Acute anejaculation, hypogonadism, and fertility preservation in the setting of neurosarcoidosis: case report and literature review

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Objective: To examine fertility preservation techniques in the setting of neurosarcoidosis, and to review the impact of corticosteroid and methotrexate therapy on fertility.

Design: Case report of a patient with infertility secondary to anejaculation associated with spinal neurosarcoidosis, treated with systemic corticosteroids and methotrexate.

Setting: Academic tertiary-care hospital.

Patient(s): A 39-year-old man presented with neurosarcoidosis complicated by acute anejaculation, erectile dysfunction, and hypogonadism. He underwent fertility consultation and sperm cryopreservation before initiating methotrexate therapy. His pretreatment total testosterone was low, at 157 ng/dL.

Intervention(s): Unsuccessful pharmacologic therapy and penile vibratory stimulation (PVS) were followed by microdissection testicular sperm extraction (microTESE). Clomiphene was administered for optimization of spermatogenesis before microTESE.

Main Outcome Measure(s): Vials of cryopreserved sperm, testis histopathology, and serum testosterone levels.

Result(s): Eight vials of viable sperm were harvested by means of micro-TESE and cryopreserved. Despite intraoperative appearance of hypospermatogenesis, 90% of seminiferous tubules had active germ cell sloughing. Total testosterone increased to 278 ng/dL 2 months after initiating clomiphene.

Conclusion(s): Conventional fertility preservation techniques may be effective in the setting of neurosarcoidosis-induced infertility owing to largely intact spermatogenesis. PVS, though not effective for this patient, should be considered along with electroejaculation, given high success rates in other patients with neurogenic anejaculation. Corticosteroid-mediated hypogonadism also must be considered in these patients, because it can negatively affect downstream spermatogenesis. In addition, evidence for the impact of paternal methotrexate exposure on fertility is limited and requires further investigation. As such, fertility consultation before initiating methotrexate is highly recommended.

Key Words: Anejaculation, fertility preservation, sarcoidosis, erectile dysfunction, methotrexate

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Sarcoidosis is a rare granulomatous disease of unknown etiology, with a prevalence of 1–40 cases per 100,000 individuals (1). Neurologic involvement in the setting of sarcoidosis is rare, with spinal involvement estimated to be present in <1% of cases (2). To our knowledge, the present case is the first reported case of anejaculation associated with neurosarcoidosis. In discussing this patient’s clinical course, this case highlights many areas of current unknowns in the management of fertility. We hypothesize that conventional fertility preservation strategies would be effective in patients with spinal neurosarcoidosis, based on evidence in patients with neurogenic anejaculation secondary to spinal cord injury (SCI). Corticosteroids and methotrexate, medical therapies commonly used to manage sarcoidosis, have also been suggested to potentially adversely affect male fertility, thus posing additional urologic considerations in patients with neurosarcoidosis who are seeking...
fertility consultation. We conducted a literature review to better understand and characterize this evidence to provide a framework for approaching these patients clinically.

**MATERIALS AND METHODS**

A retrospective chart review was performed to obtain the patient’s clinical history and treatment course. To conduct the literature review, an extensive search was performed through PubMed and Google Scholar by a single investigator (B.Y.).

For the literature review on fertility, sexual function, and corticosteroid therapy, search terms included “corticosteroid therapy,” “prednisone,” “prednisolone,” “dexamethasone,” “hypogonadism,” “testosterone,” “spermatogenesis,” “semen,” “erectile dysfunction,” and “fertility,” used in various combinations. All relevant articles with primary evidence were considered for inclusion. Articles were excluded if they did not examine long-term corticosteroid therapy as a primary exposure for a nonfertility inflammatory, rheumatologic, or dermatologic disease or if they did not report measured T levels. Articles without an available English translation also were excluded.

