Rare Cancers

Extramammary Paget's disease

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Extramammary Paget's disease is an uncommon cutaneous adenocarcinoma, characterized by glandular differentiation and an insidious course. The condition may or may not be associated with an underlying adnexal or visceral malignancy. Because of its rarity, the pathogenesis is unclear, and standardization of treatment is lacking. The diagnosis is made histopathologically, and management is based on wide surgical excision. Long-term follow-up is essential to exclude a recurrence of the disease and monitor the patient for an underlying or associated cancer. Here, we report a case of this rare disorder involving the perianal region and briefly review the available literature. This case report draws attention to extramammary Paget's disease, which should be considered in the differential diagnosis of perianal disorders.

Case report

A 74-year-old white female with a past history significant for hemochromatosis, osteoporosis, arthritis, and hypothyroidism presented with a 3-year history of occasional perianal itching. The pruritus initially responded to topical therapy but then slowly progressed to become painful with a lumpy sensation.

The patient did not have any constitutional symptoms or changes in bowel habits or abdominal pain, although she complained of minor anal irritation on moving her bowels. Her past surgical history included uterine dilatation and curettage, hysterectomy, cataract surgery, upper eyelid surgery, and knee meniscus repair. She was a nonsmoker and nondrinker. Her medications included hydrochlorothiazide, folic acid, calcium, levothyroxine, alendronate (Fosamax), and diclofenac and misoprostol (Arthrotec).

A physical examination, including clinical examination of the patient's breasts, uncovered no significant findings. Examination of the anal region revealed a leukoplakia-like white lesion, an erythematous zone extending from 7 to 11 o'clock, and some tenderness. A rectal examination revealed no masses.

She underwent a biopsy of the involved skin at three positions in the perianal area. All three lesions were positive for extramammary Paget's disease. The tumor cells (Paget's cells) were positive for cell adhesion molecule (CAM) and carcinoembryonic antigen (CEA) on immunohistochemical staining. The nevus cells were positive for S100, Melan-A, and focally HMB-45.

Her initial blood tests, including routine screening for electrolytes, renal and liver function, lactate dehydrogenase (LDH), and a complete blood count, were all normal.

Because of the possible association of extramammary Paget's disease with intra-abdominal malignancy, a computed tomographic (CT) scan of the chest, abdomen, and pelvis was performed. The liver, spleen, pancreas, adrenal glands, and kidneys were all normal. A small inguinal hernia was evident on her right side. Chest findings were negative except for mediastinal or hilar lymphadenopathy. There was mild scarring at the lung apices; however, there were no lung parenchymal lesions.

She had a colonoscopy, which revealed a single 10-mm polyp in the sigmoid colon. It was resected, and a biopsy showed that the polyp was benign.

The three perianal lesions were excised. Pathology revealed a close margin of resection of 1 mm from the normal tissue. Rather than starting on topical imiquimod (Aldara) therapy, the patient decided to have the involved region biopsied periodically. She was also scheduled for a repeat colonoscopy in 6 months and for her usual quarterly phlebotomy for hemochromatosis to keep her target serum ferritin level at ≤ 50 ng/mL.

Follow-up 3 months later showed that the patient was doing fine.

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About this rare disorder

Sir James Paget first described Paget's disease of the nipple in 1874 in a report of 15 patients with underlying intraductal carcinoma of the breast.[1] Fifteen years later, H. Radcliffe Crocker described the first case of extramammary Paget's disease affecting the scrotum and the penis.[2] Darier and Couillaud reported the first case of perianal Paget's disease in 1893.[3] Dubreuith described the first case of vulvar Paget's disease in 1901.

