Extramammary Paget disease (EMPD) is a rare cutaneous malignancy. The most common presentation of EMPD is the vulva followed by perianal involvement. Most cases are localized to the dermis with treatment focused on surgery, topical treatment or radiotherapy. Recurrence is frequent despite therapies utilized. Metastatic extramammary Paget disease is uncommon and, as such, standard treatment guidelines do not exist. This study sought to evaluate the treatment regimens and outcomes of patients treated at a Mayo Clinic Center from 1998-2012. Cancer registry inquiry revealed 261 patients with report advanced Paget disease during these years. Ten cases of metastatic EPMD were identified with sufficient documentation for review. This review reveals support for utilizing localized radiation therapy for bulky disease sequentially with systemic chemotherapy consisting of carboplatin and paclitaxel or irinotecan. Further studies are necessary to define the optimal treatment regimen.

Abstract

Extramammary Paget disease (EMPD) is a rare cutaneous malignancy. EMPD is believed to arise from epidermal structures containing apocrine glands. It can develop as an intraepithelial neoplasm or it can be associated with an underlying carcinoma with local or distant intraepithelial spread. In one review of 197 cases of localized EMPD, 46 patients were found to have concurrent cutaneous adnexal carcinoma. Adnexal carcinomas are malignancies arising from one of the four primary adnexal structures present in normal skin tissue including hair follicles, sebaceous glands, apocrine glands and eccrine glands. This review contained 153 patients with adequate information for further evaluation, of these cases 18 (12%) had concurrent internal malignancy while 109 (71%) had no associated malignancy. This distinction in clinical presentation, and prognosis, has led some to characterize EMPD as either a primary intraepithelial neoplasm without an underlying carcinoma, or a secondary manifestation of intraepithelial spreading of an associated malignancy.

Paget disease of the breast is frequently associated with an underlying breast cancer. This was demonstrated by a review of the Surveillance, Epidemiology, and End Results Program from 1988-2002 revealing 86% (1477/1704) of Paget disease diagnoses were associated with infiltrating ductal carcinoma or ductal carcinoma in situ. However, most EMPD is not associated with an underlying malignancy. For example, in penile EMPD, synchronous internal malignancy is rare, with one study of 38 patients indicating 0% (0/38) cases associated with an underlying malignancy, and another study revealing 9% (3/33 cases) of penile EMPD associated with an underlying malignancy.

One review of 196 cases from 1962-1982 revealed 12% of cases were associated with a concurrent underlying internal malignancy. A review of invasive EMPD cases in the Netherland Cancer Registry from years 1989-2001 noted 32% of cases were associated with an underlying internal malignancy, diagnosed either before or after the EMPD diagnosis. In the Siesling review, the 5-year survival for patients with invasive EMPD was 72% and the presence of an associated underlying malignancy portended a worse prognosis. The most common presentation of EMPD is the vulva followed by perianal involvement. EMPD is rare representing approximately 13% of Paget disease. Most cases are localized to the dermis with treatment focused locally with surgery, topical treatment or radiotherapy. Recurrence is frequent despite therapies utilized. Metastatic EMPD is a rare presentation of an uncommon cutaneous malignancy, which has contributed to difficulty establishing standard systemic therapies. Most therapies are based on case reports of successful chemotherapy treatments. We sought to describe the clinical experience of metastatic EMPD as experienced at the Mayo Clinic Cancer Center from 1998-2012.

Results

The cancer registry inquiry revealed 261 patients with report advanced Paget disease to...
the Mayo Clinic Cancer Registry. Ten cases of metastatic EMPD were identified with documentation provided (Table 1). As some of these patients were seen only in consultation with treatment provided elsewhere, chemotherapy dosages and details were not elucidated in the record.

Prior Paget history

Our search revealed 5 confirmed cases of metastatic EMPD, and 5 probable cases. Of the five confirmed cases, three had a preceding history of localized Paget disease: 1 perianal and 2 groin locations. One of the patients with a preceding history of localized Paget was treated with surgical resection and radiation therapy, while the other two cases were treated initially with surgical resection alone. The remaining 2 cases were metastatic Paget at diagnosis, one with extensive pelvic and retroperitoneal lymphadenopathy and osseous involvement, the other with right inguinal lymphadenopathy at diagnosis.

