Immunotherapy as an Adjuvant Therapy for Malignant Melanoma of the Female Urethra

Report of a Case

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(Received March 29, 1979)

ABSTRACT

Primary malignant melanoma of the female urethra is extremely rare with poor prognosis. In 1976, Jeffrey reviewed the literature and found a total of 34 cases. The case reported herein is of interest for the reason that the patient is living without any evidence of recurrence over 36 months after a combined therapy of cryosurgery, topical administrations of Bleomycin, and active immunotherapy with BCG and a streptococcal agent.

Key Words: *immunotherapy*; *melanoma*; *female urethra*

INTRODUCTION

Although most organs and mucosal sites have been described as being primary sites of melanoma, a review of the Japanese literature by Oosumi et al.[1] showed that the eyes, oral cavities and palatal region were highly dominant primary sites, but that the external genitals made up only 4.5% of the primary sites. Katz et al.[2] reviewed 37 melanoma cases of the female urethra and reported that primary malignant melanoma of the female urethra was a disease of old age; the average age being 64. We present a case and gathered three cases of malignant melanoma of the female urethra from the Japanese literature[3)-5)] and showed their age distribution, presenting symptoms, therapy, and prognosis (Table I). Since 1975 chemoimmunotherapy has been favored in Japan. We also discussed the immunological aspect in the patient with malignant melanoma.

A CASE REPORT

A 53 year-old Japanese housewife of good health noticed sudden bleeding from the meatus 5 days prior to her first visit. On physical

examination, a dark brown growth approximately 10 mm in diameter was discovered at the terminal urethra. The growth bled easily with a granular appearance and wase believed to be a caruncle. The mass was excised without difficulty and the base was fulgurated.

Table I Malignant melanoma of the female urethra in Japan

Reporter	Age (years)	Presenting symptoms	Therapy	Prognosis
Maeda 3)	64	terminal hematuria urethral tumor	Bleomcin urethrectomy (450mg)	dead (2. 8y)
Shoji 4)	75	dark brown dischage from vagina	Radiation BCG	dead (1. 6y)
Tadara 5)	73	urethral tumor miction trouble	Excision OK-432	survived
Present case	53	hematuria	Cryosurgery immunochemo- therapy	survived (3. 0y)

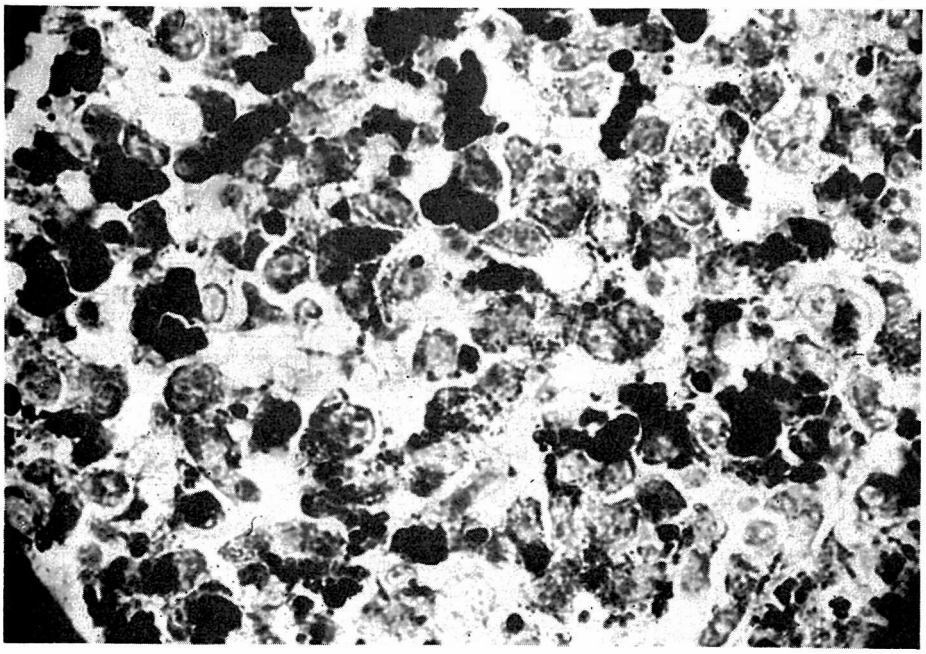

Fig. 1 Histology of urethral tumor.
Brown pigmentation, pleomorphism, large nucleoli and a few mitotic figures.