For the literature review on fertility and methotrexate, the search strategy combined “methotrexate” and one of the following: “infertility,” “pregnancy,” “semen analysis,” “sperm analysis,” “sperm,” “oligospermia,” “azospermia,” and “fertility.” All relevant articles with primary evidence were considered for inclusion. Given the availability of more robust data for methotrexate and pregnancy outcomes, only observational studies were included for that particular analysis. Regarding methotrexate and semen parameters, case reports, case series, and observational studies were included. Articles without an available English translation, and articles with only evidence on methotrexate use in female partners (38 years old, regular menses). He had no history of cryptorchidism, scrotal trauma, or spermatotoxic exposure. The patient had not received any formal urologic evaluation before his neurosarcoioidosis diagnosis, and as such, he did not have a formal baseline assessment of his erectile, ejaculatory, or orgasmic function. However, he did not report any previous difficulty with erectile, ejaculatory, or orgasmic function or any previous use of pharmacologic therapy for ED. At his initial urologic evaluation following his neurosarcoioidosis diagnosis, he reported increased difficulty with sustaining erections, as well as new anorgasmia and anejaculation compared with his baseline.

Physical examination revealed a well appearing, well virilized man. Genitourinary examination was notable for bilaterally descended testes, each measuring 24 mL according to orchidometer and without palpable masses. A small, subcentimeter right epididymal head cyst was detected. Bilaterally descended testes were palpable, and there were no varicoceles. Laboratory studies were notable for morning total T 185 ng/dL (immunoassay; normal 300–1000 ng/dL), FSH 7.6 mIU/mL (normal 1.3–7.6 mIU/mL), LH 4.1 mIU/mL (normal 1.2–9.0 mIU/mL), E2 15 pg/mL (normal ≤32 pg/mL), and PRL 7.4 ng/mL (normal 2.6–13.1 ng/mL). Repeat morning total T was 157 ng/dL, and the patient was started on 25 mg/d clomiphene citrate for treatment of hypogonadism.

He was prescribed 100 mg sildenafil citrate for initial management of his sexual dysfunction, and he was sent for semen analysis. While his erectile function did improve with pharmacologic therapy, he had persistent anorgasmia and anejaculation. He attempted penile vibratory stimulation (PVS) on multiple occasions, but he remained unable to achieve orgasm or ejaculation.

Given his inability to provide a semen specimen for analysis and cryopreservation, the patient was offered additional treatment with either electroejaculation (EEJ) or surgical sperm retrieval. The patient elected to proceed with surgical sperm retrieval, particularly given the elevated FSH suggestive of compromised sperm production. Owing to urgent need for methotrexate in the setting of slowly progressive neurologic symptoms, the patient underwent sperm retrieval just 2 weeks after initiating clomiphene citrate.

Left hemiscrotal exploration was undertaken, revealing a normal–appearing testis and nondilated epididymis. An equatorial mid-pole testicular incision was made, and microTESE was performed with the use of the operating microscope. On initial inspection, the seminiferous tubules had a normal, dilated appearance. There was no intratesticular scarring or masses. Intraoperative microscopic evaluation revealed nonmotile sperm with normal morphology in each high-
powered field, but a global picture of hypospermatogenesis. A biopsy was sent for histopathologic analysis, and multiple samples of testicular tissue were extracted for cryopreservation. Testis histopathology demonstrated active spermatogenesis with germ cell sloughing in 90% of tubules and hyalinization of the remaining 10% with no evidence of testicular granuloma. Eight vials of sperm were cryopreserved.

The patient had no complications after the surgery. He began systemic therapy for sarcoidosis soon thereafter, consisting of methotrexate and infliximab. He remained on clomiphene citrate, and morning total T was 278 ng/dL 2 months later. His E2 level was stable at 19 pg/mL. Repeated imaging revealed resolution of his spinal cord lesion, and although he continued to have impaired sexual function, he was able to successfully achieve orgasm and ejaculate on two occasions.

