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Case report

Stage 3 perianal extra mammary Paget's disease: A case report of a non-operative approach

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ABSTRACT

Introduction and importance: Extra mammary Paget's disease (EMPD) is a rare disease characterised by intra-epithelial involvement of the skin by non-squamous carcinoma cells in the vulva, perineum, and scrotum. Secondary EMPD is even rarer and accounts for roughly 25% of cases (Delport, 2012) [1]. Surgery (Mohs/wide local excision) is the standard treatment for primary non-invasive disease, but management of secondary invasive EMPD is less defined as there are no current treatment guidelines.

Case presentation: A 76-year-old lady had a 1-year history of a pruritic perianal rash that was refractory to multiple topical agents. A biopsy confirmed a diagnosis of EMPD in June 2020 and on staging imaging was found to have metastatic disease in her right inguinal lymph node. Upon discussion at a multi-disciplinary team (MDT) meeting, she proceeded chemo radiation therapy followed by systemic chemotherapy as she had such extensive perianal disease that would make surgery quite morbid. She had interval imaging 3 monthly to assess response to treatment. In June 2021, the patient had a complete clinical response and has ongoing 6 monthly surveillance.

Clinical discussion: EMPD is extremely rare and currently treatment options for secondary EMPD are still being navigated. Specifically, there are no current randomised control trials (RCTs) that compare outcomes in secondary EMPD between radiation therapy and surgery and in the context of stage III disease. This case report documents the treatment approach governed by MDT consensus and has a 1 year follow up. The case report has been reported in line with the SCARE 2020 criteria (Agha et al., 2020) [2].

Conclusion: The patient has had a good outcome with treatment, however ongoing surveillance is required.

1. Introduction

EMPD is a rare slow growing cutaneous adenocarcinoma that originates in regions with apocrine glands, usually in patient aged between 60 and 80 years [4]. They often present in anogenital or axillary areas as pruritic, erythematous, eczematous plaques that do not resolve with varying topical agents, often resulting in a delay in diagnosis. Primary EMPD is a carcinoma insitu of the apocrine gland ducts. Secondary EMPD is an invasive carcinoma which may be associated with an underlying carcinoma [5]. The secondary form is much rarer occurring in up to 25% of cases and it is pertinent to investigate and establish an underlying carcinoma from either skin or other organs [1]. Staging is also crucial and again the utility of an FDG PET scan is not well established in the context of stage III and IV EMPD [3], however was used successfully in this case report.

Definitive treatment for the primary cohort is wide local excision or Mohs surgery of the affected region. Prognosis in the primary EMPD group is often excellent in patient who receive appropriate treatment [7]. Recurrence rates in this group have been reported to range from 12 to 58% [11]. Hence long term follow up is required. Treatment options for those with secondary or invasive disease is also surgical, with treatment of the primary tumour. The mortality rate of patients with invasive disease if thought to be between 13 and 18% with a 5-year survival of 72% [7]. Patients with distant metastatic disease have an overall survival of 1.5 years and 5 year survival rate of 7% [14].

Currently there are no treatment guidelines for the management of patients with stage 3 or 4 disease- this produces a therapeutic challenge. We present a case with chemoradiation used as a definitive treatment option in a patient with stage 3 disease where an operation would have carried high risk and significant morbidity.

2. Case presentation

A 76-year-old lady had a 1-year history of a perianal rash that was

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non-responsive to multiple agents inclusive of antifungal ointments, steroid creams, and antibiotics. The rash had started at the anal verge and progressively increased in size, spreading to both buttocks. The rash was pruritic in nature with occasional contact bleeding. There was no history of urinary or vaginal symptoms and pap smears were otherwise always unremarkable. She had no altered bowel habit, unexplained weight loss, anorexia, or night sweats. She had presented to a gastroenterologist for a surveillance colonoscopy and at the same time had her perianal rash biopsied which subsequently revealed a diagnosis of extra mammary Paget's disease in May 2020.

