

# Semen uric acid crystals in azoospermia linked to Sertoli cell-only syndrome: A rare case report

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**Abstract.** The occurrence of crystals in semen is rare, with spermine phosphate crystals being the only type commonly described. Uric acid crystal formation is significantly influenced by pH levels. The present study reported a rare case of uric acid crystals in the semen of a patient with azoospermia associated with Sertoli cell-only syndrome (SCOS). A 28-year-old male with a four-year history of primary infertility underwent clinical assessment, including a normal physical examination with small testes. Seminal fluid analysis revealed abnormal uric acid crystals. Elevated follicle-stimulating hormone, luteinizing hormone and prolactin levels were observed. The diagnosis of SCOS was confirmed through testicular sperm aspiration. Azoospermia is a medical condition characterized by the absence of sperm in the semen, specifically the absence of sperm in the pellet obtained after centrifugation. It is classified into two primary types: Obstructive and non-obstructive azoospermia. Non-obstructive azoospermia is subdivided into three categories: SCOS, hypospermatogenesis and maturation arrest. The occurrence of SCOS in azoospermic males ranges from 26.3 to 57.8%. The diagnosis of azoospermia with SCOS can be achieved through the analysis of multiple semen samples, medical history, physical examination, hormonal analysis, histopathological examination and genetic testing. The presence of uric acid crystals in seminal fluid was first reported in patients with chronic prostatitis symptoms in 2005.

Despite the rarity of crystals in semen, uric acid crystals were found in the semen of an azoospermic male with SCOS.

## Introduction

Infertility has been recognized as a significant public health concern in recent decades, affecting ~15% of couples attempting to attain pregnancy (1). Approximately half of these infertility cases are attributed to factors related to males (2). Among all cases of male infertility, ~10-15% of men are diagnosed with azoospermia, a condition defined by the absence of sperm in the semen, or more precisely, the lack of sperm in the pellet following centrifugation (3,4).

Azoospermia is typically classified into two main types: Obstructive azoospermia (OA) and non-obstructive azoospermia (NOA), with the majority of cases being NOA (4). This differentiation is important in a medical setting, as it influences treatment strategies and their success rates (5). NOA is further categorized into Sertoli cell-only syndrome (SCOS) and maturation arrest (MA) (6). The prevalence of SCOS in individuals with azoospermia ranges from 26.3 to 57.8% (1). SCOS is characterized by the complete absence of germ cells in seminiferous tubules, accompanied by normal secondary sexual characteristics and reduced testicular size (7). This disorder manifests in two forms: Focal SCOS and complete SCOS (2). Focal SCOS shows some normal areas of sperm production in the testis. By contrast, complete SCOS is marked by gonocytes that fail to migrate properly to the embryonic gonads, leading to the absence of germinal epithelium formation (2).

The occurrence of crystals in semen is rare, with documented instances limited to spermine phosphate crystals (8). Due to the rarity and pH-dependence of uric acid crystals in semen, this study aims to report a case of uric acid crystal presence in semen of a patient with azoospermia associated with SCOS.

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## Case report

**Patient information.** In October 2023, a 28-year-old male with a four-year history of primary infertility visited the Smart Health Tower in Sulaymaniyah, Iraq, and sought assistance for his fertility issues. Gynecologists had conducted multiple examinations of the patient's wife and determined that no noticeable female fertility issues were present.

**Clinical findings.** During the physical examination, there were no signs of gynecomastia and the patient exhibited normal secondary sexual characteristics. While the penile size and shape were normal, both testes were relatively small for the patient's age. However, there was no palpable mass or significant varicocele detected.

