CASE REPORT

Successful control of recurrent angiosarcoma in the external auditory canal with CyberKnife radiosurgery and bisphosphonate risedronate sodium

Eimei Iwama, Taku Fujimura*, Akira Hashimoto, Yukikazu Numata, Takahiro Haga, Setsuya Aiba

Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan

A R T I C L E   I N F O

Article history:
Received: Sep 2, 2014
Revised: Nov 28, 2014
Accepted: Dec 15, 2014

Keywords:
angiosarcoma
bisphosphonate
CyberKnife
stereotactic radiotherapy

A B S T R A C T

Angiosarcoma (AS) is a highly aggressive vascular tumor that spreads widely throughout the skin. Since AS tends to recur locally and metastasize early, an additional intensive therapy is necessary. In this report, we describe an 83-year-old man with recurrent AS that metastasized to the right external auditory meatus, who achieved complete remission with CyberKnife and weekly administration of bisphosphonate risedronate sodium. Results of the present study might suggest the novel possibility of using CyberKnife with weekly administration of bisphosphonate risedronate sodium for the treatment of inoperable metastatic AS.

Introduction

Angiosarcoma (AS) is a highly aggressive type of vascular tumor that spreads widely throughout the skin, recurring locally and metastasizing early.1 Standard treatment with resection and adjuvant radiotherapy results in local control in approximately 50% of patients at 1 year and a median survival of approximately 8 months.1,2 Therefore, further intensive therapy is necessary for the treatment of AS. We previously reported that immunosuppressive cells, such as tumor-associated macrophages and regulatory T cells, were dominant in the lesional skin of AS and that tumor-associated macrophages might be one of the substantial targets for supportive therapy when used with bisphosphonate (BP) risedronate sodium for AS.3,4 In this report, we describe a case of recurrent AS that metastasized to the right external auditory meatus, which was successfully treated with CyberKnife and weekly administration of BP risedronate sodium.

Case Report

An 83-year-old man consulted us with a symptomatic red nodule on his scalp. On his initial visit, physical examination revealed a red, easy-to-bleed, dome-shaped nodule, 30 mm in diameter, on his forehead (Figure 1A). Histologically, irregular anastomosing vascular channels lined by single layers of enlarged endothelial cells existed between collagen bundles, with dense infiltration of lymphocytes (Figure 1B). Immunohistochemical staining revealed that these enlarged endothelial-like cells were strongly positive for CD31 and MMP-9 (Figure 1C), and negative for CD34, AE1/AE3, and Factor VIII. From the above findings, we diagnosed this case as MMP-9 expressing cutaneous AS. We resected the tumor with a 1 cm surgical margin. After surgical treatment, we administered radiation therapy (60 Gy in 30 fractions) to the scalp. Then, we administered paclitaxel monthly at 80 mg/m² intravenously. After 3 months of using paclitaxel, we stopped the administration because of arrhythmia. One year later, purpura was extended around the engrafted skin, which histologically revealed...
We then administered radiation therapy (60 Gy in 30 fractions) at the site of purpura. Seven months after the additional radiotherapy, an easy-to-bleed red nodule developed on the right external auditory meatus (Figure 2A), which histologically revealed AS. Since the standard surgical therapy would be impractical, we employed a CyberKnife and administered 17.5 mg sodium risedronate hydrate weekly, as we previously reported.5 The lesion was irradiated with 40 Gy in eight fractions. One month after the irradiation, the tumor mass regressed completely (Figure 2B). No severe side effect such as radiation dermatitis was observed at the site of the irradiated lesion. We monitored local recurrences of AS by regular physical examination (no purpura and no dermal nodule) for the skin lesion, by magnetic resonance imaging for the external auditory canal (every 3 months), and by positron emission tomography for the systemic metastasis (every ½ years). No sign of local recurrence or systemic lesions was observed for 1 year.

**Discussion**

In this report, we describe a case of recurrent AS that metastasized to the right external auditory meatus, which was treated successfully with CyberKnife and weekly administration of BP risedronate sodium. AS is a highly aggressive type of vascular tumor, and it is difficult for dermatologists to control AS systemically, or even locally, with standard treatment such as surgical resection or radiation.1–3 Recently, Fujisawa et al7 reported that chemoradiotherapy with taxane was superior to conventional surgery and radiotherapy, which suggested the necessity of systemic therapy to control AS after local treatment, such as radiotherapy and surgical treatment.

As we previously reported, CyberKnife is useful to treat various cutaneous malignancies such as Merkel cell carcinoma, dermatofibrosarcoma protuberance, and metastatic porocarcinoma, even in inoperable cases.8,9,16 CyberKnife delivers extracranial stereotactic radiotherapy with millimetric precision, leading to disease control and toxicity profiles that are equal to or better than those of other available therapies.10 Although areas irradiated using conventional radiotherapy show local recurrence, in the present case, AS could be controlled for 1 year using CyberKnife, even the remote metastatic lesions. Our present case suggested that CyberKnife is one of the optimal tools for the local control of AS.