Because a pathologist made a diagnosis of malignant melanoma (Fig. 1), a further search was made for primary or metastatic lesions, including the eyes and skin, after she was admitted to our hospital on February 6, 1976.

All routine laboratory studies including excretory urography, tomography of the chest, liver scanning, tumor scanning and gastrointestinal series were negative. Prior to the start of the treatment, antimelanoma antibody was not examinen, but both Mantox and DNCB test were negative. The degree of blastogenesis of lymphocytes by phytohemagglutinin was 52%.

On cystourethroscopy a dark ulcerous lesion remained along the right surface of the distal urethra and extended over about 1 cm from the meatus. Clinical symptoms of metastasis were not found. Since the patient was anergic to DNCB and tuberculin, we decided to perform cryosurgery on the urethra and immunotherapy with hostmediated immunoactivating agents.

On February 18, a hemisphere cryolysis of the meatus about 2 cm in diameter was carried out at the temperture of $-147°C$, using liquid nitrogen, for 2.5 minutes. During several postoperative days, she had no trouble with miction and other complications. But 3 weeks later, the meatus and anterior urethra became necrotic, and she experienced transient urinary incontinence. After that, the recovery of the patient was uneventful.

On March 15, for the prevention of local recurrence, a total of 150 mg of Bleomycin in oil was injected into the subcutaneous tissue of the bilateral vulvae and around the urethra. Then, for the purpose of enhancing host immunocompetence, a total dose of 147 K.E. of OK-432, a streptococcal agent, was administered, followed by double BCG vaccinations during her stay in the hospital. Prior to the initiation of immunotherapy, PPD test and DNCB skin test were both negative, but they became positive after the immunotherapy. Paticularly, the DNCB skin test flared up the second week after the initiation of immunotherapy. The degree of blastogenesis of lymphocytes increased from 52% to 58% and the peripheral lymphocyte counts increased from 1800 to 3500. Fig. 2 shows the course of the therapies and their effects. All the tests before discharge, including the liver function test and other laboratory data showed normal findings. She was discharged from the hospital on the 42nd day. Thirty months later, a careful clinical search revealed no evidence of recurrent disease. She has maintained good continence and regular micturition.

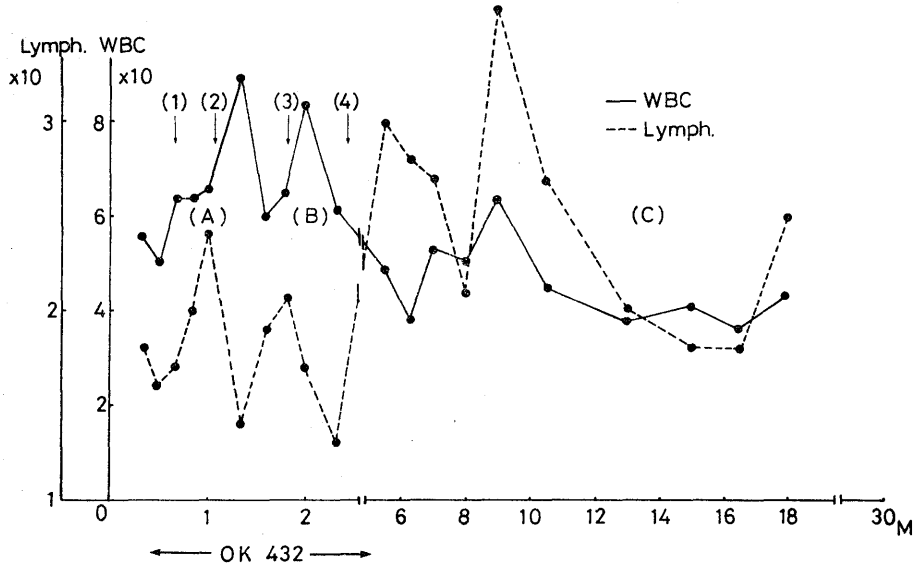

Fig. 2 Clinical course concerning peripheral WBC and peripheral lymphocyte counts.

The course of the therapies and their effects (1) : Cryosurgery, (2) : Bleomycin in oil 150mg, (3) and (4) : BCG vaccination, (A): Degree of blastogenesis of lymphocyte is 52%. DNCB and PPD tests were negative. (B) : Degree of blastogenesis is 58%. Both tests became positive. (C) : Degree of blastogenesis is 52%. Both tests were positive also.

