

Case Study

Radiotherapy and Perianal Paget's Disease

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Abstract

The aim of this study is to document a case of Extra Mammary Paget's Disease (EMPD), which was treated with radiotherapy at the Suffolk Oncology Centre. We have shown evidence, both in the reviewed literature and in this study, that radiotherapy can be used successfully as a primary form of treatment for this disease.

The patient discussed in this paper had EMPD in the perianal region. 40 Gy in 10# using a parallel-opposed pair field arrangement was prescribed. However due to mental and physical frailty only 90% of the dose could be delivered. The patient suffered only minor side effects and three years post-radiotherapy was still disease free. We can therefore say that radiotherapy was successful in this instance.

We concluded that there is a definite role for radiotherapy in the management of EMPD and that it can be effective as a primary treatment, where the only other option could be mutilating surgery.

Keywords

Extra Mammary Paget's Disease; perianal; mucin; radiotherapy; anogenital region; treatment

INTRODUCTION

The aim of this study is to document a case of Extra Mammary Paget's Disease (EMPD), which was treated with radiotherapy at the Suffolk Oncology Centre. There are two classifications for Paget's Disease; Mammary Paget's Disease (MPD), which was discovered by James Paget in 1874, and predominately affects the nipple, and Extra Mammary Paget's Disease (EMPD), which was discovered 15 years later by Radcliffe Crocker. EMPD was found to be histologically identical to MPD and occurs at other sites of the body.¹

Brown² documented that EMPD usually occurs in areas of the body containing apocrine glands, for example: perineum, perianal region, vulva, penis/scrotum, and axilla. EMPD is a rare adenocarcinoma, which occurs most frequently in the anogenital region. The disease presents as infiltrated grey-white plaques. These may be eczematoid, crusting or scaling.³

Radiotherapy is not often used to treat EMPD and when it has, success has been difficult to determine. Published reports on radiotherapy, either as a primary or secondary mode of treatment, are scarce. Amin⁴ discovered that these reports do not fully describe the techniques employed or the outcome of the treatment. Therefore any use of radiotherapy to treat EMPD should be documented to assist future treatment modality choices.

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CASE REPORT

Relevant past medical history:

- 1967 – BCC right nose, surgically removed.
- 1970 – BCC Bridge of nose and BCC left lower eyelid, treated with radiotherapy.
- 1980 – BCC cheek, surgical excision incomplete, therefore treated with radiotherapy.
- 1990 – diagnosed Left Breast Cancer, T4 N0 2.5 × 3 cm mass in upper outer quadrant, with 1–1.5 cm area of infiltration and fixation of skin. Treated with radiotherapy to left breast and nodes.

The 85-year-old patient, presented with a history of pruritus ani (a chronic, persistent itchy feeling around the anus) in late 2000 with one year of increased perianal discomfort. This was initially thought to be a fungal infection, and treated as such. However, the patient's perianal area did not respond to this treatment. It was therefore decided to perform a biopsy. The biopsy report from August 2000 read:

“The skin sample shows the epidermis with scattered single pleomorphic polygonal cells mainly in the basal layer but also extending up through the various layers within the epithelium. These cells are positive for epithelial mucin, carcinoembryonic antigen, epithelial membrane antigen and cytokeratin CAM 5.2. They are negative for S100. The features are consistent with extra mammary Paget's disease. No neoplastic infiltration is seen.”

After confirming the histology of the disease, an examination showed the patient's groins to be clear, with florid perianal Paget's Disease involving the distal anal canal and extending onto the posterior labia. No palpable anal or rectal masses were found.

Once a positive diagnosis of Paget's Disease had been established, the patient was referred to Oncology for management. Radiotherapy was recommended as the primary mode of treatment, as the patient was deemed unsuitable for surgery. This was due to age, frail condition and early stages of dementia.

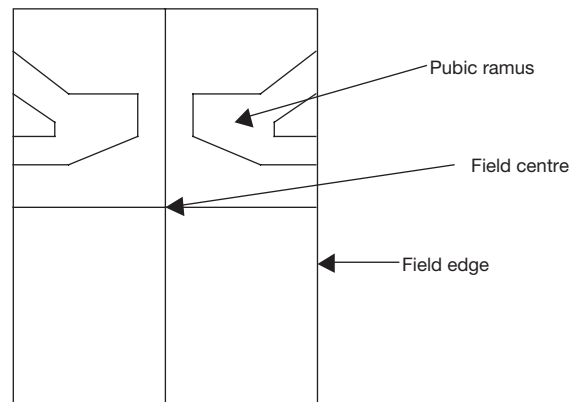


Figure 1. Diagram of the field size used in relation to bony anatomy.

The radiotherapy for this patient was planned for 40 Gy/10#/3 × wk, using 16 Mv photons in a parallel opposed, ant and post field arrangement.

