technique (ART). This method has an aggregate opportunity of 25% of live birth and sperm retrieval by testicular sperm extraction (TESE) with a percentage chance of 50% in NOA and the following use of these spermatozoa in one or more intra-cytoplasmic sperm injection (ICSI) treatments results in a live birth rate of 50%. There are many challenges in working on NOA case, including defining the etiology of the cause because it's important for fertility prognosis, and the treatment (pharmacological and ART treatment consideration). The following is a case that we have in the Andrology Department of Dr. Soetomomo.

2. Case

A 28-year-old man came to our hospital for treatment of infertility. His wife was 28 years old also. He was referred by the chief complaint of wanting to have a child two and a half years ago. The patient has undergone a previous semen analysis workup on January 11th, 2022. He has worked in a car paint workshop and has been exposed to inhaling thinner in the last five years and never wore appropriate personal protective equipment, i.e., a mask until the beginning of the COVID-19 pandemic. He got to work by motorcycle every day with the distance between his home and his workplace about 25 kilometers. He denied any complaints of headache, visual disturbances (double or blurred vision), anosmia, or hyposmia. The patient has a normal libido, has sexual intercourse 3 to 4 times a week (with IELT of approximately 10 minutes and post-coital reflux is present), and denies any complaints of pain during intercourse. The patient reached puberty at 14 years old and has never had pre-marital intercourse. He denied any previous medical conditions. The patient has a sister and his sister is married with two children while the wife is an only child. The patient denies any psychological problems in the workplace or in the family. He has been a smoker since first grade in high school with 3 to 4 cigarettes per day and denied any history of drug or alcohol abuse.

The patient has normal vital signs, an athletic body stature (BMI 20.3 kg/m² and waist circumference of 80 cm), a normal visual field and an unremarkable smell test. The virilization was also in a normal range (normal hair distribution and already has a voice break). External genitalia examination showed a normal penile size (with a stretched penile length of 10 cm and penile circumference of 9 cm), a normal position of the urethral orifice, and no urethral discharge. There were no inguinal anomalies such as hernia, hydrocele, or dermatitis. The patient has a relatively small testicular volume (12 ml in each testis) with a normal testicular consistency and no testicular pain when we palpate the testis. Epididymal examination showed normal size, thickness, surface, and no epididymal pain on palpation. Vas deferens and spermatic cord palpation were unremarkable. The patient did not have varicocele when examined with palpation (and Valsalva maneuver) and with an additional test, ultrasound of the testis. (Figure 1.).

**Figure 1. Testes Ultrasound Result Shows No Abnormalities Present.**

The patient has undergone two semen analyses, and both analyses gave similar results which are azoospermia (Table 1.). The second semen analysis showed that the volume of the semen was lacking (1.1 mL), and the patient had told us that he felt uncomfortable when he collected the semen in the sample room. We assessed the accessory gland for additional testing (quantitative value for fructose and α-glucosidase) to look for any obstruction in the reproductive tract. We concluded that there is no obstruction present in the reproductive tract. After that, we ordered hormonal profiles to conclude the working diagnosis in this patient. However, because of the patient’s financial situation, we can only order two hormonal profiles which are FSH and testosterone. Two days later, the patient returned with the lab results showing...
that FSH is high (15.03 mIU/mL) and relatively low testosterone (2.31 ng/mL).

We concluded the working diagnosis of the patient as primary male infertility with azoospermia and hypergonadotropic hypogonadism. We educated the patient on the lab results and his two semen analyses. We educate the patient on how we’re going to approach the treatment. Firstly, we need to add one extra hormonal profile which is Estradiol (E$_2$) to view the testosterone/estradiol ratio for consideration in aromatase inhibitor treatment. Secondly, we approach this patient to prepare for a possible ART (educate the patient about the cost, the preparation before, and the percentage of succession in this therapy). Additionally, the patient is educated also about genetic testing, in this case, chromosomal analysis, and Y-Chromosome microdeletion to look for sperm retrieval rate percentage.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>January 11$^{th}$, 2022</th>
<th>January 25$^{th}$, 2022</th>
<th>Reference Value (WHO 2021 5$^{th}$ Percentile) $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual abstinence</td>
<td>4 days</td>
<td>3 days</td>
<td>2-7 days</td>
</tr>
<tr>
<td>Sample completion</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>Smell</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Semen color</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Semen Viscosity</td>
<td>2 cm</td>
<td>1 cm</td>
<td>&lt; 2 cm</td>
</tr>
<tr>
<td>Liquefaction</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>&lt; 60 minutes</td>
</tr>
<tr>
<td>pH</td>
<td>No data</td>
<td>8.0</td>
<td>7.2 – 8.0</td>
</tr>
<tr>
<td>Semen Volume</td>
<td>2.6 mL</td>
<td>1.1 mL</td>
<td>&gt; 1.4 mL</td>
</tr>
<tr>
<td>Concentration</td>
<td>0/mL</td>
<td>0/mL</td>
<td>≥ 16 millions/mL</td>
</tr>
<tr>
<td>Total Sperm Count</td>
<td>0</td>
<td>0</td>
<td>≥ 39 millions/mL</td>
</tr>
<tr>
<td>Progressive Motility</td>
<td>-</td>
<td>-</td>
<td>≥ 30 %</td>
</tr>
<tr>
<td>Non-Progressive</td>
<td>-</td>
<td>-</td>
<td>1 %</td>
</tr>
<tr>
<td>Motility</td>
<td>-</td>
<td>-</td>
<td>20 %</td>
</tr>
<tr>
<td>Immotile</td>
<td>-</td>
<td>-</td>
<td>≥ 4 %</td>
</tr>
<tr>
<td>Morphology</td>
<td>-</td>
<td>-</td>
<td>20 %</td>
</tr>
<tr>
<td>Fructose</td>
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<td>23</td>
<td>&gt;13 µmol/ejaculate</td>
</tr>
<tr>
<td>Alpha Glucosidase</td>
<td>No data</td>
<td>80</td>
<td>&gt;50 MU/ejaculate</td>
</tr>
</tbody>
</table>