DISCUSSION
To our knowledge, this is the first reported case of anejaculation and secondary infertility due to neurosarcoidosis. In the setting of systemic sarcoidosis, patients more commonly experience secondary infertility due to urogenital involvement, which occurs in 0.2% of cases (3–7). Urogenital sarcoidosis most commonly involves the testis, epididymis, or both (8). Some cases of urogenital sarcoidosis will remit spontaneously, though for severe or nonremitting cases, the current mainstay of treatment remains corticosteroids (8). The evidence supporting this recommendation is equivocal and consists primarily of case studies owing to the rarity of this condition. The majority of reports have noted improvements in radiographic disease burden, azoospermia, oligospermia, and gonadal function with the use of steroid therapy (3, 5, 8–10). However, urogenital sarcoid has also been seen to progress during steroid administration (11). For patients with significant pain secondary to epididymal sarcoidosis, excisional biopsy may provide additional symptomatic relief (5).

Although this patient presented with borderline high FSH, suggestive of impaired sperm production and possible testicular sarcoid, biopsy indicated normal spermatogenesis and did not reveal any testicular granulomas or other abnormalities. Infertility in this patient was exclusively a manifestation of sexual dysfunction secondary to neurosarcoidosis.

Neurogenic Anejaculation

Neurologic control of male sexual function is complex and depends on both peripheral supply from the pelvic plexus (thoracolumbar sympathetics, pelvic parasympathetics, and somatic), as well as modulation by central descending inhibitory and excitatory pathways (12). As a result, involvement of any portion of the spinal cord, including the pelvic plexus, may interfere with normal sexual function. This can be seen in patients with SCIs at the cervical and thoracic levels, who may present with significant ED and anejaculation (13).

This patient with neurosarcoidosis was able to recover erectile function with use of a PDE-5 inhibitor, which suggests sparing of the penile vasculature and an intact S2–S4 bulbocavernosus reflex arc that is commonly seen in upper motor neuron SCI (14).

Initial management of fertility preservation in the setting of anejaculation should include pharmacologic and other nonsurgical interventions. Men capable of achieving orgasm who report anejaculation should be evaluated for retrograde ejaculation with the use of postorgasm urinalysis. Men confirmed to have retrograde ejaculation can be treated with sympathomimetic agents such as pseudoephedrine (15). For men with concurrent ED, such as this patient, PDE-5 inhibitors can improve erectile rigidity, which may also improve orgasmic and ejaculatory function. Men refractory to these medications should proceed to PVS, which uses a vibrating disc to stimulate the dorsal and ventral glans, thereby activating the ejaculatory reflex (16, 17). In the setting of neurogenic anejaculation secondary to SCI, PVS has a success rate (defined as anterograde ejaculation) of 86% in patients with T10 injuries or above, although success in non-SCI patients is less well studied (18).

Surgical interventions for men with refractory anejaculation include EEJ and sperm extraction. EEJ involves...
Steroid-Induced Hypogonadism

Chronic treatment with high-dose corticosteroids can lead to suppression of the hypothalamic-pituitary-gonadal (HPG) axis at several levels (24). Based on early animal studies, glucocorticoids appear to have an inhibitory effect at the level of the hypothalamus to decrease the secretion of GnRH (25, 26). This, in turn, leads to an indirect glucocorticoid-mediated reduction of LH secretion from the pituitary (24). In addition to decreasing upstream signaling, glucocorticoids may also act directly at the testicles to further down-regulate LH receptors and inhibit steroidogenesis (27).