Extramammary Paget's disease is a rare cutaneous neoplasm that occurs mainly in the elderly. Caucasian women in their 60s and 70s appear to be more at risk than other populations.[4] It predominantly involves apocrine gland-bearing areas, especially the vulva, scrotum, and perianal areas. However, it has also been described in other apocrine gland-bearing areas, including the axilla, groin, thigh, eyelid, external ear, umbilicus, and nose.[5] It is generally thought to be an epidermal adenocarcinoma extending into the contiguous epithelium of the hair follicles and eccrine sweat ducts.[6]

In contrast to mammary Paget's disease, which is almost always associated with an underlying malignancy of the breast, extramammary Paget's disease may or may not be associated with internal malignancy.[7] When an underlying internal malignancy is present, its location is linked to the location of extramammary Paget's disease: A perianal location may be associated with adenocarcinoma of the gastrointestinal tract, whereas a penile, scrotal, or groin location may signify an underlying genitourinary malignancy.[8]

Clinical manifestations

Extramammary Paget's disease tends to occur as a slowly growing lesion that may be invasive or noninvasive pathologically. Pruritus in the affected area is the only complaint in most patients, although some patients complain of an irritation or a rash. Pain and bleeding may occur in long-standing cases. Initially, the lesion is typically erythematous, dry, and raised but later may turn into an eczematoid, crusted, ulcerated, or papillary lesion. The lesions have sharply defined margins with plaques and distinct erythema.[9] Superficial erosion or scaling may develop in old lesions. It is unusual to make the diagnosis clinically. Patients often give a history of prolonged treatment with topical corticosteroid and antifungal agents before a diagnosis is made by biopsy of the lesion.

The diagnosis of extramammary Paget's disease, especially perianal Paget's disease, is often delayed while

TABLE 1

Extramammary Paget's disease at a glance

Feature	Description
Epidemiology	Rare; primarily found in postmenopausal Caucasian women in their sixth to seventh decade of life but may also occur in men and other racial/ethnic groups
Tumor site	Epidermal apocrine gland-bearing areas, especially the vulva, scrotum, and perianal areas, but also the axilla, groin, thigh, eyelid, external ear, umbilicus, and nose
Growth rate	Slow growing; may or may not be invasive or associated with an underlying malignancy
Gross appearance	Erythematous, dry, raised lesion(s), which may turn into eczematoid, crusted, ulcerated, or papillary lesion(s)
Clinical presentation	Long-standing pruritic lesion(s) refractory to topical corticosteroid and antifungal therapy
Differential diagnosis	Bowen's disease, the epidermal phase of neuroendocrine carcinoma, mycosis fungoides, psoriasis, leukoplakia, superficial fungal infection, superficial spreading melanoma, Toker cell, clear-cell papulosis, and pagetoid spread of visceral carcinoma
Work-up	Medical history, clinical examination, biopsy and pathologic and immunohistochemical examination of the involved skin, and clinical evaluation for an underlying adnexal or visceral malignancy
Morphology	Single or small clusters of large, faintly basophilic or vacuolated cells (Paget's cells) with large nuclei and often prominent nucleoli and an amorphous, granular cytoplasm
Histochemistry	Positive for hematoxylin and eosin, Alcian blue, aldehyde fuchsin, the periodic acid Schiff reaction, and mucicarmine
Immunohistochemistry	Positive for CEA, S100, Melan-A, CAM 5.2, EMA, CK 7, GCDFP-15, and syndecan-1
Management	Depends on the extent of involvement; wide surgical excision is the treatment of choice; other treatment modalities that have met with varying success, alone or in combination, include topical application of imiquimod 5% cream, photodynamic therapy, Mohs surgery, and irradiation
Prognosis	Varies, depending on the success of surgery in obtaining clear margins and whether an underlying malignancy is present
Long-term follow-up	Essential to exclude recurrence of the disease and development of an underlying or associated cancer

