Clinical Science

Staged marginal contoured and central excision technique in the surgical management of perianal Paget’s disease

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KEYWORDS:
Extramammary Paget’s disease; Perineal; Marginal contoured excision; Surgical management; Clear margins

Abstract

BACKGROUND: Extramammary Paget’s disease (EMPD) is an adenocarcinoma of the apocrine glands with unknown exact prevalence and obscure etiology. It has been divided into primary EMPD and secondary EMPD, in which an internal malignancy is usually associated. Treatment for primary EMPD usually consists of wide lesion excision with negative margins. Multiple methods have been proposed to obtain free-margin status of the disease. These include visible border lesion excision, punch biopsies, and micrographic and frozen-section surgery, with different results but still high recurrence rates.

METHODS: The investigators propose a method consisting of a staged contoured marginal excision using “en face” permanent pathologic analysis preceding the steps of central excision of the lesion and the final reconstruction of the surgical defect.

RESULTS: Advantages of this method include adequate margin control allowing final reconstruction and tissue preservation, while minimizing patient discomfort.

CONCLUSIONS: The staged contoured marginal and central excision technique offers a new alternative to the armamentarium for surgical oncologists for the management of EMPD in which margin control is imperative for control of recurrence rates.

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Extramammary Paget’s disease (EMPD) is a rare skin disease consisting of adenocarcinoma of the apocrine glands, with slow progression and obscure etiology. EMPD is considered a heterogeneous condition that comprises 2 different classifications. Primary EMPD is a neoplasm thought to originate in the Paget’s cells of the epidermis in the sweat glands. Secondary EMPD originates from epidermotropic spread of malignant cells from an underlying carcinoma. The most frequent carcinomas include those of the adnexal organs, genitourinary area, and gastrointestinal tract. Still, associated neoplasms are found in only 25% of patients with EMPD.1,2

The precise etiology of EMPD has not been completely elucidated. Cell origin remains controversial. Although immunohistochemical staining shows the epithelial glandular nature of these cells, a precise origin remains unclear for
primary EMPD. For EMPD associated with malignancy, an oncogenic stimulus has been suspected, but there is no conclusive evidence.

**Epidemiology**

Because EMPD is considered a rare condition, its incidence and prevalence are not known. The majority of papers published in the medical literature consist of retrospective studies or small case series. It has been reported that in breast cancer, the proportion of Paget’s disease is 0.7% to 4.3%.2 EMPD accounts for 6.5% of all cutaneous Paget’s disease and is more common among women. Generally, the tumor affects older patients, with an average age at diagnosis of 68 years.3,4

Because EMPD affects areas of the skin containing apocrine sweat glands, its location can vary widely. The most commonly affected site is the vulva. In one of the largest case series, the vulva was affected in 65% of cases, followed by the perianal region, penis, scrotum, or inguinal region.5 Perianal EMPD is uncommon, either with or without association with carcinoma of the anus or rectum. Only 180 cases have been described in the medical literature.6 The rate of concomitant malignancy in perianal EMPD ranges from 33% to 86%, the majority consisting of tubo-ovarian and colorectal cancers. When underlying invasive carcinoma is diagnosed, the prognosis is dismal.7

**Histology and progression of disease**

The most important aspect of the pathologic examination consists of the presence of Paget cells. These malignant cells are usually larger than keratinocytes, with enlarged, clear cytoplasm and large nuclei, located in the epidermis as solitary cells or in clusters (Pagetoid arrangement). These nests can displace basal keratinocytes. All layers of the epidermis can be affected.1

When the diagnosis is supported by immunohistochemical studies, attention must be paid to the presence of carcinomaembryonic antigen and cytokeratins such as CK7, PKK1, GR 53, and 35βH11. These antigens are present in Paget cells as well as apocrine and exocrine glands, which favors the hypothesis of the origin of these tumors.5 Recently, the presence of human epidermal growth factor receptor 2 was found in >30% of patients studied, with a possible implication on disease severity.9

Metastasis is usually characterized by contiguous spread followed by lymphatic drainage. The main sites of metastasis are ipsilateral or bilateral inguinal lymph nodes followed by para-aortic nodes and lungs. Secondary EMPD is an expression of intraepithelial metastasis of a primary tumor.3

**Clinical presentation**

Because EMPD consists of a slow-growing intraepidermal neoplasm, its clinical presentation is often insidious and nonspecific. For perianal EMPD, it presents as a rash in the affected region with itching and pain. Other rare presentations include bleeding, presence of a lump, or alterations in defecation.