**Diagnostic approach.** The patient provided a single specimen, which underwent repeated seminal fluid analyses to ensure accuracy of the results. Both analyses revealed azoospermia with abnormal uric acid crystals through microscopic examination. The identification of uric acid crystals relied on microscopic examination, revealing characteristic needle-like shapes and strong negative birefringence under polarized light, which are specific markers for distinguishing uric acid crystals from the crystals of other compounds, such as phosphate crystals (9). A thorough microscopic analysis was conducted, with polarized light microscopy being leveraged to differentiate uric acid crystals from other potential crystalline compounds. In the examination, phosphate crystals were specifically ruled out, as they typically appear as prismatic or rosette-shaped structures and exhibit different birefringence characteristics. Positive birefringence is usually shown by phosphate crystals, in contrast to the negative birefringence of uric acid crystals (9). In addition, the possibility of oxalate crystals was considered, which often present as envelope-shaped crystals with a different pattern of birefringence (10). By systematically comparing the morphological features and birefringence properties under polarized light, the presence of uric acid crystals was confirmed, effectively excluding other crystalline forms such as phosphate and oxalate crystals (11) (Fig. 1). The pH of the seminal fluid was 7.9 (normal value, pH  $\geq 7.2$ ) and the volume was 5.5 ml (normal volume,  $>1.5$  ml/ejaculation), both within normal ranges. Scrotal Doppler ultrasound (U/S) indicated normal positioning and texture of both testes, while they were relatively small in size (Fig. 2). The right testis measured 9 ml, while the left testis measured  $\sim 8$  ml. These measurements are below the average testicular size range, which typically ranges from 15 to 25 ml in adult males (12). Furthermore, the U/S revealed no focal lesion, hydrocele or apparent inguinal hernia. Hormonal assays showed elevated levels of follicle-stimulating hormone (FSH) (normal range, 1.5–12.4), luteinizing hormone (LH) (normal range, 1.7–8.6), and prolactin (normal range, 4.04–15.2) with 12.7, 16.6 mIU/ml and 35.1 ng/ml, respectively (Table I). Genetic analysis showed no evidence of Y-chromosome microdeletion (Table II).

**Histological examination and findings.** Under local anesthesia, both right and left testicular aspirations were performed for the extraction of sperm, which retrieved a small tissue sample, ranging from 5 to 10 mg per each testicle. The specimen

was fixed for 1–3 days in 10% neutral buffered formalin at room temperature and then processed using the DiaPath Donatello automated processor (Diapath S.P.A). This process involved holding the specimen in formalin (average 20 min) and deionized water (10 min), and dehydrating it in alcohol with increasing concentrations of 70% (1 h), 95% (1 h) and 99% (two stages of 1 h 30 min each). Clearing was achieved through three stages of xylene (1 h each), followed by infiltration with paraffin wax in three stages (1 h each). The blocks were embedded in paraffin wax using the Sakura Tissue-Tek embedding center (Sakura Finetec), faced and sectioned using the Sakura Accu-Cut SRM microtome. Sections were floated in a 40–50°C water bath and placed on glass slides, which were then oven-dried at 60–70°C overnight.

The following day, the slides were stained using the DiaPath Giotto autostainer (Diapath S.P.A). The staining process included stages of xylene (three stages of 7, 7 and 5 min), alcohol (100% in three stages of 7, 6 and 5 min, followed by 90% for 4 min and 70% for 3 min) and tap water (2 min). Hematoxylin Gill II staining was applied for 8 min, followed by washing with tap water (4 min), ammonia water (1 min) and another tap water wash (1 min). This was followed by 70% alcohol (2 min) and Eosin Y staining (5 min), with a final wash in tap water (1 min). The slides were then dehydrated in alcohol (70% for 15 sec, 90% for 2 min and 100% in three stages of 3, 3, and 4 min) and cleared in xylene (three stages of 3, 5 and 4 min). After drying for 5 min, the slides were mounted with SurgiPath Sub-X medium (Surgipath Medical Industries, Inc.) and covered with a coverslip. The histological examination of both right and left testicular sperm extraction (TESA) confirmed SCOS, with no evidence of granulomas or malignancies. Histological findings included a reduction in the diameter of the testicular tubules, thickened basement membranes and the presence of Sertoli cells aligned perpendicularly to the basement membrane. These Sertoli cells exhibited nuclear indentations with prominent nucleoli. In addition, no germ cells were observed (data not shown).

**Follow-up and outcome.** The patient's postoperative period was uneventful and he has been undergoing routine follow-up assessments, scheduled monthly, to monitor the patient's fertility status.

## Discussion

NOA is identified by impaired spermatogenesis, which can be caused by a variety of endogenous or exogenous abnormalities. Histological examination of the testicular biopsy is employed to categorize NOA into three groups: SCOS, hypospermatogenesis and MA. Del Castillo was the first to describe SCOS in 1947. It is characterized by the total absence of germ cells in seminiferous tubules, accompanied by reduced testicular size and normal secondary sexual features. The condition presents in two forms: Focal SCOS and complete SCOS (2). Focal SCOS is defined by the presence of residual areas of normal spermatogenesis in the testis. By contrast, complete SCOS is identified by gonocyte failure to migrate to the embryonic gonads, leading to the subsequent absence of germinal epithelium formation (7). The current case was a 28-year-old