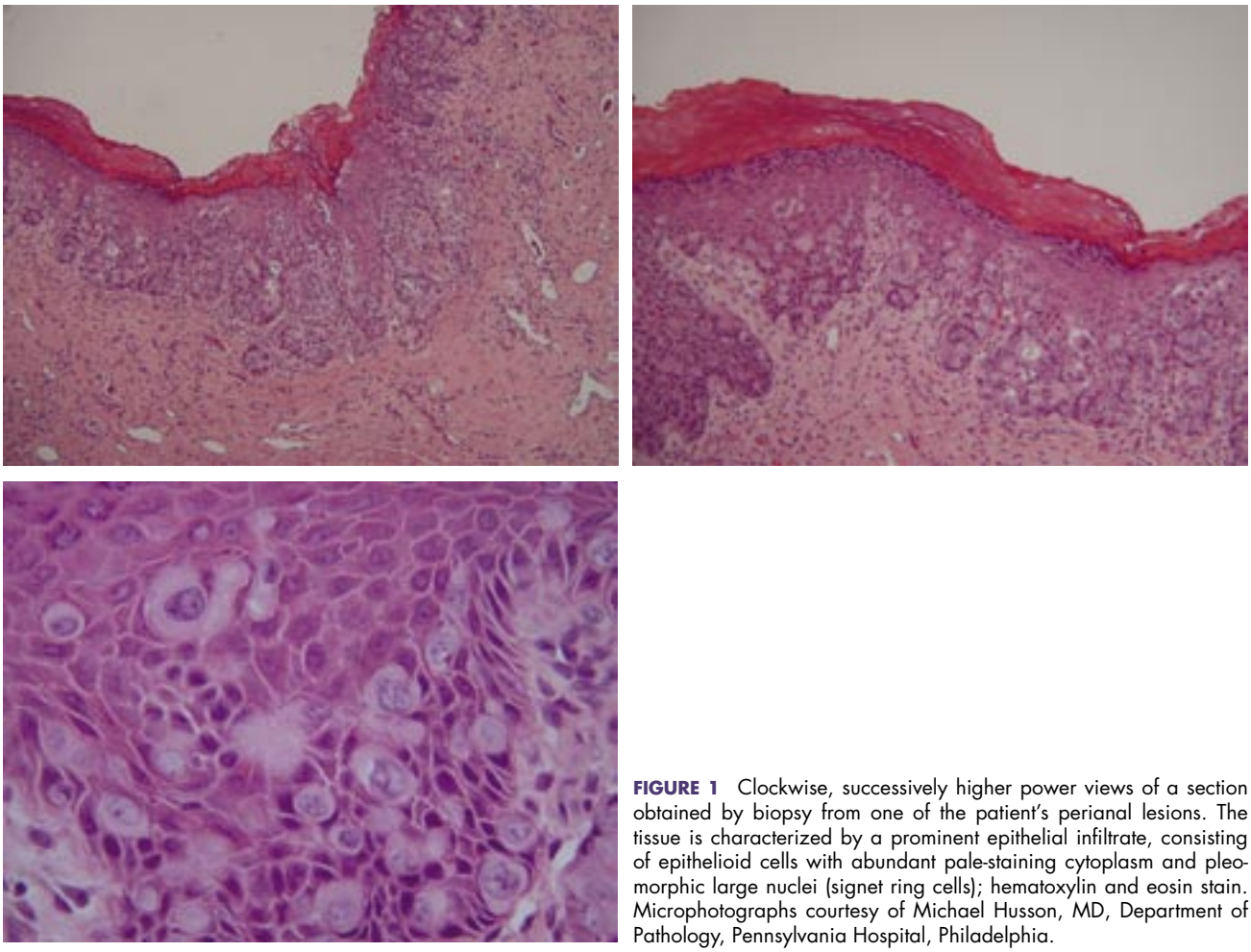

FIGURE 1 Clockwise, successively higher power views of a section obtained by biopsy from one of the patient's perianal lesions. The tissue is characterized by a prominent epithelial infiltrate, consisting of epithelioid cells with abundant pale-staining cytoplasm and pleomorphic large nuclei (signet ring cells); hematoxylin and eosin stain. Microphotographs courtesy of Michael Husson, MD, Department of Pathology, Pennsylvania Hospital, Philadelphia.

other conditions are entertained before the final diagnosis is made.[10] In fact, clinicians should have a high index of suspicion for extramammary Paget's disease if a skin lesion fails to clear with topical steroid and antifungal treatment.[11] The investigation of choice is a sharp punch biopsy of the involved skin to obtain an adequate amount of tissue. The diagnosis is then confirmed by histopathology and immunohistochemistry. Extramammary Paget's disease, especially perianal Paget's disease, is regarded primarily as a histopathological entity (Table 1).

The differential diagnosis includes superficial spreading melanoma, Bowen's disease, the epidermal phase of neuroendocrine carcinoma, mycosis fungoides, psoriasis, leukoplakia, superficial fungal infection, Toker cell, clear-cell papulosis, and pagetoid spread of visceral carcinoma.