Because of the relatively benign appearance of the lesions, they tend to progress over decades before proper medical evaluation. Usually, this condition is approached as a non-specific rash and treated initially with topical drugs, obtaining only partial relief of symptoms. Differential diagnoses are vast and include Bowen’s disease, Langerhans cell histiocytosis, malignant melanoma, squamous cell carcinoma, condyloma acuminatum, spread of rectal carcinoma, Crohn’s disease, hidradenitis suppurativa, mycosis fungoides, and Merkel cell carcinoma. It is usually after the persistence of symptoms that biopsy is solicited and diagnosis made.1,10

Lesions can vary in color from pink to dark red; larger lesions usually present with a variety of colors. Its surface may have a scale or oozing with crusts. There may also be patchy erosions or leukoplakia. More advanced lesions may be irregular with poorly defined borders. Given the centrifugal growth, there may be complete involvement of the anogenital region, leading to the formation of polygonal borders.11 Once the diagnosis is obtained, workup seeking a primary neoplasm is mandatory.

**Treatment**

Myriad treatment options have been proposed for EMPD in the perianal region. The mainstay of therapy for noninvasive disease remains the surgical wide excision of the lesion. Surgeons may face multiple challenges in these patients, such as the extent of the lesion, damage to structures related in the anogenital region, the morbidity they constitute by themselves, diminished quality of life, and high recurrence rates.

A staging classification for perianal Paget’s disease was proposed by Shutze and Gleysteen12 in 1990 (Table 1) showing the description of each stage and the recommended therapy. This classification can be used as a guideline, but it has not been validated in further studies, and its recommendations should be taken with caution. We propose a new staging and treatment classification for EMPD that includes more updated data on this disease as an update for the previous system proposed by Shutze and Gleysteen (Table 2).

It is clear that local control of the disease is the mainstay of therapy for perianal EMPD. The main variables to be evaluated are the extent of the tissue to be removed and the potential curability of the disease with this method.

Current reports in the literature for surgical management of EMPD reveal that surgical excisions (with 1-cm to 3-cm margins and 0.5 cm deep into subcutaneous fat) have a recurrence rate of 33% to 60% for patients with perianal disease and 18% to 50% for those with vulvar EMPD.13,14 Intraoperative biopsies are usually taken 1 cm from the visible lesion edges and are analyzed in the 4 quadrants, including...
the outer skin margins and, if necessary, the anal canal margins up to the dentate line. After the initial procedure, the wound is closed. If a positive margin is reported, the patient undergoes an additional operation for further excision.

The average recurrence rate if the 4 regions are affected is 35% to 44%. In a retrospective study, Hatta et al reported an 8% chance of local recurrence after performing wide excisions with 2-cm margins of the lesion. The presence of nodules in the primary tumor, elevated serum carcinoembryonic antigen levels, tumor invasion level, and lymph node metastasis were significant prognostic factors.

Because of no clear evidence regarding the extent of the free margins needed to clear the lesion and lower the recurrence rates, margin status gained interest. The extent of histologically demonstrable disease can be greater than the clinically visible lesion with limited use in multicentric disease. The use of intraoperative frozen sections revealed a rate of false-negative margins in 40% of the cases. Because frozen sections sample around 0.1% of the surgical margin, other techniques have been used for the margin clearance of the lesion. Mohs micrographic surgery (MMS) has been advocated for the treatment of patients with EMPD, with the goal of obtaining complete tumor-free margins and preserve unaffected tissue. O'Connor et al reported a recurrence rate of 8% after a follow-up period of 65 months. Other studies have found less favorable results, with a recurrence rate after treatment with MMS of 16% for primary EMPD and 50% for recurrent EMPD. The 5-year tumor-free rates were 80% for primary tumors and 56% for recurrent tumors. When using MMS, margins of 5 cm were required to clear 97% of the tumors. Other retrospective studies of the use of MMS in multiple skin malignancies have reported no recurrence after treatment for EMPD with MMS in 10 patients (9 primary and 1 recurrent). Average time to recurrence of EMPD is 2.5 years.