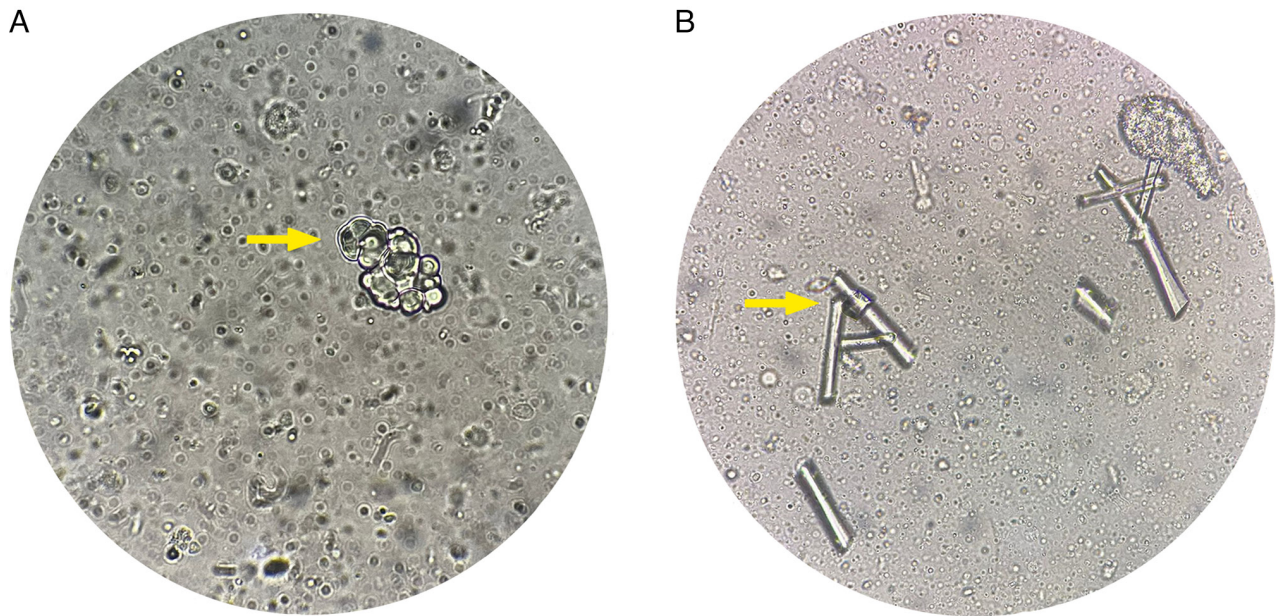


Figure 1. (A) Microscopy view of the patient's semen sample showing uric acid crystal aggregates. (B) Microscopy view of the same sample showing individual uric acid crystals (magnification, x100).