Pathogenesis

Perhaps the most controversial aspect of extramammary Paget's disease pertains to its pathogenesis. Paget believed mammary Paget's disease to be a malignant papillary dermatitis and not a simple eczema, in view of his finding an underlying carcinoma.[12] The histopathological features are similar in mammary and extramammary Paget's disease. The Paget's cells are present singly or in small clusters and characteristically stain with hematoxylin and eosin. These large, faintly basophilic or vacuolated cells have large nuclei and often prominent nucleoli, with an amorphous and granular cytoplasm (Figure 1). They have been described as signet ring cells.

The genesis of the Paget's cell is controversial. There are four different theories that explain the four different patterns of presentation. One theory proposes that stem cells present in the basal cell layer of the epidermis change into Paget cells as a result of faulty development of these cells in their attempt to mature into an apocrine structure. The second theory hypothesizes that epidermal Paget cells originate from cells that have migrated from an adjacent malignant region—either an adnexal sweat gland or anorectal mucosa—or from another contiguous structure. A third theory suggests that Paget's cells may represent a form of metas-

ease, but not in extramammary Paget's disease.[15] However, HER2 protein overexpression in extramammary Paget's disease is common and due exclusively to gene amplification.[16] Some data suggest that P53 may play a role in the progression of vulvar Paget's disease and may be a terminal event in some cases, especially those associated with invasive disease. P53 is not a prognostic factor in Paget's disease of the breast.[17] A novel tumor marker (RCAS1, or receptor-binding cancer antigen expressed on SiSo cells) has been identified in cases of extramammary Paget's disease and has the potential of becoming a biomarker for monitoring therapeutic efficacy.[18]

Histochemistry

Staining with hematoxylin and eosin can usually distinguish Paget's disease from malignant melanoma in situ and Bowen's disease.[9] Doubtful presentations may be differentiated by other staining techniques. Paget cells contain mucin and therefore stain positively with Alcian blue, aldehyde fuchsin, the periodic acid Schiff reaction, and mucicarmine. When these techniques fail, immunohistochemical staining for CAM 5.2, EMA, CK 7 (cytokeratin 7), and GCDFP-15 (gross cystic disease fluid protein 15) is helpful; Paget cells react positively with all of these stains, indicating the glandular differentiation of these cells. GCDFP-15, a marker of apocrine epithelium, is strongly expressed in cases of vulval and perianal extramammary Paget's disease without any underlying internal malignancy, and thus staining for this marker is useful in establishing a prognosis.[19]

Although the histopathological differential diagnosis of pagetoid neoplasm is broad, unique histopathologic identifiers and clinical correlation can often identify the process. CAM 5.2 and CK 7 are immunoperoxidase markers that can help in the differentiation of difficult-to-diagnose cases of extramammary Paget's disease, mammary Paget's disease, and pagetoid squamous-cell carcinoma in situ. An antibody panel consisting of S-100, CAM 5.2, and CK 7 aids in the accurate diagnosis of almost all pagetoid neoplasms of the breast or genital skin.[20] Paget's cells are strongly immunoreactive to CEA antibodies, and melanocytes stain positively with S100.[21] Low-molecular-weight keratin may be used for confirmation of extramammary Paget's disease.[22] Patterns of syndecan-1 immunoreactivity may also be useful in differentiating extramammary Paget's disease from Bowen's disease and pagetoid malignant melanoma in situ.[23]

The diagnosis of extramammary Paget's disease warrants a thorough search for an associated adnexal or visceral malignancy. The disease process is generally a prolonged one, marked by frequent recurrences.[5,24] The incidence of associated malignancy ranges from 50% to 85% over different periods of follow-up.[9,25]

Management

Once a patient is suspected of having extramammary Paget's disease, a logical approach to management includes an initial clinical assessment, evaluation of the extent of involvement of the lesion, and, finally, a work-up for the possibility of an underlying malignancy.