As there is no “gold standard” dose for this disease yet, the prescription was decided upon taking into consideration the patient's mental and physical condition. Following discussions with the family it became clear a daily treatment regime would cause repercussions in behaviour, and wellbeing. Therefore treatment three times a week was deemed more appropriate. It is acknowledged that 16 Mv is a high energy considering there were no palpable mass or positive lymph nodes, however it was justified in this case as the patient was obese.

To cover the extent of the disease, a 12.5 cm long by 7 cm wide field size was used (Fig. 1).

This particular field size was decided upon using basic localisation techniques i.e. palpation and simulation.

The treatment started well and was uneventful for the first five fractions.

By the sixth fraction some mild urethritis had occurred together with moist desquamation in the treatment area. These treatment reactions would be expected to occur at this time and a 1% Hydrocortisone cream was given to try and ease the symptoms.

The urethritis and moist desquamation continued unchanged, until the eighth fraction when the patient started to experience pain from the anus/rectum and intermittent stabbing pains from the bladder. Although these severe side effects were unusual, radiotherapy was likely to be the causative factor. By this stage the patient was very distressed due to the pain, was becoming increasingly confused, and appeared more frail than usual.

A clinical decision was made to rest the patient for one week and then re-assess physical and mental condition prior to the next scheduled fraction. Nevertheless the general state of the patient remained poor after the 1 week gap in treatment. The family informed the department that the patient had been eating a little better and seemed stronger. Following an examination, the Paget's disease appeared to be responding well to treatment. Due to the patient's general condition and the good response to the radiotherapy treatment the decision was made that it would be reasonable to stop at this dose. The patient would be closely monitored to check for any relapse.

In total 36 Gy/9#/3 × wk was given, over 24 days rather than the 40 Gy/10#/3 × wk over 22 days, prescribed.

The first follow-up appointment was 1 month after treatment. There was noted to be a good response to the treatment in terms of the patient's disease.

The acute moist desquamation radiation reaction had by then almost completely settled and there was a significant decrease in the itching of the perianal region.

The patient's next follow-up appointment was scheduled for 2 months after treatment.

At this consultation it was found that the perianal irritation had resolved completely and the skin had totally healed.

6 months post radiotherapy, the patient was still asymptomatic, it was therefore decided that due to the mental and physical frailty of the patient no further formal reviews were to be arranged.

The patient returned just over 2 years post radiotherapy in early 2003. Referral was due to a recurrence of a left breast carcinoma. The perianum was also examined and found to still be clear of EMPD, with the area showing no signs of irritation.

It would appear that in this case radiotherapy has been shown to be a successful mode of treatment even though the total prescribed dose was not delivered.

DISCUSSION

EMPD is of unknown aetiology, it is a rare condition that affects women more commonly than men. The disease often occurs in the 50's or thereafter.⁴

As Paget's Disease is easily misdiagnosed in its early stages as either dermatitis or eczema, topical steroids will have no effect and symptoms may persist for many years.⁵

Symptomatically Paget's Disease presents as irritation or pruritis (in 72% of cases) and rash (in 61% of cases), these often occur together.⁶

As a disease, EMPD is described as a skin cancer wherein the tumour cells have mucin in their cytoplasm. Mucins are glycoproteins with a high molecular weight, produced by epithelial cells. Different mucin genes (e.g. MUC5AC and MUC2) are expressed in various types of tissue (e.g. intestinal mucosa and adnexal structures of the skin).⁷

MUC5AC is a unique mucin exhibited in most cases of EMPD. Intraepidermal EMPD in the anogenital areas may arise from ectopic MUC5AC, plus cells originating from Bartholin's or some other unidentified glands. The presence of MUC2 in perianal EMPD indicates its origin from colorectal mucosa.⁸

Demis³ states that EMPD is often linked with underlying carcinoma.

There have been previous incidents of carcinoma in this case, but there was no underlying

invasive malignancy found. It is unclear if a previous unrelated carcinoma could increase the chances of developing EMPD and would warrant further investigation.

The anatomic location of the disease can play a vital role in predicting the risk of an associated carcinoma. Wilde¹ approximated that 4–7% of patient's with genital Paget's Disease will have an associated malignancy and 25–35% of patient's with perianal Paget's Disease will have an underlying colorectal carcinoma.

People suffering from EMPD have excellent survival rates but local recurrence and morbidity from surgery can be high. Patients with EMPD and an adenocarcinoma have a poorer prognosis than those with EMPD alone. A much worse prognosis is seen in those patients with malignancy underlying the dermis or subcutaneous tissues, or lymph node metastases.⁹

Besa¹⁰ reported that mortality rates of up to 50% are shown where patients have an underlying malignancy. In his study of 65 patients with EMPD, 14% had an underlying adenocarcinoma and he determined that the median survival for these patients was 22 months. Where as those patients without underlying disease achieved local control.