Site of metastatic disease

Of the five confirmed cases, 4 cases of metastatic disease were identified in the inguinal lymph nodes, and 2 also had osseous involvement. Of the probable cases, 3 demonstrated sites of metastasis of the bone (1 pelvic and 2 vertebral body) while one had a presacral mass and another case had extensive abdominal wall involvement.

Immunohistochemical staining

The immunohistochemical staining of the confirmed cases was not consistent. One case demonstrated positivity for cytokeratin (CK) 7, CK20, CDX2 and villin, while another was CK7 and CK20 negative. The remaining 3 confirmed cases did not describe immunohistochemical staining, except for estrogen/progesterone receptor negative and human epidermal growth factor receptor 2/1 normal expression of 2 confirmed cases.

The probable cases were equally inconsistent. One probable case demonstrated CK7 positive and thyroid transcription factor-1 positive disease. Another case was only CK7 positive, negative for CD20. The remaining 3 probable cases did not have immunohistochemical staining reported.

Genomic analysis:

One patient had a whole exome sequencing performed. Five somatic mutations were detected in known cancer (CREBBP, FGFR1OOP, MLLT4, NST1 and THRA);F3), but none were actionable. In addition, multiple copy number variations were detected including in PIK3CA, CDKN2A, RB1, BRCa1, BRCa2, PALB2, CDH1, TP53 and MAP2K4, all of uncertain significance but possibly pathologic.

Treatment

As there is no established metastatic Paget disease treatment, the treatment plans for these patients were diverse. Patient 1 was treated with radiation therapy alone initially, with progression noted at 179 days on imaging with increased retroperitoneal and new liver lesions. The second line therapy for this patient was systemic chemotherapy with carboplatin and paclitaxel. No further imaging or office visits were conducted after initiation of second line chemotherapy. Last follow up was 36 days after initiation of systemic chemotherapy.

Patient 2 was treated with surgical resection via a lymph node dissection and no systemic therapy was provided. He was lost to follow up with the last date of contact only 55 days after treatment, and died 532 days from diagnosis.

Patient 3 was found to have metastatic Paget disease to the cutaneous tissue of the right buttock, anal region, bilateral inguinal left pelvic and retroperitoneal lymph nodes, and osseous involvement of the cervical and thoracic spine. He received radiation therapy to the cervical and thoracic spine. He then began treatment with systemic chemotherapy, consisting of 5-FU and cisplatin for 5 cycles. After the first cycle patient reported resolution of left inguinal lymphadenopathy and improved left lower extremity edema. Mixed response was noted on imaging with improvement noted in left axilla, spinal involvement and retroperitoneum but progression noted pulmonary nodule development, right hilar lymphadenopathy, left femur metastasis, and right pelvic adenopathy, 274 days since diagnosis. He was then transitioned to irinotecan therapy for an additional 5 months with imaging revealing increased pulmonary nodule size and number, mediastinal adenopathy and liver lesions. His performance status precluded him from further systemic treatment. Patient passed away 260 days after starting his 2nd line therapy, and 589 days since his metastatic diagnosis.

Patient 4 was found to have metastatic EMPD to the right pelvic lymph nodes, treated with pelvic radiation with progression of new osseous metastasis noted on imaging 316 days after therapy. He was transitioned to weekly docetaxel. Chemotherapy revealed mixed response with improved pulmonary nodules and lymphadenopathy but increased osseous disease, 162 days after chemotherapy initiation. However, clinically the patient was fatigued and treatment was discontinued. Progression was noted 102 days after discontinuation of chemotherapy, with recurrent lung disease and lymphadenopathy. Patient passed away 703 days after diagnosis.