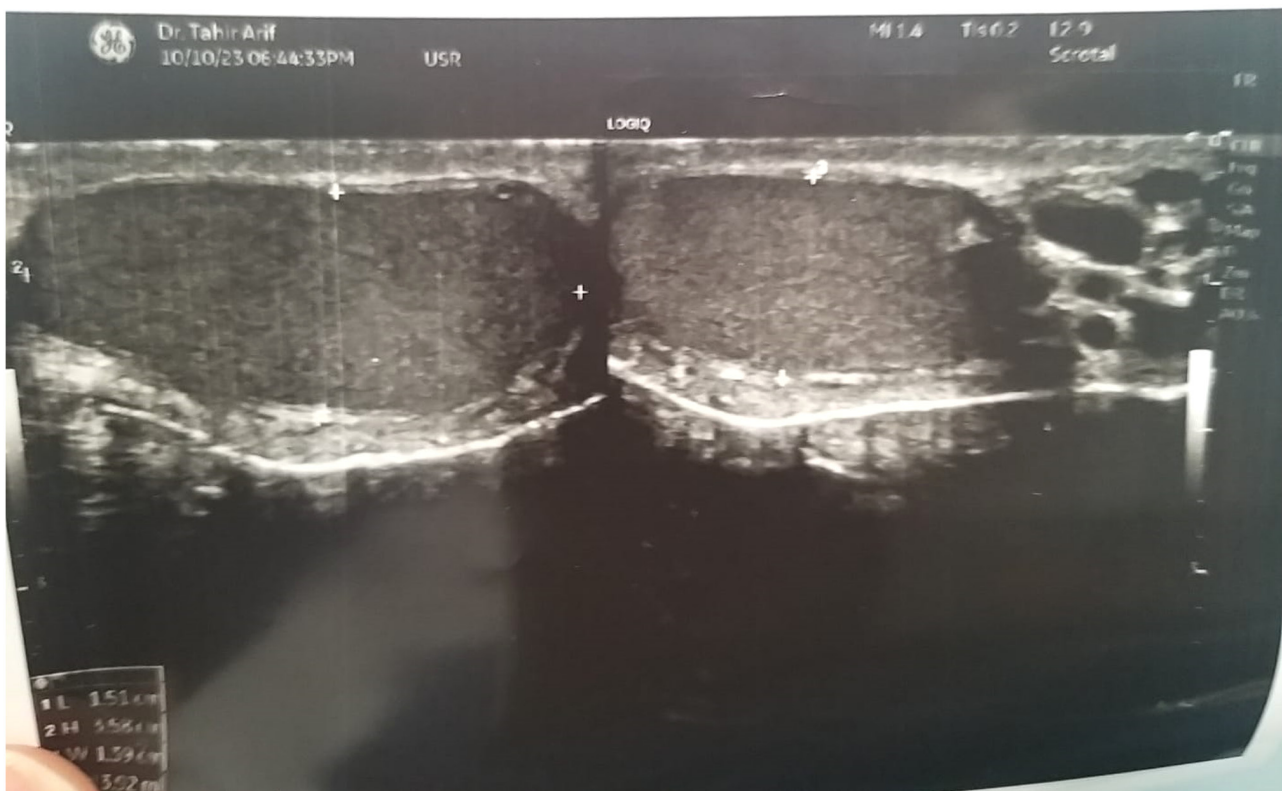


Figure 2. Scrotal Doppler ultrasound including two panels. The left panel depicts the findings of the left testis, which shows normal position and texture, albeit relatively small in size. The right panel corresponds to the right testis, also demonstrating a normal position and texture with a relatively small size.

male with a primary infertility history of ~4 years and normal secondary sexual features.

It has been observed that SCOS in infertile males can result from diverse factors, including Y chromosome microdeletions, cytotoxic drugs, undescended testis, radiation exposure and viral infections (2). The Y chromosome microdeletion is the

most significant pathogenetic defect associated with male infertility (13). According to a study by Stouffs *et al* (14) on the role of genetic investigation among azoospermic patients with SCOS, it is evident that karyotype abnormalities, particularly Klinefelter syndrome, are the most prevalent in azoospermic men with SCOS. A study reported the case of a patient with azoospermia

Table I. Laboratory evaluation: Semen fluid analysis, hormonal profiling for fertility assessment.

A, Semen fluid analysis		
Parameter	Result	WHO reference limit
Volume, ml	5.5	>1.5/ejaculation
Color	Milky white	Whitish, grey, opalescent
Viscosity	Normal	Normal
pH	7.9	Basic $\geq 7.2$
Concentration, million/ml	Azoospermia	>15
Total sperm count, million/ejaculate	Azoospermia	>39

B, Hormonal profile of testicular sperm aspiration		
Parameter	Result	WHO reference limit (for male)
FSH, mIU/ml	12.7	1.5-12.4
LH, mIU/ml	16.6	1.7-8.6
Prolactin, ng/ml	35.1	4.04-15.2
Testosterone, nmol/l	2.59	7.57-31.4

WHO, World Health Organization; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table II. Genetic analysis through reverse transcription-PCR for fertility assessment.

Chromosome	Target gene	Result
Y/STS Locus	AZF $\alpha$	Normal
3p24	DAZL	Normal
15q25	POLG	Normal
PARs	SHOX gene	Normal

Y/STS, Y chromosome associated with steroid sulfatase; AZF $\alpha$ , azoospermia factor  $\alpha$ ; DAZL, deleted in azoospermia-like; POLG, DNA polymerase gamma subunit; SHOX, short-stature homeobox gene; PARs, pseudo autosomal regions.

linked to SCOS and Leydig tumors. Unlike previous studies, the patient had normal secondary sexual features and no indication of Klinefelter syndrome. The right testis was found to be larger than the left one, which was a unique finding (1). In contrast to the studies mentioned, the current study involves a patient with both testes relatively small for their age. In addition, genetic analysis showed normal Y chromosome microdeletion and elevated FSH, LH and prolactin.

