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The Effectiveness of Medroxyprogesterone in the Treatment of Multiple Metastasizing Leiomyosarcomas: Report of a Case

TATSUO UCHIDA, KATSURA NAKAKAWAJI, JUNICHI SAKAMOTO, HIROSHI KOJIMA, HIROYA MURAKAMI, JUNJI KATO, and MITSUNORI YASUE

Department of Surgery, Aichi Prefectural Hospital, 18 Kuriyado, Kakemachi, Okazaki, Aichi 444, Japan

Abstract: A 51-year-old woman was admitted to our hospital for further investigation of chest X-ray films which showed multiple shadows that had been growing slowly over 2 years. Her only symptom was hemosputa. The lesions were suspected of being metastasizing leiomyoma due to her past history of uterine leiomyoma. Just 1 week before undergoing scheduled open lung biopsy, the lung lesions increased remarkably in size and number. A thoracotomy was performed and six of the numerous nodules were removed. The resected specimens were pathologically diagnosed as metastasizing leimyosarcoma which was positive for the progesterone and estrogen receptors. Thus, 1 month postoperatively, a course of medroxyprogesterone (MPA), 600 mg daily, was commenced. The residual lesions in her chest started to diminish, shortly afterward. She has remained well on this MPA regimen for 45 months. The prognosis of patients with metastasizing leiomyosarcoma is poor because of its low sensitivity to chemotherapy; however, some types of leiomyosarcoma are hormone-sensitive. It is therefore important to examine the hormone receptors of excised tumors from patients suspected of having metastasizing leiomyoma or leimyosarcoma.

Key Words: uterine leiomyoma, lung metastasis, hormone receptor, leiomyosarcoma

Introduction

Leiomyomatous lesions are rare metastasizing lung tumors, most of which are derived from uterine leiomyosarcoma. These tumors are associated with a poor prognosis because of their low sensitivity to radiation and chemotherapies, although some types possess hormone receptors. We report herein the case of a patient for whom low-dose medroxyprogesterone has been effective in controlling multiple metastasizing leiomyosarcoma with hormone receptors.

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Case Report

A 49-year-old woman presented to our hospital in May 1988 with a 1-year history of hemosputa which began the day prior to menstruation and continued for 7 days. A chest X-ray film and computed tomography (CT) scan revealed discrete nodules in the lung, for which she was commenced on an antifibrinolytic agent under the diagnosis of benign lung lesions. The hemosputa stopped 7 months later. Although her menstruation was regular, she suffered from hyper- and dysmenorrhea. A huge uterine myoma was diagnosed at another hospital in April 1990, and a total hysterectomy with right salpingooophorectomy was performed; the histological features were of a benign cellular fibroid nature. She was referred to our hospital again for investigation of the recurrence of hemosputa in December 1990. A chest X-ray film taken at that time revealed that the shadow had developed slightly compared with the former X-ray image, although bronchoscopic examination revealed no evidence of malignancy. However, a repeat chest X-ray done 1 week before a scheduled open lung biopsy revealed that the multiple nodules in the lung had suddenly increased in number and size (Fig. 1). In February 1991, a right thoracotomy was performed and six of the numerous nodules were resected, all of which were reddish brown, well-demarcated, and soft. Histological examination revealed spindle- and round-shaped smooth muscle cells, hyperchromatic nuclei, conspicuous nucleoli, and mitosis (Fig. 2). All the resected tumors were histologically diagnosed as leiomyosarcoma possessing high hormone receptor levels, being 370 fmol/mg protein for the estrogen receptor and 1,400 fmol/mg protein for the progesterone receptor. A histogram of one lesion using a flow

