CASE REPORT

Multiple metastasized extramammary Paget's disease cured with bisphosphonate risedronate sodium after CyberKnife radiosurgery and docetaxel chemotherapy

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ABSTRACT

Invasive extramammary Paget's disease (EMPD) is highly metastatic to lymph nodes and other organs, including bone, and when metastatic lesions have expanded beyond the inguinal lymph node, it is difficult to cure. In this report, we present a case of multiple metastasized, receptor activator of nuclear factor kappa-B ligand-expressing EMPD in the pelvic lymph nodes successfully cured with continuous administration of bisphosphonate risedronate sodium after intensive CyberKnife radiotherapy and docetaxel monochemo therapy. Our present case suggested the usefulness of bisphosphonates as a maintenance therapy for metastatic invasive EMPD after the intensive chemoradiotherapy.

Introduction

Extramammary Paget's disease (EMPD) is a skin adenocarcinoma that mainly occurs in the anogenital region. Once Paget's cells infiltrate into the dermis, EMPD is highly metastatic to lymph nodes and other organs, including bone. Meanwhile, the use of bisphosphonates (BPs) in receptor activator of nuclear factor kappa-B ligand (RANKL)-expressing apocrine-origin tumor (e.g., breast cancer, prostate cancer) has been increasing. As we have previously reported, Paget cells in EMPD strongly express RANKL, which stimulates tumor-associated macrophages (TAMs) to recruit regulatory T cells (Tregs) in the lesional skin of EMPD. These reports suggested that TAMs could be a therapeutic target for the treatment of EMPD. In this report, we present a case of multiple metastasized EMPD in the pelvic lymph nodes successfully cured with continuous administration of BP risedronate sodium after intensive CyberKnife radiotherapy and docetaxel (DTX) monotherapy.

Case Report

A 53-year-old man presented to our institution with a 6-month history of painful erythema on his scrotum. On his initial visit, physical examination revealed a red, easy-to-bleed plaque with necrotic tissue from the right inguinal region (Figure 1A) to the perianal region. The skin biopsy revealed rounded cells that were devoid of intracellular bridges and large nucleus, from the epidermis to the superficial dermis of EMPD. From the above findings, we diagnosed this case as RANKL -expressing, invasive EMPD. We screened for a possible internal malignancy with positron emission tomography–computed tomography (PET–CT), which revealed significant

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enlargement of the right inguinal lymph nodes. We resected the tumor with a 3-cm surgical margin together with bilateral ingrown lymph node dissection. Then, we used immunohistochemical staining of RANKL (Figure 1D), MMP7 (Figure 1E), and CD163 (Figure 1F) for metastatic lymph node, which revealed that Paget's cells in the metastatic lymph nodes also expressed RANKL and MMP7, and were surrounded by CD163⁺ TAMs such as skin lesions. Additional radiotherapy after the surgical treatment was performed on the pelvic and bilateral inguinal region with a total dose of 60 Gy. Two years after the tumor excision, PET–CT revealed significant enlargement of the multiple pelvic lymph nodes around the inferior vena cava (Figure 2A). As the lesion adhered to the inferior vena cava and standard surgical therapy would be impractical, we used a CyberKnife. The lesion of the pelvic lymph node was irradiated with 50 Gy in 10 fractions. One month after the irradiation, the tumor mass had completely regressed (Figure 2B). Then, we administered DTX monthly at 40 mg/m² body surface area intravenously eight times, and oral administration of 17.5 mg sodium risedronate hydrate weekly for 5 years with the patient's informed consent. Five years after the CyberKnife treatment, there was no evidence of further metastasis.

Discussion

In this report, we present a case of multiple metastasized EMPD in the pelvic lymph nodes successfully cured with continuous administration of BPs risedronate sodium after intensive CyberKnife radiotherapy and DTX monochemotherapy.

As a previous report suggested, invasive EMPD is highly metastatic to lymph nodes (47%), and when metastatic lesions expand beyond the inguinal lymph node and have metastasized systematically, it is difficult to cure.1 For treatment, although radiotherapy is useful for local control of noninvasive EMPD,2,3 it is difficult to irradiate at the appropriate therapeutic dose of radiation by conventional radiotherapy for lymph nodes adhering to vital organs. Based on the above findings, and because CyberKnife is useful to treat various inoperable, metastatic cancers with minimal side effects,4–11 we selected CyberKnife for the local control of metastatic EMPD.

Like other apocrine-origin cancer such as breast cancer, Paget cells express RANKL and MMP7 in the lesional skin of EMPD.1 To induce the immunological effects on other cells, such as TAMs around the tumor cells, membrane-bound RANKL should be
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