Observational studies in humans have consistently demonstrated depressed T levels in men treated with long-term systemic corticosteroids for management of various inflammatory diseases (28). In a case series by MacAdams et al., 16 men taking oral glucocorticoids for more than 1 month for chronic pulmonary disease had lower average T compared with health control subjects (270 ng/dL vs. 449 ng/dL; \( P = .01 \)). In addition, they found an inverse relationship between corticosteroid dosing and T level (\( r = -0.78 \)) (29). Similar results were demonstrated in a cross-sectional study by Kamischke et al., who examined 16 men receiving oral glucocorticoids (mean daily dose 9.4 mg) and found that serum T was significantly lower compared with patients with chronic obstructive pulmonary disease who were not taking oral glucocorticoids (141.2 ± 6.7 pmol/L vs. 197.15 ± 10 pmol/L, \( P < .05 \)) (30). Fitzgerald et al. had similar findings in 17 men taking long-term prednisolone (mean daily dose 16.3 mg); although this cohort was noted to have similar mean T concentrations compared with control subjects (14.9 nmol/L vs. 18.7 nmol/L; \( P = .08 \)), they had significantly lower T/SHBG ratios (\( P = .026 \)) (31). In addition, Morrison et al. performed a cross-sectional study of 35 male patients with respiratory disease on either long-term oral or inhaled corticosteroids. Although mean T levels were not reduced in patients taking high-dose inhaled beclomethasone, mean serum T for patients on oral prednisolone (14.5 ± 6.0 nmol/L) was 33% lower compared with healthy control subjects (32). Similar conclusions were found in a case series by Stafford et al., as well as a cohort study by Martens et al. with patients taking 5–10 mg prednisone daily (33, 34). Taken together, there appears to be consistent evidence that long-term enteral corticosteroid therapy results in a drop in serum T by ~28%–40%. These findings correlate well with the proposed inhibitory actions of glucocorticoids on the HPG axis.

The present patient also presented with hypogonadism in the setting of long-term high-dose prednisone therapy, and his low-normal LH possibly indicated corticosteroid-mediated suppression of the endocrine axis at the hypothalamic-pituitary level. This hypogonadal state could have also resulted in his ED. Indeed, corticosteroid therapy-induced ED has been observed by Contreras et al., who noted that in 17 male patients (ages 23–56 y) with uveitis or asthma on daily chronic 10 mg methylprednisolone, spontaneous erections were absent in 58% of subjects (35). Another observational study by Merayo-Chalico et al., examining 174 male patients with systemic lupus erythematosus (SLE) found a prevalence of ED of 69% in the cohort taking corticosteroids versus only 23% in healthy controls (\( P = .001 \)). In addition, they noted that patients with ED were more likely to be taking a higher daily dose of prednisone (9.3 mg vs. 5.3 mg; \( P = .02 \)) and more likely to have had exposure to any dose of corticosteroids within the past year (\( P = .02 \)) (36). This suggests both a possible dose-dependent relationship with ED as well as a prolonged adverse effect of corticosteroid therapy. Outside of these two observational studies, however, the evidence examining this relationship remains otherwise limited.

In addition, our patient presented with some degree of hypoposmatogenesis, which may have been, in part, corticosteroid induced. However, there are limited human data available exploring the direct impact of chronic corticosteroid use on spermatogenesis. One early study by McDonald and Heckel found that compared with healthy control subjects, there was no significant difference in sperm concentration, motility, or morphology in four men who were treated with prednisone for 23–334 days (37). Consensus opinions from several reviews on this topic have suggested that chronic corticosteroid use does not impair spermatogenesis, despite its potentiation of hypotestosteronemia (28, 38, 39). However, given the scarcity of primary data, further studies are needed to demonstrate whether corticosteroid-mediated decreases in T actually translate to clinically meaningful hypogonadism.