3. Discussion

In this case, the couple has tried to have an offspring for two and a half years (without ever conceiving or experiencing abortion). He and his wife were regularly having intercourse (3 to 4 times a week) with the wife’s medical record is unremarkable, which falls under the diagnosis of primary male infertility. One of our main suspects of etiology is the job of the patient, who is a car paint shop worker without wearing a mask (he only wears a mask when the pandemic begins). He was exposed to the paint thinner solution, which consists of benzene, toluene, and xylene. Xiao et.al. explained that benzene, toluene, and xylene appear in the blood and semen, suggesting that these solvents permeate the blood-testis barrier. But the effects of thinner exposure are known as endocrine disruptors, which result in disorder in the hypothalamus-pituitary-gonadal axis. This mechanism did not match with this patient who showed the mechanism of testicular failure. After that, the patient was a light smoker when calculated with Brinkman index (<200), denied any history of other medical conditions, such as previous infection in the testes, any complaints of visual disturbances, headache, galactorrhea that leads to possible disorder in the Hypothalamus-Pituitary Gonadal Axis, metabolic profile disorder, and testicular trauma. General physical examination showed that the patient has no abnormalities present.

The testis volume is an important indicator for possible spermatogenesis activity. If the testis is small, it means the testes’ spermatogenesis is inactive. In patients with NOA, the testes are typically less than 15 cc with flat epididymis. In this case, the patient’s testes volume is relatively low.

Azoospermia is defined as the complete absence of sperm in the ejaculate in this patient. This diagnosis must be confirmed by centrifugation of a semen specimen for 15 minutes at room
temperature with a high-powered microscopic examination of the pellet and a centrifugation speed of at least 3,000 G and at least two semen samples obtained more than two weeks apart in the same lab. The semen analyses showed that in the two examinations, the patient volume was normal in the first analysis. The second was low, but because of the environmental factor (the patient did not feel comfortable in the semen collecting room), that parameter showed that the patient did not have an obstructive tendency, because if we suspect the patient of obstructive azoosperma, the seminal volume is usually low. To rule out obstructive azoosperma, we examined the patient’s accessory gland functions with additional semen analyses which resulted in normal value.

The fertility prognosis in NOA is poor in most patients because spermatogenesis is generally stopped. Pharmacotherapy’s aim in the case of azoospermia is to regulate the hormonal imbalance and rejuvenate the spermatogenesis process. The main drugs used in azoospermia are Selective Estrogen Receptor Modulator (SERM), Aromatase Inhibitors (AI) if the T/E2 ratio is lower than 10, hCG, and Recombinant FSH. For example, the SERM drug clomiphene citrate function blocks the negative feedback in the hypothalamus and anterior pituitary resulting in increased FSH and LH to improve spermatogenesis and testosterone production. Aromatase inhibitor (AI) mechanism inhibits aromatase enzyme which blocks the conversion of testosterone to estradiol. The optimal dose of AI’s drug to stimulate spermatogenesis remains unknown. Additional basic and clinical studies are needed to establish the dose and timing of aromatase inhibitor medication. However, in NOA patients without any abnormalities in history and general examination, we need to look for Y-Chromosome microdeletion because it can predict Sperm Retrieval Rate (SRR) in this patient. Selman et al reported that in a patient with microdeletion of the DAZ, BPY2, and CDY1 in the AZF region, with the therapy of the recombinant FSH and hCG, and after that ICSI was performed and successful pregnancy was achieved. Hence, the only possible way for the couple to achieve pregnancy without a donor is to retrieve spermatozoa directly from the testes for ICSI. There are a couple of procedures to recover the sperm, such as Testicular Sperm Extraction (TESE) and Fine Needle Aspiration (FNA). In patients with NOA, micro-TESE (57%) has a higher Sperm Retrieval Rate (SRR) than the conventional technique (32%). Vahidi et al. conducted research with 130 men who underwent Micro-TESE – ICSI cycle with results of successful fertilization, biochemical pregnancy, and live birth were seen in 111 (85,4%), 29 (22,3%), 29 (22,3%), and 14 men (10,75%), respectively.

4. Conclusion
This case is interesting because with azoospermia, some abnormalities are usually present in the physical examination and on additional testing (testes ultrason and accessory gland obstruction analysis). When diagnosed with this kind of case, it is important to assess the suspected factors thoroughly such as complete hormonal profile, karyotyping and Y-Chromosome microdeletion, and thinner exposure in the sperm if able. Managing this patient will be challenging, with the goal of the therapy being to achieve spermatogenesis to use the spermatozoa available for ICSI.

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Authors’ Contributions
All authors have contributed to the final manuscript. The contribution of each author as follow: collected the data, drafted the manuscript and designed the figures, devised the main conceptual ideas and critical revision of the article. All authors discussed the results and contributed to the final manuscript.

Conflict Of Interest
The authors state there is no conflict of interest.

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1. WHO. International Classification of Diseases, 11th Revision (ICD-11).