The use of BPs in malignancy has been increasing.11–13 A previous in vitro study revealed that the antitumor effect of BPs for breast cancer cells was equal or even superior to that of docetaxel.13 In addition, as we previously reported, BPs modified the production of chemokines from M2 macrophages, which might modulate the tumor microenvironment optimally in the lesional skin of AS.7 Moreover, another report also suggested the pharmacological inhibition of MMP-9 by aminobisphosphonate, which leads to the induction of antitumor immune responses by the abrogation of immunosuppressive macrophages.14 MMP-9 is a stromal factor that remodels the extracellular matrix, and promotes sprouting and growth of new blood vessels by producing vascular endothelial growth factor.15 Notably, as we previously reported, about 80% of AS cases in our institute expressed MMP-9,6 and all cases of AS that clinically responded to BP expressed MMP-9.6 In aggregate, these reports suggested that BP could be one of the optimal supportive therapies to inhibit remote metastasis of AS and tumor-induced angiogenesis by its immunomodulatory effects.

In the present case, there was no sign of local recurrence or systemic lesions for 1 year after the CyberKnife therapy in combination with weekly administration of BPs. Our present study might suggest the novel possibility of using CyberKnife with weekly administration of BPs for the treatment of inoperable metastatic AS.

![Figure 1](A) A red, easy-to-bleed, dome-shaped nodule, 30 mm in diameter, on the forehead. (B) Irregular anastomosing vascular channels lined by single layers of enlarged endothelial cells existing between collagen bundles, with dense infiltration of lymphocytes. (C) Paraffin-embedded tissue sample was deparaffinized and stained with anti-MMP-9Ab. Section was developed with 3,3'-diaminobenzidine tetrahydrochloride. (Original magnification of 200× in parts B and C.)

recurrent AS. Then, we administered radiation therapy (60 Gy in 30 fractions) at the site of purpura. Seven months after the additional radiotherapy, an easy-to-bleed red nodule developed on the right external auditory meatus (Figure 2A), which histologically revealed AS. Since the standard surgical therapy would be impractical, we employed a CyberKnife and administered 17.5 mg sodium risedronate hydrate weekly, as we previously reported.5 The lesion was irradiated with 40 Gy in eight fractions. One month after the irradiation, the tumor mass regressed completely (Figure 2B). No severe side effect such as radiation dermatitis was observed at the site of the irradiated lesion. We monitored local recurrences of AS by regular physical examination (no purpura and no dermal nodule) for the skin lesion, by magnetic resonance imaging for the external auditory canal (every 3 months), and by positron emission tomography for the systemic metastasis (every ½ years). No sign of local recurrence or systemic lesions was observed for 1 year.

**Discussion**

In this report, we describe a case of recurrent AS that metastasized to the right external auditory meatus, which was treated successfully with CyberKnife and weekly administration of BP risedronate sodium. AS is a highly aggressive type of vascular tumor, and it is difficult for dermatologists to control AS systemically, or even locally, with standard treatment such as surgical resection or radiation.1–3 Recently, Fujisawa et al7 reported that chemoradiotherapy with taxane was superior to conventional surgery and radiotherapy, which suggested the necessity of systemic therapy to control AS after local treatment, such as radiotherapy and surgical treatment.

As we previously reported, CyberKnife is useful to treat various cutaneous malignancies such as Merkel cell carcinoma, dermatofibrosarcoma protuberance, and metastatic porocarcinoma, even in inoperable cases.8,9,16 CyberKnife delivers extracranial stereotactic radiotherapy with millimetric precision, leading to disease control and toxicity profiles that are equal to or better than those of other available therapies.10 Although areas irradiated using conventional radiotherapy show local recurrence, in the present case, AS could be controlled for 1 year using CyberKnife, even the remote metastatic lesions. Our present case suggested that CyberKnife is one of the optimal tools for the local control of AS.

The use of BPs in malignancy has been increasing.11–13 A previous in vitro study revealed that the antitumor effect of BPs for breast cancer cells was equal or even superior to that of docetaxel.13 In addition, as we previously reported, BPs modified the production of chemokines from M2 macrophages, which might modulate the tumor microenvironment optimally in the lesional skin of AS.7 Moreover, another report also suggested the pharmacological inhibition of MMP-9 by aminobisphosphonate, which leads to the induction of antitumor immune responses by the abrogation of immunosuppressive macrophages.14 MMP-9 is a stromal factor that remodels the extracellular matrix, and promotes sprouting and growth of new blood vessels by producing vascular endothelial growth factor.15 Notably, as we previously reported, about 80% of AS cases in our institute expressed MMP-9,6 and all cases of AS that clinically responded to BP expressed MMP-9.6 In aggregate, these reports suggested that BP could be one of the optimal supportive therapies to inhibit remote metastasis of AS and tumor-induced angiogenesis by its immunomodulatory effects.

In the present case, there was no sign of local recurrence or systemic lesions for 1 year after the CyberKnife therapy in combination with weekly administration of BPs. Our present study might suggest the novel possibility of using CyberKnife with weekly administration of BPs for the treatment of inoperable metastatic AS.
References