Methotrexate and Spermatogenesis

The recommendation for fertility preservation before starting methotrexate therapy is also a topic of continuing research. Methotrexate is a folate antimetabolite that is used to inhibit DNA synthesis in treating a wide variety of malignancies and inflammatory conditions. Despite recent development of
| Study                          | n     | Design          | Condition                  | MTX dose | Concomitant treatments | Findings                                                                 |
|-------------------------------|-------|-----------------|----------------------------|----------|------------------------|--------------------------------------------------------------------------|
| Van Scott and Reinertson 1959 | 2     | Case series     | Psoriasis                  | Single dose 0.5–5 mg/kg | None                   | Oligospermia                                                             |
| Hinkes et al. 1973 (50)       | 1     | Case report     | Acute lymphocytic leukemia | 2.5 mg/d | Mercaptopurine,        | Oligospermia (<1 × 10⁶/mL), reversible                                    |
|                               |       |                 |                            |          | cyclophosphamide       |                                                                           |
| El-Beheiry et al. 1979 (52)   | 26    | Prospective cohort | Psoriasis                  | 25 mg/wk | None                   | No effect on semen parameters                                              |
| Sussman and Leonard 1980 (45) | 1     | Case report     | Psoriasis                  | 15 mg/wk | None                   | Oligospermia (1 × 10⁹/mL), reduced motility, reversible                   |
| Shamberger et al. 1981 (49)   | 19    | Prospective cohort | Sarcoma                    | Six doses, 50–250 mg/m² | Doxorubicin, cyclophosphamide, radiotherapy | Oligospermia (2.4 × 10⁶ to 185 × 10⁹/mL), azoospermia, elevated LH and FSH, reversible |
| Shafik 1993 (47)              | 1     | Case report     | Testicular seminoma        | Ten 50-mg intratunical injections | None                   | Oligospermia (82.2 × 10⁹/mL decreased to 51.3 × 10⁹/mL), abnormal morphology, reversible |
| Pandhi et al. 2006 (46)       | 1     | Case report     | Psoriasis                  | 20 mg/wk | None                   | Oligospermia (0.015 × 10⁹/mL), decreased motility, abnormal morphology    |
| Melnyk et al. 1971 (56)       | 1     | Case report     | Psoriasis                  | 25–30 mg/wk | None                   | Chromosomal ploidy, breakage, and degeneration abnormalities not different from normal patients |
| Martin et al. 1995 (55)       | 1     | Case report     | Lymphoma                   | Three doses, 400 mg/m² | Doxorubicin, cyclophosphamide, vincristine | Structural and numeric chromosomal abnormalities not different from normal patients |
| Ley et al. 2018 (54)          | 7     | Case-control with age-matched controls | Inflammatory bowel disease | 12.5–25 mg/wk | TNF-α inhibitors, 5-aminosalicylates | Increased DNA fragmentation and oxidative stress compared to healthy controls |

Note: TNF = tumor necrosis factor.
* Concomitant treatments reflect the variety of treatment regimens across an individual study; not every patient in the study used all of the listed treatments.

Yu. Anejaculation, hypogonadism, and neurosarcoidosis. Fertil Steril Rep 2020.
| Study                      | No. of pregnancies | Design               | Condition                        | MTX dose | Concomitant treatments<sup>a</sup> | Findings                                                                 |
|---------------------------|--------------------|----------------------|----------------------------------|----------|-----------------------------------|--------------------------------------------------------------------------|
| Østensen et al. 2007 (63) | 11                 | Retrospective cohort | Rheumatic                        | NR       | TNF-α inhibitors                  | 9 live births with 2 major birth defects, 1 elective abortion, 1 unknown pregnancy outcome |
| Lee et al. 2010 (58)      | 7                  | Retrospective cohort | NR                               | NR       | NR                                | 7 live births, no major birth defects or abortions                        |
| Beghin et al. 2011 (62)   | 42                 | Prospective cohort   | Inflammatory, rheumatic, cancer, miscellaneous | 7.5–30 mg/week | DMARDs, biologics, NSAIDs, corticosteroids | No major birth defects in this cohort                                      |
| Viktil et al. 2012 (59)   | 50                 | Retrospective case control | NR                               | NR       | NR                                | 50 live births with 2 major birth defects                                 |
| Weber-Schoendrfer et al. 2013 (60) | 113 | Prospective cohort | Inflammatory, rheumatic           | ≤ 30 mg/week | DMARDs, biologics, NSAIDs, miscellaneous | No differences in rates of major birth defects, spontaneous abortion rates, gestational age, or birth weight compared with healthy control subjects |
| Wallenius et al. 2015 (61)| 49                 | Retrospective cohort | Inflammatory joint disease        | 12.5–20 mg/week | Sulfasalazine, TNF-α inhibitors, thiopurines | No differences in rates of major birth defects, spontaneous abortion rates, gestational age, or birth weight compared with healthy control subjects |

Note: DMARD = disease-modifying antirheumatic drug; NR = not reported; NSAID = nonsteroidal antiinflammatory drug; TNF = tumor necrosis factor.