She had a past medical history of hypertension, gastro-oesophageal reflux disease (GORD), type 2 diabetes mellitus (diet controlled), and obstructive sleep apnoea (not on CPAP). The patient's father died at a young age due to colon cancer. The patient was an ex-smoker (previously 50 cigarettes per day from age 15 to 62), regular alcohol consumption (1–4 standard drinks daily) and lives independently at home.

On examination there was an eczematous rash in the perianal region with irregular boarders extending to bilateral buttocks (approximately 5 cm bilaterally). Anal canal contained some exophytic lesions which were taken for biopsy. The rash extended upwards toward vulva but did not grossly involve the vaginal vault. Normal cervix and no palpable lymphadenopathy.

Biopsy of the perineal rash confirmed EMPD, immunohistochemical staining was positive for CK7, CK20, CAM 5.2, CDX2 and CEA with invasive carcinoma confirming secondary EMPD [7]. Staging scans including MRI pelvis revealed perineal disease and a suspicious right inguinal node that was FDG avid on PET-CT (Images 1 and 2). On biopsy it was confirmed to be metastatic adenocarcinoma.

Through MDT discussion, the patient proceeded to neoadjuvant chemo radiation therapy (54 GY in 30 fractions with oral capecitabine) over 6 weeks from August 2020 followed by adjuvant 12 cycles fluorouracil plus oxaliplatin (FOLFOX) eventually finishing the last cycle May 2021. The patient had experienced some defecation proctalgia that was eventually managed effectively with a perianal Botox injection. According to the Common Terminology Criteria for Adverse Events (CTCAE) [10], the patient had grade 2 symptoms in regard to fatigue with chemotherapy and grade 1–2 paraesthesia of the fingertips. As a result, she had a break from chemotherapy and eventually a 20% FOLFOX dose reduction.

PET-CT was performed a few months after chemoradiation therapy demonstrating a good response- no FDG avid nodes and no metastases (Image 3). Perineal biopsy after therapeutic intervention showed no EMPD or malignancy. Further CT Chest/Abdomen/Pelvis (CT CAP) performed post cycle 8 of chemotherapy demonstrated no recurrence or residual disease. Surveillance CT CAP 3 months later (1 year surveillance) showed no recurrence, lymphadenopathy, or metastases. The patient will remain under long-term surveillance with interval imaging and examination under anaesthesia to ensure she remains in remission. This case was reported in line with the SCARE criteria [2].

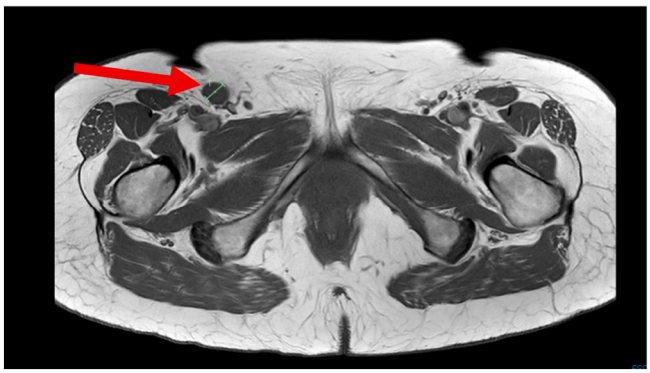

Image 1. MRI Pelvis showing an enlarged right iliac lymph node.

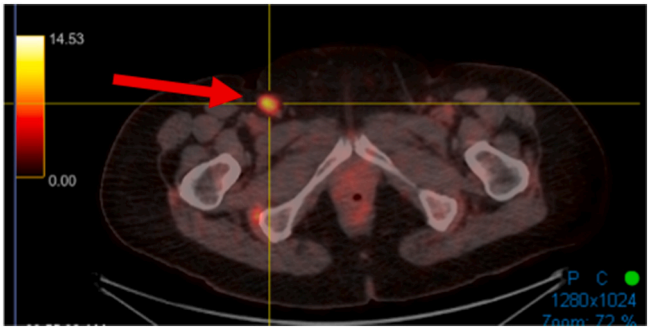

Image 2. Staging PET scan showing increased FDG uptake in the right iliac lymph node.