Patient 5 had metastatic EMPD to pelvic lymph nodes and osseous structures. His first treatment was radiation therapy. Progression was noted by imaging revealing new liver lesions and pulmonary nodules 44 days after radiation started. He was transitioned to weekly carboplatin and paclitaxel. Hematologic toxicity required dose reduction and delay of therapy. Imaging 58 days after initiating systemic chemotherapy revealed substantial response for liver lesions and stability of pulmonary nodules. However, patient was reporting fatigue and poor appetite. Chemotherapy was held for 1 month, with imaging 22 days after last infusion of chemotherapy demonstrating extensive osseous involvement. The patient could not tolerate further systemic therapy. Patient passed away 29 days after therapy was discontinues and a total of 204 days after metastatic diagnosis. The first probable case, Patient 6, with metastatic adenocarcinoma of unknown primary of the pelvic bones with a history of Paget disease of the scrotum, was treated with radiation therapy with pain improvement. No imaging was performed to assess radiographic response. It was recommended after radiation for systemic chemotherapy to be provided with cisplatin and paclitaxel, unfortunately Patient 6 passed away 31 days after diagnosis.

Probable case, Patient 7, with history of scrotal Paget 2 years prior to development of metastatic adenocarcinoma of unknown primary to the axial and appendicular skeleton. Patient 7 was treated with paclitaxel and carboplatin initiated 7 days after diagnosis with mixed imaging results after 151 days. He had symptomatic improvement in bone pain, but unfortunately developed neuropathy after 7 cycles and treatment was changed to carboplatin and gemcitabine. Sixty-four days after treatment change, bone pain symptoms returned and imaging revealed progressive diffuse lymphadenopathy. He was then transitioned to palliative care and passed away 37 days later, 322 days since his diagnosis.

Patient 8, a probable case, with presacral mass without tissue pathology was treated with concurrent 5-FU chemoradiation with imaging revealing progressive disease. Patient transitioned therapy to weekly irinotecan with a reported radiographic response. Patient was lost to follow up, 196 days since his diagnosis.

Patient 9, a probable case with abdominal wall and inguinal lymph node metastatic adenocarcinoma with a history of vulva Paget disease 3 years prior, was treated surgical resection and 6 cycles of paclitaxel and carboplatin with stability noted on imaging. Three months after chemotherapy was completed imaging revealed hepatic metastases and she was restarted on carboplatin and paclitaxel. Imaging revealed worsening liver metastases 99 days after restarting therapy, and 405 days after initial therapy. Subsequent therapy is unknown. Patient passed away 814 days after diagnosis.
Therapy outcomes
For the patient with surgical resection as treatment overall survival was 104 days, due to loss of follow-up.

Six patients treated with radiation (case 1, 3, 4, 5, 6 and 8) experienced mean progression free survival (PFS) from radiation therapy ranging of 177.6 days (range 44-316 days).

Five of the patients treated with chemotherapy were treated with a regimen of carboplatin and paclitaxel (case 1, 5, 7, 9 and 10) with progression free survival of 167.4 days (range 76-306 days). Three patients treated with carboplatin and paclitaxel required transition to a different regimen not due to progression but based on toxicities of treatment (case 10 and 7 for neuropathy and case 5 fatigue). One patient treated with 5-FU and cisplatin (case 3) experienced a PFS 262 days. Two patients were treated with irinotecan as second line therapy, with an average PFS of 175.5 days, (range 91-260 days). The median overall survival for the confirmed and probable cases was 406 days.

Discussion and Conclusions
We have described the Mayo Clinic experience with metastatic EMPD. EMPD is an exceedingly rare malignancy and little is known about the natural history and the optimal management of patients with advanced disease. The available literature mostly consists of small case series and case reports. Very little is known about genomic aberrations in EMPD. One of our patients had a whole exome sequencing performed on a biopsy of a metastatic inguinal node. Five potentially pathogenic mutations and multiple copy number variations involving multiple genes were observed, none of which were actionable.

Surgery is the recommended therapy for surgically resectable and localized disease. In a review of 197 of localized EMPD, 174 underwent surgery with 44 local recurrences. The role of radiation therapy following resection is uncertain but should be considered for those patients with close or positive resection margins or bulky disease.

Chemotherapy has been recommended for locally advanced and metastatic disease but the optimal regimen for metastatic EMPD remains to be defined. One case report of a 60-year-old man with metastatic EMPD to inguinal, pelvic and retroperitoneal lymph nodes had persistent disease despite radiation therapy. He was treated with systemic chemotherapy with mitomycin C every 8 weeks and 5-fluorouracil continuous infusion for 96 hours every 4 weeks. Imaging after 1 cycle of chemotherapy reportedly revealed complete normalization of lymphadenopathy. He remained on this regimen but recurred with liver and pulmonary metastases approximately 5 months later. He refused further treatment and died two months after recurrence was noted. The treatment was based on a case report by Secco that utilized radiation and chemotherapy with 5-fluorouracil and mitomycin C that produced complete and prolonged remission.