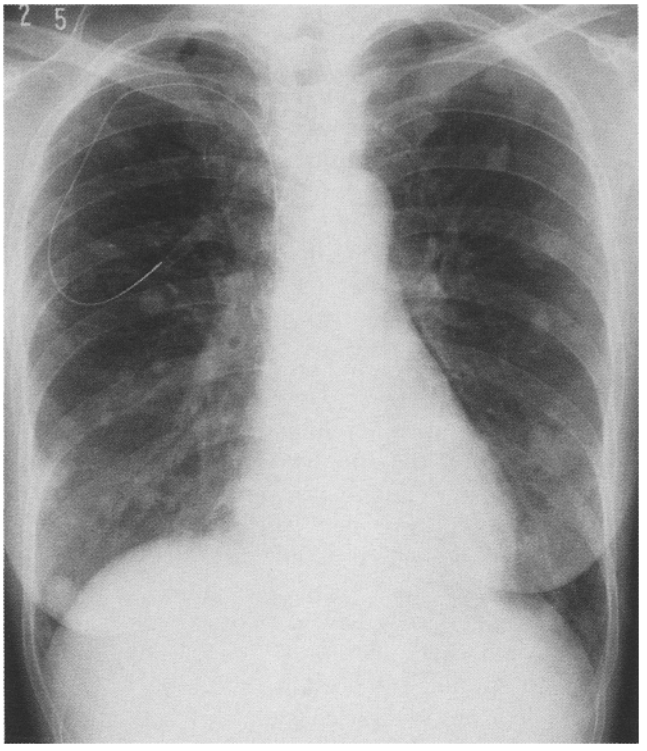

Fig. 1. Chest X-ray taken in February 1991, showing bilateral numerous nodules which had suddenly increased in size and in number before surgery

cytometer, analyzed by B.M.L. Laboratories (Tokyo, Japan), showed a diploid pattern with 2.1% in the S phase and 1.1% in the G2 + M phase. Thus, in March 1991, according to the standard hormone therapy of cancer of the uterine corpus, she was commenced on medroxy-progesterone acetate (MPA) 600 mg daily, following which the remaining pulmonary metastases gradually diminished. In April 1993, due to enhanced activity of the extrinsic pathway of the coagulation cascade, the dose of MPA was decreased to 400 mg daily and aspirin dialuminate was added to prevent thrombosis. To date, no pulmonary lesions have regrown and, as of December 1994, she remains well on treatment with MPA (Fig. 3), with only one lesion in the left lung, 1 × 1 cm in size, having been revealed by the most recent CT scan.

Discussion

Leiomyosarcoma accounts for 1%–6% of all malignant tumors of the uterus,[1] with an overall 5-year survival rate of 25%.[2] The prognosis of patients with stage III or IV disease is especially poor, with a 5-year survival rate of 0%, and with most of these patients dying within 2 years.[3] There are two reasons for the poor prognosis of leiomyosarcoma of the uterus: its tendency to produce remote metastases, especially to the lung, and its rapid growth. Multimodality therapy to treat advanced or recurrent disease includes radiation, chemo-, and hormone therapy; however, no objective effects of radiation were observed in a report by Gilbert et al.,[4] while combination chemotherapy using doxorubicin produced a 19% response rate,[5] and high-dose VP-16 combined with cisplatin (CDDP) produced a partial but temporal response.[6] On the other hand, although it is well accepted that uterine leiomyomas appear to be