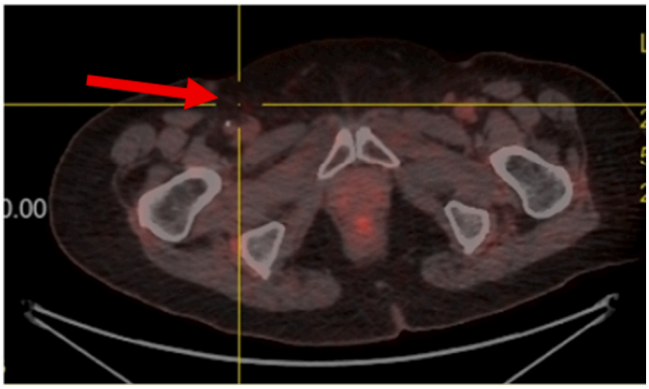

Image 3. PET scan post treatment, no FDG activity in right iliac lymph node.

3. Discussion

Secondary EMPD is a rare entity and there are no current treatment guidelines for patients with invasive disease and local lymph node metastasis or widespread metastases [6]. There have been a few reported treatment modalities in these scenarios including the role of radiation therapy in invasive disease as either definitive treatment or as an adjunct to surgery, chemotherapy (systemic and topical), combined modality, photodynamic therapy, and other topic agents like Imiquimod [8]. Unfortunately, it is hard to discuss overall survival and recurrence rates with these modalities given the rarity and often short term follow up.

In this case report, through MDT discussion it was opted that the patient receive multimodal treatment in the form of chemo radiation therapy followed by systemic chemotherapy. This was due to the extensive area that the disease occupied in the perineum, an operation was thought to have been too morbid. There are no current randomised control trials to compare the outcomes of radiation versus surgery in regard to stage 3 disease. Two systematic reviews and meta-analysis showed various usage of radiation therapy including primary localised disease through to metastatic disease, treatment regimens also varied with setting dosage and variation in fractions [9,12]. Response to radiation therapy ranged from 50 to 100% with variable rate of relapse/local recurrence from 0 to 80%. There is certainly a role for radiation therapy in the treatment of EMPD in certain contexts, however given its rarity there is only low level evidence [12]. Radiation therapy is a relatively safe and in some studies shown to be effective treatment for EMPD [13], whether or not it can be a definitive and potentially curative treatment option remains to be shown and requires more studies and longer term follow up.

Systemic chemotherapy can be used as monotherapy or in combination with other methods, although again there are no current

guidelines for what agents are most efficacious and there are various regimens that have been reported with varying rates of efficacy, disease recurrence and toxicity. Several chemotherapy regimens have been used to treat metastatic EMPD; however, they present limited effect and patients with distant metastasis exhibit a poor prognosis [14]. In this case study a FOLFOX regime was used with thus far good effect and mild toxicity (grade 2 fatigue, paraesthesia).

Given the rarity and lack of level 1 evidence, the management of invasive EMPD, currently staging, treatment options and long term surveillance should be discussed through a MDT meeting. In this case we opted for chemoradiation therapy for definitive management as an operation would have been high risk with extreme risk of morbidity.

4. Conclusion

Chemoradiation therapy and systemic chemotherapy have been used in this case report for definitive treatment in a patient with stage 3 EMPD. So far the outcomes have been good with resolution of disease and minimal toxic side effects, additionally she has avoided surgery which would have conferred significant morbidity given how extensive her perineal disease was. She will require long-term surveillance given the known higher recurrence rates of invasive EMPD.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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CRediT authorship contribution statement

Dr Sharie Apikotoa – design, data collection, interpretation writing the paper.

Dr Joel Stein – Treating general surgical consultant.

Declaration of competing interest

None.

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