Surgery

The treatment of choice for noninvasive extramammary Paget's disease is wide surgical excision, as it offers a chance for cure and because microscopic spread of the disease may extend beyond the macroscopically involved area of the skin.[9,10,13,26] A precise, preoperative histological examination by multiple sharp punch biopsies from the periphery of the lesions is a necessity because frozen sections may yield false-negative results and have not been completely reliable in this condition. Even though the mainstay of treatment is wide local excision, positive margins remain a major problem.[7]

Noninvasive Paget's disease of the rectum can be treated by excision of the lesion with a sphincter-saving technique.[27] Extramammary Paget's disease of the vulva is a localized disease, as it is almost always noninvasive, and can be managed by skin vulvectomy and a split-thickness skin graft without loss of sexual function. The margins of the excised lesion can be temporarily closed using vacuum-assisted closure devices until the final histopathological results are available. These devices also may be used to secure the skin graft to a large and an irregular surface.[28]

Another approach is Mohs micrographic surgery, which allows maximal tissue sparing of critical anatomic structures. The advantage of Mohs surgery is that it can be performed as an outpatient procedure under local anesthesia. Its drawback, however, is recurrence of the lesion.[29]

Nonsurgical approaches

In recent studies, clinical and histological cure has been enhanced with topical application of imiquimod 5% cream, used daily for 6 weeks. [30,31] Treatment-associated morbidity is minimal when compared with that of more invasive therapies, and self-application by the patient improves convenience and appeal. No recurrences have been reported during follow-up with this therapy.

Photodynamic therapy can also be used as an effective treatment for extramammary Paget's disease. Systemic administration of porfimer (Photofrin) may be better suited than topical aminolevulinic acid (Levulan) for bulky disease.[32]

Radiotherapy—including high-dose-rate brachytherapy, electron-beam radiation therapy, superficial x-ray therapy, and photon treatments—can play a useful role in the management of perianal Paget's dis-

TABLE 2

Staging of extramammary Paget's disease with respect to perianal involvement

Stage	Criterion
I	Paget's cells found in perianal epidermis and adnexae without underlying carcinoma
IIA	Cutaneous Paget's disease with associated adnexal carcinoma
IIB	Cutaneous Paget's disease with associated anorectal carcinoma
III	Paget's disease in which the underlying carcinoma has metastasized to regional lymph nodes
IV	Paget's disease with distant metastases of underlying carcinoma

Adapted from Shutze and Gleysteen[9]

ease, as evidenced from some studies.[33,34] The role of chemoradiotherapy remains undefined in this disease.

Invasive disease

The prognosis remains poor in cases of invasive extramammary Paget's disease.[35] For locally invasive perianal extramammary Paget's disease, abdominoperineal resection or chemoradiotherapy can be attempted, as are used for treating adenocarcinomas of the rectum. If there is an underlying carcinoma, treatment includes management of the carcinoma with wide local excision of the cutaneous lesion. Some studies have suggested even more extensive surgery, including pelvic exenteration for diffuse involvement in extraordinary cases.[36]

Inguinal lymph node dissection may be considered if the nodes are involved or are associated with dermal spread of the disease. Clinically, however, patients with extramammary Paget's disease are usually elderly and frail, and the nodal involvement may simply be a reactive lymphadenopathy due to perianal infection. An algorithm for indication of lymph node dissection has been delineated from recent studies. Extramammary Paget's disease has been staged into four stages with regard to treatment (Table 2).[9] Stage III is defined as Paget's disease in which an associated underlying carcinoma has spread to regional lymph nodes. Lymph node dissection along with resection of the lesion is the treatment of choice for stage III disease.

Follow-up

Long-term follow-up of patients with extramammary Paget's disease is required to exclude recurrence of the disease and development of an associated cancer.[5] Some authorities recommend lifelong follow-up after radical treatment of perianal disease. Examination includes a punch biopsy from the margin of the old perianal lesion once a year, in addition to colonoscopy once every 2–3 years.[11]

Discussion

Extramammary Paget's disease of the perianal area remains a rare and unexpected tumor. It took some time (3 years) until our patient's symptoms became chronic and irritating enough for a biopsy to be performed. Once a biopsy is performed, excellent pathology support is necessary to make the proper diagnosis, as this lesion is so uncommon. The pathologists at our institution were very helpful by suggesting the diagnosis via light microscopy and then confirming the diagnosis with immunohistochemical staining.

It is important to distinguish invasive from noninvasive extramammary Paget's disease, as the treatment and prognosis of each are so different. Fortunately, our patient's lesions were noninvasive, and clear margins were obtained at re-excision. The results of a colonoscopy were, fortunately, normal, as other lower gastrointestinal tract neoplasms can occur in association with this disease.

