CASE REPORT

Metastatic extramammary Paget's disease responding to weekly paclitaxel

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SUMMARY

Metastatic extramammary Paget's disease (EMPD) is a rare cancer with no validated systemic treatment. Regimens including FECOM 5-fluorouracil (5-FU, epirubicin, carboplatin, vincristine and mitomycin C), 5-FU/cisplatin and single agent docetaxel exhibited varying levels of efficacy in case reports. A 58-year-old man with EMPD diffusely metastatic to bone presented with worsening shortness of breath, significant pancytopenia and disseminated intravascular coagulation (DIC). He was started on low-dose heparin for the DIC and weekly paclitaxel. Initially requiring almost daily transfusions, his shortness of breath improved after two doses of paclitaxel, and he became transfusion-independent after only three doses. Correlating with his disease course, the patient's prepaclitaxel carcinoembryonic antigen level of 62.1 ng/mL decreased to 7.4 ng/mL on 3-month follow-up, and he showed no progression of disease on imaging. With no validated chemotherapy regimen currently, this case can help guide consideration of paclitaxel in future treatment of metastatic EMPD.

not respond to typical therapy, then one should begin suspecting less common differential diagnoses and pursue punch biopsy. Poor prognostic factors include depth of invasion, presence of lymphovascular invasion, negative E-cadherin expression and regional lymph node metastasis at diagnosis.⁵ Carcinoembryonic antigen (CEA) levels can be used to help parallel disease course and correlate with tumour progression in patients with significantly elevated CEA at diagnosis.⁶

Mohs microscopic surgery remains the treatment of choice for operable tumours with reported lower recurrence rates compared to wide excision, and radiotherapy can be utilised for large or inoperable tumours, in older patients with other comorbidities, or for postoperative recurrences.⁷ However, currently, no validated systemic therapy exists for metastatic EMPD, so more awareness of the recognition and diagnosis as well as potential treatment options may benefit future patients. We report a case of a 58-year-old man with metastatic EMPD with diffuse bone metastases and bone marrow involvement responding to weekly paclitaxel.

BACKGROUND

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma outside of the mammary gland. It typically arises in areas rich in apocrine sweat glands, most commonly the vulva, followed by perianal skin, scrotum, perineum and axilla. EMPD has been reported most frequently in the Caucasian population with a European age standardised incidence of 0.6/100 000 person years¹ and a female predominance (male-to-female ratios ranging from 1:2 to 1:7), but studies of different Asian populations in Japan, Korea and China show a male predominance (between 2:1 and 4:1).²

The average age of diagnosis of EMPD occurs from ages 64 to 72 years, and EMPD can present along a wide clinical spectrum ranging from burning paraesthesias, oozing erosions, or eczema-like papules to leukoplakia-like keratosis or changes in pigmentation. The pattern of metastasis of primary EMPD is typically by continuous, or lymphogenous and less often haematogenous spread.³ One study by Karam and Dorigo shows 2–5% of patients with EMPD present with distant disease, and there is a significant increase in rate of secondary colorectal and anal malignancies associated with the site of initial EMPD.⁴

Diagnosis of EMPD is often delayed for years due to its rarity and wide clinical spectrum, being mistaken for more common conditions such as eczema, psoriasis, mycosis, etc. If such a presentation does

CASE PRESENTATION

A 58-year-old Caucasian man with no significant medical history was initially diagnosed with perineal EMPD. He underwent Mohs surgery, and radiation to the perineum and scrotum, with subsequent remission of disease. One year later, he developed a T8 pathological compression fracture, and MRI showed diffuse osseous malignancies. Bone biopsy of the iliac crest was positive for metastatic adenocarcinoma with positive GCDFP15, KRT7 and weakly positive MGB, supporting diagnosis of metastatic EMPD. Bone marrow biopsy showed slightly hypercellular bone marrow with moderate panhypoplasia and extensive involvement by metastatic adenocarcinoma, likely related to bone marrow involvement by EMPD. One month following the biopsy, the patient began palliative radiation to the spine but soon developed worsening fatigue and shortness of breath with any exertion. Physical examination was significant for pallor and tachypnoea with desaturation on minimal exertion, requiring at least 2 L nasal cannula oxygen supplementation.

INVESTIGATIONS

The patient presented to the hospital and was found to have significant pancytopenia with haemoglobin of 8.0 g/dL, platelets of $12 \times 10^9/L$, and leucocytes of $3.1 \times 10^9/L$. Haematological work up proved consistent with disseminated intravascular coagulation (DIC) secondary to his malignancy with D-dimer of

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8845 ng/mL, fibrinogen 221 mg/dL, schistocytes on peripheral blood smear, mildly prolonged prothrombin time of 14.3 s, activated partial thromboplastin time of 85 s, factor II activity of 70% and factor VII activity of 57% on admission. His initial CEA level on presentation measured 62.1 ng/mL.

TREATMENT

The patient's fatigue and shortness of breath improved with transfusions of packed red blood cells (PRBCs) to a haemoglobin goal greater than 8.0 g/dL with his symptoms or greater than 7.0 g/dL if he was asymptomatic. He was also initiated on low-intensity heparin to prevent thrombosis in his hypercoagulable state with malignancy and DIC, and he received platelet transfusions for a goal above $20 \times 10^9/L$ to lower his risk of bleeding. To address the underlying cause of his DIC and pancytopenia, he was started on weekly doses of paclitaxel 80 mg/m²/week for metastatic EMPD 2 days after admission.