Another method for establishing margin control consists of scouting biopsies. First reported by Beck and Fazio as quadrant biopsies, multiple biopsies have been studied for its application before MMS or wide excision to suggest the subclinical extension of the tumor. A retrospective review of patients from the Mayo Clinic studied patients with EMPD who had multiple circumferential punch biopsies (5–30) before MMS. Four of the 5 patients who received this management had a true-positive result in clinically uninvolved area. The scouting biopsies give a better idea of the general extent of the disease to guide the initial Mohs layer. The drawbacks of this technique consist of an additional office visit for the biopsies, delay of operation, and additional cost. Scouting biopsies cannot be relied as the sole method to define tumor-free margin because of the false-negative results shown in 2 of the 5 patients in this series.

In an article by McCarter et al, the published Sloan-Kettering experience on long-term outcome of EMPD in the perianal region reported a local recurrence rate of 37% for wide lesion excision. Disease-free survival at 5 and 10 years was 64% and 39%, respectively.

### Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>I</td>
<td>Paget’s cells found in perianal epidermis and adnexa without primary carcinoma</td>
<td>Wide local excision</td>
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<tr>
<td>IIA</td>
<td>Cutaneous Paget’s disease with associated adnexal carcinoma</td>
<td>Wide local excision</td>
</tr>
<tr>
<td>IIB</td>
<td>Cutaneous Paget’s disease with associated anorectal carcinoma</td>
<td>abdominoperineal resection</td>
</tr>
<tr>
<td>III</td>
<td>Paget’s disease in which associated carcinoma has spread to regional nodes</td>
<td>Inguinal node dissection and abdominoperineal resection</td>
</tr>
<tr>
<td>IV</td>
<td>Paget’s disease with distant metastases of associated carcinoma</td>
<td>Chemotherapy, radiotherapy, local palliative management</td>
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### Table 2

<table>
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<tr>
<th>Stage</th>
<th>Description</th>
<th>Therapy</th>
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<tr>
<td>I</td>
<td>Epidermal/intradermal Paget’s cells found in perineal, scrotal, or vulvar area</td>
<td>WLE/MMS/TSE; if not amenable to resection or patient refusal of surgical treatment, consider 5% imiquimod</td>
</tr>
<tr>
<td>IIA</td>
<td>Epidermal/intradermal Paget’s disease with involvement of anal canal</td>
<td>WLE plus transanal resection</td>
</tr>
<tr>
<td>IIB</td>
<td>Epidermal/intradermal Paget’s with synchronous malignancies</td>
<td>Treat malignancy accordingly (eg, abdominoperineal resection for rectal malignancy)</td>
</tr>
<tr>
<td>III</td>
<td>Epidermal/intradermal Paget’s with node involvement (inguinal, iliac)</td>
<td>Chemotherapy</td>
</tr>
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<td>Chemotherapy, radiotherapy, local palliative management</td>
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MMS = Mohs micrographic surgery; TSE = traditional surgical excision; WLE = wide local excision.
After lesion excision, reconstruction is required in most patients because of the extent of the surgically removed tissue. For EMPD in the perianal region, attention must be paid to preserve anal sphincter function to avoid the necessity of protective colostomy. Some techniques previously used consist of a V-Y advancement flap or the use of gluteal or thigh flaps in cases with defects in the anal tract. These procedures are usually well tolerated with minor complications such as superficial wound separation, flap hematoma, and anal stricture. Patients may present initially with some degree of gas incontinence, without significant fecal incontinence.\(^ {23-27}\)

Other treatment modalities, such as the use of topical chemotherapy and radiotherapy, have been reported, although their indications are not clearly defined. Radiotherapy for EMPD in the perianal region has been studied in sporadic cases and is poorly documented with respect to technical radiotherapy details. Main indications for radiotherapy include large or inoperable tumors, especially in older patients or in those with significant morbidities.\(^ {28}\)

Also, Shaco-Levy et al.\(^ {29}\) reported that the use of radiation therapy given to patients who either had multiple positive surgical margins or experienced disease recurrence and refused additional surgery resulted in complete response with no further recurrences. Radiotherapy has been used as primary, definitive treatment for postexcisional relapse and adjuvant treatment. In a study by Luk et al.,\(^ {30}\) the use of radiotherapy in 6 patients obtained complete response in 5 patients, with 1 partial response. One patient with complete response but marginal failure was successfully managed with further surgery. In conclusion, radiation therapy for EMPD has been used in isolated cases without proper indications or on the basis of solid evidence, but the results are promising and a potentially curable option for patients with lesions that would otherwise be inoperable because of the extent of invasion or for recurrences after local surgery.