We had not seen extramammary Paget's disease of the perianal region before, and thus a review of the literature, as described here, and discussions with our gastrointestinal disease colleagues were essential and very helpful in arriving at an acceptable management plan.

Our patient continues to do well but must return every 6 months for a perianal exam and a liberal biopsy if any changes are seen. Her insurance company was quite understanding as we worked through her diagnosis and treatment, and we had no reimbursement problems in establishing the pathologic diagnosis or in re-excising her lesions.

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Lessons learned

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EXTRAMAMMARY PAGET'S DISEASE is a rare cutaneous adenocarcinoma of epidermal origin (usually) and characterized by glandular differentiation and an insidious course. It is frequently associated with an underlying adnexal carcinoma and, in many cases, with an underlying malignancy. A recent review of published cases revealed only 196 reported cases of extramammary Paget's disease in the English literature over a 20-year period.

So although extramammary Paget's disease is an extremely important diagnosis to arrive at, it is not a diagnosis each of us will make in our medical careers. It is primarily seen in older Caucasian women but can occur in a variety of patient populations. It is important, too, to recognize that 26% of patients with extramammary Paget's disease will ultimately die of the disease itself or an associated malignancy and, therefore, is a key diagnosis to make in our patients.

Diagnosis frequently overlooked

What is also evident is that the diagnosis is frequently overlooked. The presenting signs of scaling, itchiness, and erythema are often mistaken for other, more common problems. In addition, physical examination of the genital and perianal areas is frequently not as thorough as is examination of other areas. The lesson learned from this is that we must take our patients' complaints seriously and conduct a complete physical examination.

The next problem we encounter, however, is that the diagnosis is best made by biopsy. Clearly, obtaining frequent biopsies in the perianal or genital area is not well received by patients, but there are times when the diagnosis must be made and a biopsy is indicated.

It is very interesting to encounter a disease that presents on the surface of the body and the skin but may be a harbinger of a more serious problem in the abdomen or elsewhere. It has always raised the question in my mind as to what is the shared background of these diseases. Is it possible that these lesions, in fact, represent micrometastatic foci? There certainly is very little evidence to support such a proposal, although it has been raised more than once. It is difficult, however, to find other logical medical explanations as to why the skin lesions predict internal adenocarcinomas in a fairly high percentage of patients with extramammary Paget's disease.

Management requires close consultation

The secret to managing this disease is first making an accurate diagnosis. This will require interaction with a pathologist to ensure that what is being seen is, in fact, consistent with extramammary Paget's disease. After that will come direct interaction with the surgical team. Clearly, a variety of surgical options, performed by different surgical subspecialists, will present themselves, depending upon the location and the extent of the disease. A high priority must be placed on balancing the adequacy of a wide local excision with remaining function of the involved area. A difficult issue remains the decision about whether to dissect the regional lymph nodes. Although there is some evidence to support taking such a course, the morbidity of lymph node dissection, particularly in the inguinal region, is not insignificant and must be weighed against the potential benefit.

Likewise, an extensive search for an intra-abdominal malignancy is controversial. Clearly, with computed tomography, this becomes an obvious choice, but the extent to which one pursues gynecologic and other abdominal work-ups may depend on the performance status of the patient and the coexistence of other medical conditions. However, it cannot be neglected in any way once the diagnosis of extramammary Paget's disease is made.

I found most interesting the discussion in this report about the use of a topical immunostimulant, imiquimod cream, having never used this agent in clinical practice. In fact, there is a fairly significant literature supporting its use, not only in extramammary Paget's disease but also in other skin lesions that do not have a viral etiology. As one who remains quite interested in the immune system's impact on the treatment of cancer, it was particularly enlightening to review the literature supporting the use of this local immunostimulant. This option was appropriately offered to the patient described in this case study, even though the patient opted not to pursue it, one presumes, due to its local toxicity.

Case reports are important

When one contemplates developing better treatments for such a rare disease, it is obvious that large studies will never be performed on patients with extramammary Paget's disease. Therefore, it is paramount for us to place into the literature as many cases as we can to help guide each other on the use of different therapeutic options. With the worldwide Web as it is today, searching out information about rare disorders such as extramammary Paget's disease is becoming increasingly easy and useful for our patients.

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