OUTCOME AND FOLLOW-UP

Initially requiring transfusions of PRBCs and platelets every other day, the frequency of required transfusions gradually decreased after starting paclitaxel until he became transfusion-independent after only three doses (table 1).

His transfusions on days 30 and 51 were for anaemia felt to be due more to paclitaxel toxicity rather than his prior pancytopenia. By his 3-month follow-up, the patient had no progression of disease on imaging, resolution of his pancytopenia and DIC, and improvement in his CEA level to 7.4 ng/mL. He also achieved pain control with additional palliative radiation of his spine, becoming well enough to undergo T8 vertebroplasty for his prior pathological compression fracture.

DISCUSSION

Case reports and case series primarily out of Asia reported several different chemotherapy regimens attempted for metastatic EMPD.

The frequently cited FECOM regimen 5-fluorouracil (5-FU, epirubicin, carboplatin, vincristine and mitomycin C) trialled on 7 patients in Japan resulted in median overall survival of 9.4 months and progression free survival of 6.5 months.⁸ Single agent docetaxel showed clinical response in two case reports. One case with metastatic disease used docetaxel with concurrent radiotherapy, and had disappearance of lung and vertebral metastases as well as improvement in functional ability.⁹ One case report with stage II EMPD utilised single agent docetaxel alone and resulted in no relapse within a 2-year follow-up period.¹⁰

Two case reports of human epidermal growth factor receptor 2 (HER2) positive metastatic EMPD utilised trastuzumab and paclitaxel. One of the cases was a 75-year-old man who developed metastatic disease within his central nervous system 6 months after starting therapy,¹¹ while the other case was a 70-year-old woman with vulvar EMPD who had regression after four courses.¹²

Cisplatin with 5-FU was studied in a case series of 22 patients and one case report with advanced EMPD. Within the case series, ten patients had a partial response while four had stable disease, and three patients had progressive disease. Median survival ranged from 5 to 51 months.¹³ The case report transitioned the patient from 5-FU/cisplatin to maintenance therapy on oral tegafur uracil for 16 months before the patient developed DIC and died from multiorgan failure within 2 months.¹⁴ One case report of metastatic EMPD used 5-FU, leucovorin and capecitabine, but the patient progressed on treatment and died within 6.2 months of initial presentation.¹⁵

An additional case report utilised oral tegafur, gimeracil and oteracil potassium (S-1) in an 81-year-old man with periaortic lymph node metastases.¹⁶ He had reduction in his CEA level and improvement in his symptoms of pain, erythema and oedema of his thigh related to his metastatic disease. The patient did well until 36 months after beginning S-1 therapy, when he developed further iliac and periaortic metastatic

Table 1 Timetable of transfusions and paclitaxel dosing

Days since initial hospital presentation	Haemoglobin (g/dL)	Platelets ($\times 10^9/L$)	Units PRBCs transfused	Units platelets transfused	Paclitaxel dose number
0 (Day of admission)	8.0	12	1	1	
2	7.6	7	1	1	1
3	8.8	15	–	1	
4	7.3	24	1	1	
5	9.1	20	–	1	
7	7.9	13	–	1	
9	7.4	22	1	1	2
13	7.7	13	1	1	
15	7.7	33	2	–	
16 (Day of discharge)	9.2	27	–	–	3
23	9.0	80	–	–	4
30	7.8	122	2	–	5
37	9.0	113	–	–	6
44	9.1	175	–	–	7
51	7.9	182	2	–	8
58	9.6	170	–	–	9
65	9.2	193	–	–	10
72	8.4	201	–	–	11
79	8.6	200	–	–	12
86	8.4	183	–	–	13
93	9.1	225	–	–	14

PRBCs, packed red blood cells

disease as well as hydronephrosis, at which time the S-1 therapy was discontinued.

Single agent paclitaxel for metastatic EMPD has not yet been reported in the literature, and only two studies use it in conjunction with trastuzumab in HER2 positive disease, with mixed results.^{11 12} Paclitaxel has a significantly lower side effect profile compared to the other reported regimens such as FECOM⁸ or 5-FU/cisplatin. Paclitaxel for this particular patient in the setting of his pancytopenia offers a lower risk of myelotoxicity compared to docetaxel utilised previously in the two cases.^{9 10} This patient appears transfusion-independent by his third dose of paclitaxel (table 1), and his last two transfusions of PRBCs for mild anaemia on days 30 and 51 seem more due to paclitaxel toxicity rather than his prior pancytopenia. He remains completely transfusion-independent since his eighth dose of paclitaxel, with stable disease at 3-month follow-up.

Metastatic EMPD remains a very rarely encountered disease with little research into the management of this condition. This more simplistic regimen of weekly paclitaxel can hopefully achieve at least comparable results with lower toxicity in both HER2 positive or negative disease. With no current validated chemotherapy regimen, this case can help guide consideration of paclitaxel in future studies and treatment of metastatic EMPD.

Learning points

- ▶ Extramammary Paget's disease is often misdiagnosed as other more common dermatological conditions such as eczema or psoriasis on initial presentation.
- ▶ Consider punch biopsy when dermatologic conditions do not respond to standard treatment, as it may be something more insidious and malignant.
- ▶ A chemotherapy regimen of single agent paclitaxel should be considered in future treatment of metastatic extramammary Paget's disease given its better tolerability and lower myelotoxicity.

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