Brown² noted that survival is considerably worse for cases where EMPD has been treated primarily with radiotherapy, as opposed to those cases treated following recurrence. This prognosis can be partially explained, as radiotherapy has historically been used as a primary form of treatment only in the most palliative cases.²

Patients with invasive disease or biologically aggressive disease have significantly reduced survival rates; this is because the disease is less likely to be controlled by any treatment modality. McCarter¹¹ explains that the disease process of EMPD, when mis-managed, is generally a prolonged one with frequent recurrences.

Demis³ states that traditionally, radical surgical excision has been the treatment of choice as EMPD is localised to the skin. However recent studies have shown that there is a role for radiotherapy as a primary treatment modality.

Wide local excision is not always an appropriate treatment modality in the elderly, due to their physical condition. Simple excision will often result in relapse so can therefore be seen as an unnecessary procedure.¹²

The role of radiotherapy in the management of Paget's disease has not been widely documented in the past. Radiotherapy can be used either to treat the primary disease or to treat after surgical relapse.⁴

Brown et al.² consider that there are a number of reported roles for radiotherapy in the management of EMPD:

1. Single modality primary treatment
 - In-situ disease if unfit for surgery;
 - Avoid extensive surgery with reconstruction;
 - Keep abdominoperianal resection as salvage treatment;
 - Patient wishes.
2. Multimodality primary treatment
 - Chemo-radiotherapy for invasive disease or associated;
 - Underlying carcinoma.
3. Adjuvant therapy following primary or subsequent surgery.
4. Salvage treatment for clinical recurrence post surgery. (A number of cases reported.)
5. Palliation of symptoms if unfit for any radical treatment. (Occasional reports only.)²

Radiotherapy can be a better option for selected patients. Wide surgical excision often leads to the loss of the anal sphincter, resulting in the need for colostomy formation.¹⁰ Radiotherapy is not a physically mutilating mode of treatment. Side effects from the radiotherapy treatment often cause acute moist desquamation, which subsides after a period of time, although there is a risk of mild late skin atrophy.¹³

It is suggested that using surgery as a salvage treatment would seem a more acceptable option, especially in cases where radiotherapy has been used initially and subsequently failed. Radiotherapy is now being considered to be a satisfactory alternative to surgery as a primary mode of treatment.²

Besa¹⁰ recommends that a dose of greater than 50 Gy/25#/daily be given as a primary course of treatment for EMPD. However the occurrence of using radiotherapy to treat EMPD is still so small that this is only a recommendation, and not a definitive dose regime.

Although photons were used in this case, EMPD can feasibly be treated with an electron beam (where no underlying carcinoma/disease is evident), as only the superficial structures will be at risk from radiation damage.⁴ Using an electron beam would mean that deeper critical structures such as the bowel and bladder would be spared unnecessary dose.¹⁰

Amin⁴ discussed the management of one of his cases at Exeter using 300 kv photons to treat, as no electron facility was available to him. At follow up 10 years post radiotherapy there was an acceptable level of late radiation sequelae, and there had been no relapse, and no loss of anal function. As EMPD is probably best regarded as an intraepithelial adenocarcinoma, the dose used by Amin⁴ was as for treatment of skin malignancies.

Luk¹³ documented a study in China using radiotherapy to manage EMPD. Radiotherapy techniques included high dose rate mould brachytherapy, electron beam, superficial and photon treatments. Of the 6 patients treated with radiotherapy, 5 had a complete response and only 1 had a partial response. Marginal failure occurred in 1 of the 5 with complete response, but was successfully salvaged by surgery.

Disease recurrence was detected at follow up, this shows how important long-term follow up can be in catching recurrence quickly enough for salvage treatment. The follow up duration noted in this study was between 1.2 and 14.8 years.

It was concluded from the study that radiotherapy was a valid treatment option.

As the margins of EMPD are hard to define there are increased risks of late relapse with the use of any modality of treatment used. It is therefore vital to monitor the long-term treatment outcomes.¹³

CONCLUSION

Following the review of the limited amount of literature available regarding the use of radiotherapy as a primary treatment for EMPD, and the results of our own study, it seems that radiotherapy can be an acceptable and successful treatment modality. The rarity of the disease, however, has made statistical data on the management hard to assess. This case study indicates that the use of radiotherapy when treating EMPD warrants further investigation.

Radiotherapy should be considered to treat EMPD both with and without underlying adenocarcinoma as a means of primary control. Besa et al.¹⁰ have recommended a minimum dose of 50 Gy needs to be given, to eradicate microscopic disease, in the treatment of EMPD without underlying adenocarcinoma.

This is not a standardised dose regime, as the results of this study show.

Besa et al.¹⁰ go on to state that more than 50 Gy will be needed if there is an underlying carcinoma or concurrent chemotherapy will need to be considered.

This study shows that after 3 years the patient was still disease free even though only 90% of the prescribed dose was given.

During autumn 2003 the patient died, the death certificate states death due to,

- Left Bronchial Pneumonia and advanced Ca Left Breast.
- Both of which are unrelated to EMPD.

We do not have the opportunity now, for long-term results to be collected, but radiotherapy proved successful in the treatment of EMPD in this case.

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