<sup>a</sup> Concomitant treatments reflect the variety of treatment regimens across an individual study; not every patient in the study used all of the listed treatments.

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alternative biologic therapies, methotrexate remains a mainstay of regimens for treatment of highly prevalent diseases such as inflammatory bowel disease, rheumatic arthritis, and psoriasis (40–42).

Given its interfering role in cellular replication, methotrexate poses a theoretical risk to spermatogenesis, which is driven by rapidly dividing germ cells. Animal studies have consistently demonstrated marked adverse effects of methotrexate on testicular function, including degeneration of spermatocytes, Sertoli cells, and Leydig cells (43). In contrast, the few observational studies on methotrexate and spermatogenesis in humans have demonstrated conflicting results (Table 1). There are several case reports and case series describing male patients who developed oligospermia during treatment with methotrexate (44–47). However, many of these men were treated with multiagent chemotherapy, rendering it difficult to attribute impaired spermatogenesis to methotrexate specifically (48–50). Of note, impairment in semen parameters was reversible within a few months after cessation of therapy (45, 47, 50, 51). On the other hand, several studies have found no adverse effects of methotrexate on sperm concentration and motility compared with control subjects (48, 52). In a comparison of men with severe psoriatic arthritis treated with either methotrexate or corticosteroids, the former were actually more likely to have normal semen parameters (53).

The risk of increased sperm DNA fragmentation with the use of methotrexate therapy is also unclear. Ley et al. studied DNA fragmentation in seven men treated with methotrexate for inflammatory bowel disease compared with age-matched control subjects who underwent evaluation at a fertility center. Despite having normal semen parameters, men treated with methotrexate had increased sperm oxidative stress and DNA fragmentation compared with control subjects (54). Case reports by Martin et al. and Melnyk et al., however, found that in their patients who used low-dose and high-dose methotrexate, respectively, chromosomal ploidy and structural abnormalities did not differ significantly compared with normal patients (55, 56).

Pregnancy outcomes for couples conceiving naturally after paternal methotrexate therapy are more encouraging (Table 2). Grosen et al. performed a systematic review of all reported pregnancies after paternal methotrexate exposure. Among 284 pregnancies with known paternal methotrexate exposure at the time of conception, 248 (87.3%) resulted in live births. Of these, 13 (5.2%) had congenital malformations (57–63). The included studies were generally found to be in agreement that rates of abortion and congenital malformation were not significantly different from published rates in the general population (57, 59–61). Despite this, the evidence on safety of methotrexate during conception and subsequent pregnancy is still limited in quality and size, predominantly because of the ethical barriers in conducting randomized trials in the setting of a known potential harm. As such, there are not likely to be future well conducted studies to elucidate the safety of paternal methotrexate exposure and subsequent pregnancy.

In the absence of rigorous data, consensus guidelines from multiple professional societies regarding treatment of inflammatory bowel disease, rheumatologic disease, and autoimmune dermatologic conditions recommend cessation of methotrexate therapy in male patients 3–4 months before conception (64, 65).

CONCLUSION

Spinal involvement in the setting of sarcoidosis is rare, although the impact of central nervous system disease on sexual and reproductive function can be quite severe. Numerous approaches to fertility preservation, such as PVS, EEJ, and surgical TESE/TESA are associated with high success rates in patients with neurogenic anejaculation due to other etiologies and may be equally effective in patients with neurosarcoidosis, although limited data exist. In addition to the adverse effects inherent in the disease process itself, clinicians should also consider the impact of pharmacologic intervention on sexual and reproductive health. Although consistent evidence exists to suggest an adverse impact of chronic corticosteroid therapy on serum T levels, the clinical impact of this hypogonadism requires further characterization. Similarly, early data on paternal methotrexate exposure suggests a possible impairment of spermatogenesis, although these conclusions would benefit greatly from further investigation. Patients interested in fertility optimization or preservation should be carefully counseled on these potential risks to allow for the greatest chance of reproductive success.

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