The study of other treatment modalities has led investigators to use topical 5-fluorouracil as an alternative therapy for EMPD. Some studies have demonstrated that although 5-fluorouracil can clear the clinical lesion, further biopsies showed persistence of disease on histologic examination. For this reason, 5-fluorouracil is not recommended as monotherapy, and its use in combination with MMS or surgical excision is not clearly defined.\(^ {31,32}\)

The use of imiquimod for EMPD has been described in recent case reports and small series of patients.\(^ {33}\) Some reports of patients with vulvar EMPD treated with local 5% imiquimod cream can show clinical and histologic remission within weeks of treatment.\(^ {34-36}\) No long-term results have been published to determine the recurrence rate of this treatment modality. Nonetheless, the acceptable side effects and the possibility of cure without surgery make imiquimod treatment a promising alternative.

The use of systemic chemotherapy for metastatic EMPD to inguinal nodes has been addressed in some case reports. The application of these regimens should be evaluated with care and individualized, because there are no validated protocols. Patients with EMPD with involved lymph nodes should be directed to study protocols for chemotherapy.\(^ {37,38}\)

Recurrence rates associated with EMPD have been attributed to subclinical extension and multifocal disease. MMS improves cure rates over traditional wide lesion excision but has some disadvantages, such as the long operative time required to clear margins, the requirement of a trained physician, and the difficulty to adequately prepare frozen sections. Scouting biopsies have been used to guide the extent of the initial Mohs layer to minimize the area of treatment in multifocal disease,\(^ {21}\) to save time, and to concentrate treatment on affected skin, but the false-negative rates and the inability to completely cover the entire perimeter of the lesion makes the complete margin-free status doubtful. Because of the multifocal nature of the disease, and in an effort to preserve most tissue as possible, we describe the use of a staged technique for the treatment of EMPD.

**Technique**

We used a variation of the staged marginal excision technique initially described by Johnson et al.,\(^ {39}\) but instead of using a square peripheral incision, we made a resection line that contours the anatomic structures as described by Möller et al.\(^ {40}\) for excision of face and head melanomas.

First stage: marginal contoured excision

1. The margins of the lesion are delineated with a Wood’s lamp.
2. A contoured 1-cm to 2-cm margin is drawn and properly identified for orientation.
3. Under local or general anesthesia, 2 to 3 mm of tissue is removed at the drawn margin, using a double-bladed scalpel.
4. Each contoured rim of tissue is processed by the pathologist, and the presence of a negative or positive margin will be determined by high-quality permanent sections.
5. After the resection, the narrow wound is closed with a running poliglecaprone or nylon suture. The patient is discharged home with a closed wound.
6. If any margin of the specimen is positive during the first stage, a reexcision of that particular affected margin is performed, keeping the rest of the wound closed to allow for patient comfort. The first stage is repeated as needed to clear a particular margin.

Second stage: central excision and reconstruction

7. Once margins are confirmed to be negative by permanent pathologic analysis, the patient is brought back to surgery for central lesion removal.
8. Final wound closure and reconstruction are performed during the same procedure by means of a cutaneous flap of skin grafting as considered by the plastic surgeon.
Patient

We describe the case of an 82-year-old male patient who came to the clinic with a history of a rash he had noticed 6 months before this visit. The rash was located in his left deep groin and the posterior aspect of the scrotum. He was previously seen by his primary care physician, who recommended treatment with topical medication. Because the rash did not improve, biopsies were taken. Histopathology was consistent with EMPD. Initial workup consisted of a computed tomographic scan of the chest, abdomen, and pelvis, without identification of lymphadenopathy or other neoplastic lesions. Blood work was within normal range. The patient denied any symptoms suggestive of colon or genitourinary cancer as well as constitutional changes.

After an extensive discussion with the patient about the pathology, he declined any further and additional invasive workup to rule out a primary internal malignancy. However, he accepted the option of surgical management with wide lesion excision. He was proposed the 2-stage marginal excision technique of the disease, and informed consent was obtained.