DISCUSSION

The prognosis of malignant melanoma is widely known to be uniformly poor, although the treatment of the disease has ranged from cauterization to radical operation. Herbut[6] has pointed out that melanomas are notoriously resistant to irradiation. It is reported that only 3 cases of primary malignant melanoma of the female urethra have survived 5 years after surgery. Recently, it has been suggested from certain clinical studies of malignant melanoma that the disease may contain tumor-specific antigens which are immunogenic in the autologous host. Experimental studies provide evidence to support the presence of the antigens in the malignant tumor, and indicate that this immunological process in the tumor bearing host is aided by cell-mediated immunity.

According to Morton et al.[7], a remarkable correlation between the presence of antimelanoma antibodies and the extent of malignant melanoma has been indicated. The delayed cutaneous hypersensitivity to the DNCB test also shows a good correlation between immunological reactivity to this antigen and the extent of the disease initially as well as the

patient's responsiveness to immunotherapy. The existence of tumor-specific antigens in malignant melanoma and the well-documented resistence of malignant melanoma to radiotherapy formed a rational basis for performing immunotherapy on the patient reported herein. In this patient, the tumor was belived to be localized on the terminal urethra and no metastatic lesions were clinically discovered anywhere. However, the patient exhibited impaired immunological reactivity, and the presence of minimal metastatic lesions was suspected, because of the reports that all patients with localized malignant disease were capable of being sensitized to DNCB, and because all DNCB-negative patients so far reported to have widespread metastatic disease.

Recently, the possibility of an immuno-cryothermic responce by freezing of the local tumor in situ had been reported in several patients with malignant disease[8]. It was suggested that cryosurgery of the local tumor permits the release of tumor specific antigens leading to the formation of antibodies which subsequently leads to the destruction of the tumor.

BCG is known to be a potent immunological adjuvant and has been found to be capable of inducing a heightened immune response to melanoma-specific antigens in patients with malignant melanoma. Streptococcal preparation OK-432 has a mild anti-cancer effect, but the principal effect of this agent appears to be on cell-mediated action. Concerning the immunoreactivity of patients treated by OK-432, it was reported that an increase of lymphocyte blastogenetic activity and an enhancement of delayed cutaneous hypersensitivity tests were found[9]. This suggests the nonspecific immunoenhancement activity of OK-432. Prior to the initiation of immunotherapy, our patient did not manifest delayed cutaneous hypersensitivity to DNCB and PPD. Following a total dose of 147 K.E. of OK-432 and double BCG vaccination, both skin tests became positive, the degree of blastogenesis of lymphocytes increased from 53% to 58%, and the peripheral lymphocyte counts increased also. These suggest the effectiveness of this combined immunotherapy.

It is indicated that the host immune response to malignant melanoma is an important factor in controlling the progression of this disease. Therefore, immunotherapy may become a useful adjuvant therapy following the surgical treatment of malignant melanoma of the female urethra.

REFERENCES

1) Ohsumi, T. and Seiji, M.: Statistical observation of malignant melanoma in Japan. *J. Clin. Derm.*, 15 : 26, 1973.
2) Katz, J.I. and Grabstald, H.: Primary malignant melanoma of the female urethra. *J. Urol.* 116 : 454, 1976.

3) Maeda, Y. and Okabe, T.: Primary malignant melanoma of the female urethra, a case report (in Japanese). *Jpn. J. Urol.*, 60 : 347, 1969.
4) Shoji, R., Machida, T., Kido, A. and Nakamura, K.: A case of malignant melanoma found in the vaginal wall and the urethra (in Japanese). *Jpn. J. Urol.*, 67 : 663, 1976.
5) Tadara, K. and Fukugawa, T.: A case of malignant melanoma found in the female urethra (in Japanese). *Jpn. J. Clin. Urol.*, 7 : 641, 1977.
6) Herbut, P.A.: *Urological Pathology.* vol. 2, Lea & Febiger, Philadelphia, 1952, pp. 744, 868 and 1217.
7) Morton, D.L., Eilber, F.R., Malmgren, R.A. and Wood, W.C.: Immunoligical factors which influence responce to immunotherapy in malignant melanoma. *Surgery*, 68 : 158, 1970.
8) Gursel, E., Roberts, M. and Veenema, R.J.: Regression of prostatic cancer following sequentional cryotherapy to the prostate. *J. Urol.*, 108 : 928, 1972.
9) Kimura, I., Ohnoshi, T., Yasuhara, S. et al.: Immunochemotherapy in human lung cancer using the streptococcal agent OK-432. *Cancer*, 37 : 2201, 1976.