Another case report of a 70-year-old female with vulvar and metastatic Paget disease to the lymph nodes of the para-aortic region was associated with elevated carcinoembryonic antigen (CEA) was treated with mitomycin C 10 mg/mg², cisplatin 15 mg/m² and vincristine 1 mg/m². After 2 cycles of chemotherapy vulvar lesions and elevated CEA level both decreased. She subsequently underwent vulvectomy due to persistent pruritus. It is reported that she continued 5-fluorouracil administration and immunotherapy with agent OK-432. Five months after surgery, skin lesions reappeared and her CEA elevated. Similar chemotherapy was started and CEA decreased but skin lesions progressed and she died 10 months after diagnosis.

The analysis revealed half of patients were treated with radiation, with an average PFS of 177 days. Of the 9 patients treated with a sys-

Table 1. Clinical and treatment characteristics for confirmed and probable cases of metastatic extramammary Paget disease.

| Group | Age at dx | Sex | Sites of mets | 1st line chemo | Response yes/no | 2nd line chemo | Response yes/no | Radiation therapy yes/no | OS from dx of mets |
|-------|-----------|-----|--------------|----------------|----------------|----------------|----------------|-------------------------|--------------------|
|       |           |     |              |                |                |                |                |                         |                    |
| 1     | 72        | F   | Inguinal lymph nodes | Carboplatin      | N              | N              | NA             | Y                       | 363                |
| 2     | 68        | M   | Inguinal lymph nodes | N               | NA             | N              | NA             | N                       | 332                |
| 3     | 64        | M   | Right gluteal muscle, inguinal and retroperitoneal lymph nodes, and bone | 5-fluorouracil/ Cisplatin | Mixed response | Irinotecan | N               | Y                       | 589                |
| 4     | 61        | M   | Inguinal lymph nodes | Docetaxel        | Y              | N              | NA             | Y                       | 703                |
| 5     | 88        | M   | Pelvic side wall, inguinal lymph node, bone | Carboplatin      | Y              | N              | NA             | Y                       | 204                |
| 6     | 79        | M   | Bone            | N               | NA             | N              | NA             | Y                       | 31                 |
| 7     | 72        | M   | Bone            | Carboplatin      | Mixed          | Carboplatin Gencitabine | N          | N                       | 322                |
| 8     | 63        | F   | Presacral mass  | 5-Fluorouracil   | N              | Irinotecan     | Y              | Y                       | 196                |
| 9     | 74        | F   | Abdominal wall, inguinal lymph node | Carboplatin      | Y              | N              | NA             | N                       | 814                |
| 10    | 72        | M   | Bone, mediastinal lymph node | Carboplatin      | Mixed          | Carboplatin Gencitabine | N          | N                       | 314                |

Dx, diagnosis; Mets, metastasis; NA, not available; OS, overall survivor.
temic chemotherapy regimen, five were treated with carboplatin and paclitaxel with a PFS of 167 days. This is the most prevalent regimen utilized in this series of patients. Second line therapy of irinotecan proved effective with an average PFS of 175.5 days. It is unclear if this PFS would be seen in irinotecan treatment in the first line setting, as more studies would need to be performed.

Immunohistochemical staining for EMPD includes positive stain by periodic acid-Schiff and aldehyde fuchsin as well as glandular formation or intracellular secretory structure support.\(^\text{14}\) In the Yokoyama case report, immunohistochemical staining included AS staining, Alcian blue and mucicarmine-positive.

Metastatic EMPD is uncommon and, as such, standard treatment guidelines do not exist. This review reveals support for utilizing localized radiation therapy for bulky disease in concert with systemic chemotherapy consisting of carboplatin and paclitaxel or irinotecan. Molecular studies on EMPD may eventually lead to better treatment options but to this date, no good targets are known and the systemic therapy is therefore primarily cytotoxic and nonspecific. Further studies are necessary to define the optimal treatment regimen. Given the rarity of EMPD, prospective studies will unlikely be successful.

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