APPEARANCE OF SPERMATOZOON AFTER ADMINISTRATION OF MAST CELL BLOCKER TO A PATIENT WITH AZOOSPERMIA

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Since a close relationship has been suggested to exist between testicular disfunction and the increased mast cells in the testis, we used a mast cell blocker for the treatment of patients with idiopathic infestility. An infertile male with idiopathic azoospermia was treated with administration of a mast cell blocker, tranilast for one year. The patient was found to have sperm within his ejaculate. However, the ultimate goal of pregnancy was not achieved by the microfertilization technique. To evaluate the possible significance of this new treatment, further basic research will be needed to clarify the relationship between mast cell proliferation and impaired testicular function.

(Acta Urol. Jpn. 40: 541-543, 1994)

Key words: Spermatogenesis, Mast cell blocker, Azoospermia

INTRODUCTION

A new approach for the treatment of male infertility focuses on the role of mast cell blockers which inhibit the release of histamine and other vasoactive substances from mast cells. The rationale of this approach is based on the observation of mastocytosis in the testes of infertile males which was first reported by Maseki et al[1]. The increase in mast cells in the infertile testis may indicate some relationship between mast cell proliferation and testicular dysfunction. Hofmann et al.[2] and Schill et al.[3] reported in a pilot study positive effects of Ketotifen, a mast cell blocker, on semen parameters in infertile men. Therefore, we administered tranilast, a mast cell blocker, to idiopathic azoospermic men to determine whether this kind of treatment may have a beneficial effect on the semen quality. Here we report the first clinical case of sperm emergence after administration of a mast cell blocker in the patient with azoospermia.

CASE REPORT

A 25-year-old male presented with azoospermia diagnosed by semen analysis on three separate occasions (average pH 7.5; average volume of 3.2 mL) over the course of 1 year. Laboratory evaluation revealed a normal follicle-stimulating hormone (8.2 mIU/ml), luteinizing hormone (5.2 mIU/ml), testosterone (5.8 ng/ml), prolactin (9 ng/ml), and thyroid functions. The peripheral lymphocyte karyotype was 46,XY. Physical examination revealed normal secondary sex characteristics, normal phallus with a normal meatus and bilaterally descended testes measuring 15 ml on the left and 18 ml on the right. There was a small left varicocele. Rectal examination was normal. The patient underwent a bilateral testicular biopsy and high ligation of the gonadal vein.

On testicular biopsy, approximately 80% of the tubules contained only Sertoli cells and a slightly thickened tunica propria, and about 20% of the tubules showed incomplete maturation arrest without peritubular thickening. Only occasional tubules had germ cells present with varying stages of spermatogenesis. Leydig cells were seen in slightly increased numbers (Fig. 1). Follow-up monthly semen analysis postoperatively still revealed azoospermia up to 3 years later. The patient and his wife were offered donor insemination for a pregnancy attempt but they declined.

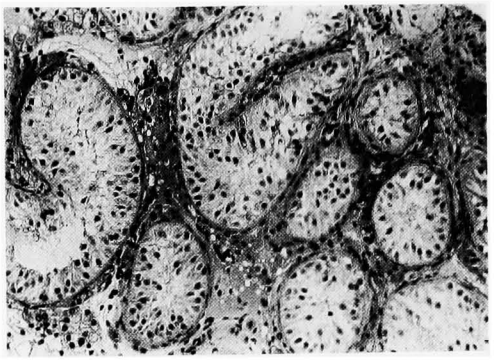

Fig. 1. Testicular biopsy demonstrating predominance of Sertoli cells.

Treatment with tranilast was started at doses of 300 mg/day for 6 months. There was no adverse effect of this drug on regular laboratory check up. A subsequent semen analysis revealed 700,000 sperm/mL with 35% motility (total volume was 2.6 mL). Endocrine profiles six months after administration of tranilast were as follows; FSH: 7.4mIU/ml, LH: 3.2mIU/ml, testosterone: 9.2 ng/ml, prolactin: 8.2 ng/ml. The treatment was continued for up to 12 months. Semen analysis was repeated every three months, but the sperm count did not improve further. No pregnancy was achieved. Not enough motile sperm were present to perform routine in vitro fertilization (IVF). This couple underwent microfertilization by using the partial zona dissection technique, but the procedure was unsuccessful.

DISCUSSION

Maseki et al. were the first to find that mastocytosis occurred in the testes from the patients with idiopathic infertility[1]. Hashimoto et al. demonstrated that the number of mast cells was increased not only in the interstitium but also in the lamina propria of the seminiferous tubules[4]. Nagai et al. attempted to determine the heterogeneity of mast cells in the testes from the patients with idiopathic infertility[6]. They demonstrated that the total number of mast cells and the ratio of chondroitin sulfate containing mast cells were significantly increased in the infertile testes[6]. Peritubular fibrosis is a common finding in the testicular biopsy specimen from the infertile males. Mast cells are known to induce fibrosis under certain conditions. The cytoplasmic granules of these cells contein numerous chemical mediators that can be released into the surrounding tissues after certain allergic, immunological, and other stimulations and can result in various effects upon the tissues involving the cells[5]. Thus, a close relationship is likely to exist between testicular disfunction and the increased mast cells in the testis. Despite the possible involvement of mast cells in idiopathic male infertility, their role in testicular tisseus remains to be elucidated

Unfortunately, in this case, we did not perform a histochemical study of testicular biopsied specimen to identify mastocytosis in the testicular interstitium. However, on the basis of our previous findings, we used a mast cell blocker for the treatment of idiopathic infertile patients with the expectation of a possible beneficial effect on semen quality. Administration of the mast cell blocker, tranilast, to men with idiopathic azoospermia for up to 1 year led to successful appearance of spermatozoa in the seminal fluid. This improvement can be explained by blocking of release of chemical mediators from mast cells which can induce some fibrotic process. Schill et al. reported hat treatment of idiopathic oligozoospermia by the mast cell blocker, Ketotifen, led to a very moderate, but statistical significant improvement of sperm count and sperm motility[3]. However, the pregnancy rate was within the range of spontaneous conceptions[3]. They speculate that the release of chemical mediator within the testis plays some role in the pathophysiology of testicular disorders[3].

In conclusion, successful sperm output was observed after treatment with a mast cell blocker in an idiopathic infertile patient. To evaluate the possible significance of this new treatment, further basic research will be needed to clarify the relationship between mast cell proliferation and impaired spermatogenesis.

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(Received on November 12, 1993
Accepted on January 14, 1994)

和文抄録

無精子症患者に対しマスト細胞ブロッカーを投与し精子の出現をみた1例

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造精機能障害と精巣をおけるマスト細胞の増加との間には密接な関係が存在する．この知見をもとに，特発男子不妊症の治療としてマスト細胞ブロッカーの使用を試みた．特発性無精子症患者に対し，マスト細胞ブロッカーの一種である tranilast を1年間投与した．その結果，精液中に精子の出現が認められた．顕微授精を施行したが，妊娠には至らなかった．この新しい治療法の意義を評価するために，マスト細胞の増加と精巣機能障害との関係を明らかにする基礎的な，研究が必要である．

（泌尿紀要　**40**：541-543，1994）