The diagnosis of azoospermia after confirmation through the analysis of multiple semen samples can be achieved through clinical differentiation between NOA and OA by evaluating diagnostic factors such as physical examination, medical history and hormonal analysis. These factors offer a prediction accuracy of >90% in determining the type of azoospermia (5). A definitive diagnosis of NOA subtypes is made through testicular biopsy and histopathological examination of the

specimens (2). Patients diagnosed with NOA are often recommended to undergo genetic testing, including cytogenetic karyotyping and molecular diagnostic techniques, such as subtyping of Y chromosome microdeletions, in accordance with guidelines from the American Society for Reproductive Medicine (ASRM) (15) and the European Association of Urology (EAU) (16). Despite the normal karyotype observed in the majority of men with SCOS, genetic factors like Klinefelter syndrome, Y chromosome microdeletions and other genetic determinants can still be relevant (2). In the current case, two seminal fluid analyses showed azoospermia with an abnormal uric acid crystal through microscopic examination. To identify uric acid crystals in the semen sample, thorough microscopic analysis was conducted, leveraging polarized light microscopy to differentiate uric acid crystals from other potential crystalline compounds. Uric acid crystals exhibit distinctive needle-like shapes and demonstrate strong negative birefringence under polarized light, which is a hallmark feature. In this examination, specifically phosphate crystals were ruled out, which typically appear as prismatic or rosette-shaped structures and exhibit different birefringence characteristics. Phosphate crystals usually show positive birefringence, in contrast to the negative birefringence of uric acid crystals. In addition, the possibility of oxalate crystals was considered, which often present as envelope-shaped crystals with a different pattern of birefringence. By systematically comparing the morphological features and birefringence properties under polarized light, the presence of uric acid crystals was confirmed. Scrotal Doppler U/S showed that both testes had a normal position and texture, but they were relatively small, while histopathological examination of both right and left testicular TESA revealed Sertoli cell-only syndrome, with no granuloma or malignancy detected.



The management of SCOS remains uncertain, with no effective treatments for achieving biological parenthood (2). Patients with exceedingly low sperm counts or no sperm in their semen may still be eligible for assisted reproductive techniques. Microsurgical extraction of sperm directly from the testes, even a minimal quantity, can be used for intracytoplasmic sperm injection (17). The current case involved a patient who had a sperm count of zero. Furthermore, not a single sperm could be obtained for fertilization using intracytoplasmic sperm injection.

Regarding the presence of crystals in semen, it is rare and the literature mostly describes crystals composed of spermine phosphate (8,18). The crystallization of uric acid is typically associated with acidic environments where uric acid has reduced solubility. Our observation of uric acid crystals in seminal fluid with a slightly alkaline pH of 7.9 presents a paradox, as uric acid crystals are usually expected to form in more acidic conditions. Several factors may contribute to this atypical finding: Localized pH variations within the fluid could have been more acidic despite the overall alkaline measurement, specific substances or compounds in the seminal fluid may have influenced uric acid solubility and individual physiological or pathological factors could affect crystallization patterns (19). Motrich *et al* (8) first reported uric acid crystals in the seminal fluid of a patient with chronic prostatitis symptoms in 2005. The current case report documented uric acid crystals in the semen of a male patient with azoospermia and SCOS. The patient's semen had a normal volume and pH. While recent studies indicate that factors such as dietary habits and genetic predispositions significantly influence the occurrence of uric acid crystallization in the urinary tract (20), their appearance in semen is relatively rare and may suggest specific reproductive health concerns. However, this case is significant, as it represents the first documented instance of uric acid crystals in the semen of an azoospermic male with SCOS in the genuine literature (21).

The current case report faced a limitation as there were no histopathological examination slides available for both the right and left testicular TESA. Another limitation is that while uric acid crystals were identified based on microscopic and chemical analysis, the potential presence of impurities or composite crystals cannot be definitively excluded without additional spectroscopic techniques.

In conclusion, despite uric acid crystals being strictly dependent on pH levels, only spermine crystals composed of phosphate have been previously reported in semen. The current study documented a case of uric acid crystal presence in the semen of an azoospermic male with SCOS.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

AKHR and RQS were major contributors to the conception of the study, as well as to the literature search for related studies. SSF, AMM and FHK were involved in the literature review, study design and writing the manuscript. HMM, NHAA and GMS were involved in the literature review, the design of the study, the critical revision of the manuscript and the processing of the figures. FHK and SSF confirm the authenticity of all the raw data. AAM and BOM were the radiologists who performed the assessment of the case. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

In our locality, ethical approval is not required for case studies involving fewer than three cases. Written informed consent was obtained from the patient for participation in the present study and related investigations, including genetic analysis.

## Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report and any accompanying images.

## Competing interests

The authors declare that they have no competing interests.

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