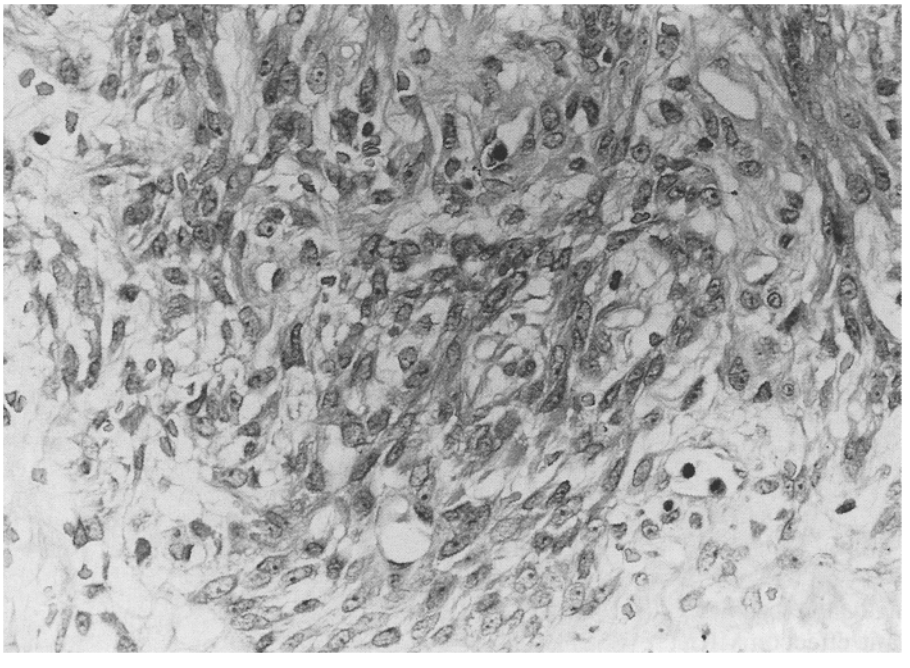

Fig. 2. Pathological examination revealed spindle- and round-shaped smooth muscle cells with hyperchromatic nuclei, conspicuous nucleoli, and mitosis. (H&E, ×150)

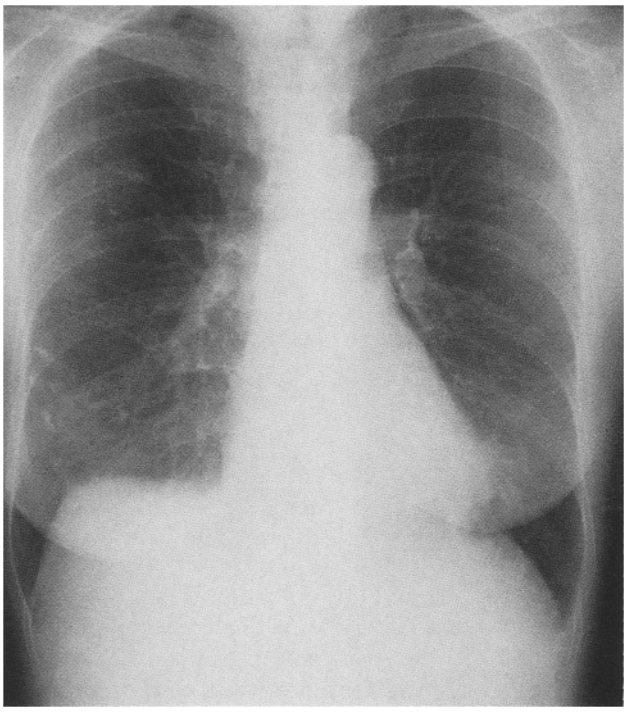

Fig. 3. Chest X-ray taken in September 1994. No obvious lesions can be seen

influenced by hormones, the administration of hormone therapy for uterine leiomyosarcomas has seldom been reported, having been thought to produce no positive effects.[7] However, preliminary studies have revealed interesting results. According to a study by Sato et al., a murine uterine sarcoma induced by methylcolantholane and planted in nude mice was controlled by high-dose MPA at 100 mg/kg, but not by low-dose MPA at 10 mg/kg.[8] Linda et al. also reported that progesterone produced some effects on a human uterine leiomyosarcoma with negative estrogen and progesterone receptors planted in nude mice.[9] In a clinical study, Pellillo reported the case of a patient with multiple pulmonary metastases from uterine leiomyosarcoma who was treated with high-dose progesterone and responded well for 2 years.[10] However, due to its rarity, no investigator has been able to demonstrate a definite correlation between the effect and dosage of MPA with the presence of hormone receptors in uterine leiomyosarcoma. Progesterone may be potentially beneficial for the treatment of a selected group of uterine leiomyosarcomas, but should be carefully administered so as not to produce severe adverse effects. The regression of the tumors in our patient was marked and the effect of MPA has continued well for more then 3 years, although it should be emphasized that a lower dosage of MPA of 400 mg daily could have been sufficiently effective. The dramatic effect on MPA therapy in our patient could be attributed to the fact that:

1. She was perimenopausal.
2. The pulmonary metastases might have been a low-grade malignancy, considering that their histogram showed a diploid pattern with only 2.1% in the S phase.
3. The metastases might have been very hormone-sensitive by nature, because their preoperative rapid growth was presumed to have been induced by a disorder of her hormone balance resulting from stress.

The case presented herein provides extremely useful information about the employment of hormonal therapy in the treatment of pulmonary metastases from uterine leiomyosarcoma, especially regarding the effective duration and minimum dose of MPA, because patients affected by pulmonary metastases from uterine leiomyosarcoma generally have a poor prognosis despite radiation and chemotherapy. In conclusion, it is important to examine the hormone receptors of resected tumors which are histologically diagnosed as being leiomyomatous, even if the primary lesion is benign.[11] By examining these hormone receptors, the selection of patients with leiomyosarcoma for whom hormonal therapy may prove effective could be more easily and rationally performed.

References

1. Norris HJ, Zaloudek CJ (1982) Mesenchymal tumors of the uterus. In: Blaustein A (ed) Pathology of the female genital tract, 2nd edn. Springer, Berlin Heidelberg New York, pp 352–392
2. Barter JF, Smith EB, Szpak CA (1985) Leiomyosarcoma of the uterus: Clinicopathologic study of 21 cases. Gynecol Oncol 21: 220–227
3. Andrew B, Stephen CR, William JH, Patricia ES, Virginia KP, John LL (1988) Treatment of uterine leiomyosarcoma. Obstet Gynecol 71:845–850
4. Gilbert HA, Kagan AR, Lagasse L, Jacobs FMR, Facog KT (1975) The value of radiation therapy in uterine sarcoma. Obstet Gynecol 45:84–88
5. Muss HB, Bundy B, Disaia PJ, Homesley HD, Fowler WC, Creasman W, Yordan E (1985) Treatment of recurrent or advanced uterine sarcoma. A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide. Cancer 55:1648–1653
6. Murao B, Fujita J, Yamagishi Y (1992) Remarkable response of lung metastases from uterine leiomyosarcoma to high-dose etoposide in combination with cisplatin (in Japanese with English abstract). Nippon Kyobu Rinsho (Jpn J Chest Dis) 51:659–663
7. Hahnel R, Martin JD, Masters AM, Ratajczak T, Twaddle E (1979) Estrogen receptors and blood hormone levels in cervical carcinoma and other gynecologic tumors. Gynecol Oncol 8: 226–233
8. Sato Y, Tanaka K, Arakawa O, Ohono M, Hirohashi T, Obata N, Takeuchi M (1988) Medroxyprogesterone therapy to a experimental uterine sarcoma (in Japanese). Gan no Rinsho (Jpn J Cancer Clin) 34:1979–1984

9. Linda T, John KT, William JM, Chumas JC, Amalfitano TG, Wallach RC (1986) Endocrine aspects of human uterine sarcoma: A preliminary study. Am J Obstet Gynecol 155:95–101
10. Pellillo D (1968) Proliferative stromatosis of the uterus with pulmonary metastases. Remission following treatment with a long-acting synthetic progestin: A case report. Obstet Gynecol 31:33–39
11. Hart WR, Billman JK Jr (1978) A reassessment of uterine neoplasms originally diagnosed as leiomyosarcomas. Cancer 41: 1902–1910