During the initial procedure (first stage), the visible margins of the lesion were identified with assistance of a Wood’s lamp (ultraviolet light), and a 10-mm peripheral margin beyond the visualized lesion perimeter was demarcated (Fig. 1). These excision margins were configured relative to the visualized lesion. The contoured margins became a geometric shape that followed the outer margin of the lesion along anatomic lines. Then, beginning at a distance 10 mm from the lesion perimeter, a small rim of contoured tissue 3 mm in width was excised to the mid to deep subcutaneous tissue and properly oriented for the pathologist using letters and describing the location of each letter (Figs. 2 and 3). The normal skin at the outside edge of each of the excised strips was marked with a suture to help orient the tissue in the case of a positive margin. The long, narrow wound thus created around the visible EMPD was reapprorimated with a running suture (Fig. 4). The pathology report confirmed that all the margins were negative, so we proceeded with the second stage.

During the second stage, the central excision, complete resection was carried out to include all the subcutaneous tissue underlying the affected skin, down to the muscle fascia and over the testicles. Special attention was paid to protect the external anal sphincter and testicles during dissection (Fig. 5).

Figure 1  Delineation of margins with assistance of a Wood’s lamp. A 10-mm peripheral margin was added to the visible margin to increase the possibility of free margin beyond macroscopic disease.

Figure 2  Contoured margins at 2 cm with specification of the strips to allow specific identification of any positive margin. Special care was taken to adequately identify the location and orientation of the specimens for correct identification by the pathologist.

Figure 3  Strips of tissue for en face permanent analysis. Each strip is appropriately identified according to the anatomic site of the lesion to identify free-margin status once analyzed.
The specimen was sent to pathology, with appropriate margins for orientation. It measured 7.5 × 6 × 3 cm. The specimen was serially sectioned at the posterior aspect in the frozen section room, and no evidence of gross tumor was identified. There was a 4 × 4 cm, irregularly shaped, variegated light brown to dark brown flat area that appeared thickened. Some excoriations were noted. The lesion was 0.5 cm from the medial margin (nearest margin). Multiple cross-sections revealed that the lesions appeared superficial. No tumor was identified within the subcutaneous and adipose tissue. Once this was confirmed, the plastic surgery team came to the room to perform a posterior thigh flap, without complications (Fig. 6).

Microscopic examination confirmed the presence of Paget’s disease without an invasive component (Fig. 7). All margins were free, and the closest margin on this specimen was 0.5 cm from the lesion. In addition to the margin taken in the first stage, the margin was 0.5 cm from the lesion. In addition to the margin taken in the first stage, the margin was 0.8 cm, which accounts for shrinkage artifact.

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The patient has continued observation in the clinic without any complications. He returned to his normal activities 5 weeks after surgery. After 25 months, no signs of recurrence have been noticed.

Prognosis

The prognosis of EMPD is generally favorable. For primary EMPD, the prognosis depends mainly on the level of invasion related with spread and depth, with near 100% survival rates in patients with noninvasive disease. In one of the largest case series published in Europe, the 5-year survival rate was 72% for invasive tumors. For secondary EMPD, the main variable for survival depended on the prognosis of the primary tumor and its treatment, with an average survival rate of 3 years.

Conclusions

Despite numerous reports in the literature on EMPD, it remains a largely unknown disease, mainly because it is not a frequent type of malignancy. The current knowledge on the treatment of EMPD is based on small case series, which makes it complicated to elaborate a consensus on diagnostic and treatment guidelines. Because of the nature of the disease, its rarity, and its clinical presentation, the chances of conducting a controlled prospective randomized trial remain low. We propose a new alternative for the treatment of this disease from an oncologic standpoint. The experience of this technique is transferred from the surgical management of melanoma in situ proposed previously. This approach not only encompasses the oncologic principle of complete resection with clear margins but is a convenient approach for avoidance of open wounds and preservation of function and cosmesis for patients requiring large tissue excisions. This technique also avoids some of the disadvantages associated with MMS, because it does not require specialized personnel in the processing of the samples for frozen sections for evaluation of margins or pose difficulty in interpreting the sometimes subtle nature of the tumor on frozen sections. For this procedure, it is important to approach the patient with an interdisciplinary team consisting of a surgical oncologist, a pathologist, and a plastic surgeon; depending on the scenario, involvement of a colorectal surgeon may be necessary.

Evidence of the success of this technique will require further follow-up and a larger number of patients. Nonetheless, it is our intent to add an alternative surgical approach for those surgeons facing this medical problem who can offer to their patients a procedure that could reduce morbidity, allowing final reconstruction without compromising oncologic outcomes.

References


