



Case report

Invasive Vulval Paget's disease treated with primary radiotherapy: A rare case report and literature review

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ABSTRACT

Extramammary Vulval Paget's Disease (VPD) is rare neoplasm of post-menopausal women. In relatively young perimenopausal patients, it can cause both diagnostic dilemma and therapeutic challenges. Majority of VPD is of non-invasive variety. Among invasive Paget's disease, only 20% cases show invasion more than 1 mm. The present report describes a unique case of an invasive extra-mammary VPD with depth of invasion more than 4 mm presenting at a relatively young perimenopausal lady. Only 14 cases of VPD has been treated with primary radiotherapy in literature till date. We report this case to be the 15th case where radiotherapy was solely used to treat an invasive VPD.

1. Introduction

Paget's disease of the vulva accounts for less than 1% of all vulval cancers (Barmon et al., 2012). Originating in the apocrine gland bearing skin cells, it mostly manifests as an intra-epidermal adenocarcinoma but sometimes involve the underlying dermal appendages in the form of focal invasions (Shaco-Levy et al., 2010). Secondary Paget's may arise from an underlying malignancy from urogenital tract or gastrointestinal tract, etc. Histopathological diagnosis includes the detection of characteristic Paget cells with cytoplasm containing diastase resistant PAS positive material (Baker et al., 2013). Vulvectomy remains the mainstay of treatment. Role of primary radiotherapy as a treatment option has not been extensively evaluated till date.

2. Case report

A 51 years old multiparous lady with history of stable angina 2 years back (on oral nicorandil and ecospirin) and who had undergone hysterectomy 13 years back due to symptomatic fibroid uterus, presented to us with an erythematous patchy lesion over the inner aspect of right labium majus associated with itching for 3 years. There was no ulceroproliferative growth, discharge or active bleeding from the patchy lesion. She consulted local medical practitioners and received multiple over the counter drugs but symptoms were not relieved. Dermatology

consultation was sought and biopsy outside was suggestive of Bowen's disease. She did not have post coital bleeding, anorexia or weight loss. There was no history of high-risk sexual behavior.

On local examination, an erythematous patch of 5x5 cm in the right labium majus extending up to the clitoris and urethral meatus was observed. Induration was present. There was no area of hypopigmentation. Speculum examination revealed a healthy vault with no discharge. On bimanual examination, there was no pelvic mass. Per rectal examination was normal. No inguinal lymph nodes were palpable. Repeat biopsy at our institute showed atypical cells with large round to oval nuclei, prominent eosinophilic nucleoli and abundant vacuolated cytoplasm which stained positive for periodic acid Schiff (PAS) stain. Since features were similar to Paget's cells so a provisional diagnosis of extramammary Vulval Paget's disease (VPD) was made. Tumor cells were Her2-neu positive but carcino- embryonic antigen (CEA) negative. Pap smear from vaginal vault showed benign cellular changes of inflammation. PET-CT showed focal low grade FDG avidity in right labial region.

A wide local excision with 2 cm free surgical margin was performed. Under spinal anesthesia, incision was given over the right labium majus extending upto the clitoris and specimen was excised out. Clitoris was removed. Defect was closed with interrupted delayed absorbable vicryl sutures in two layers. Vaginal packing was done for 24 h. Post-operative period was uneventful. Histopathological report confirmed the presence

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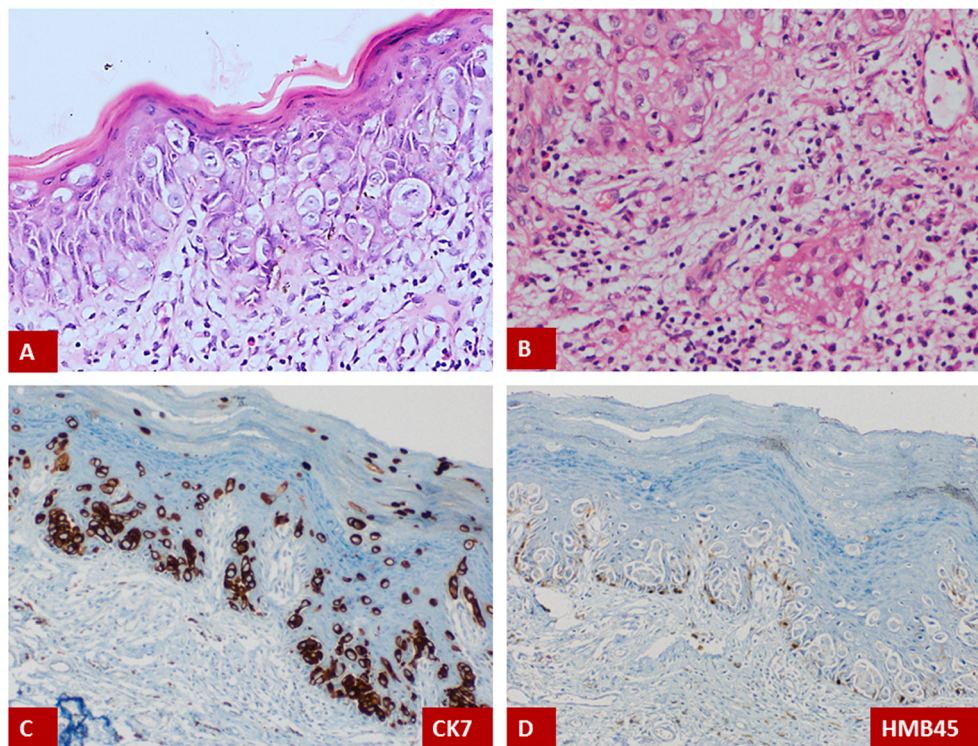


Fig. 1. (A) Section showing full thickness involvement of the epithelium of vulva with large Paget's cell having enlarged nuclei and vacuolated cytoplasm (Haematoxylin and Eosin stain X 240). (B) Focal invasion of the tumour cells into the deeper tissue. (Haematoxylin and Eosin stain X 240). (C) The Paget's cells are positive for CK7 (X 240). (D) The tumour cells are negative for HMB 45 (X 120).

of Paget cells with PAS positivity involving whole of the epithelium [Fig. A](#). Foci of dermal invasion with maximum extent of invasion of 4 mm was noted [Fig. B](#) Superior and lateral margins of the excised specimen and clitoris were involved although inferior margin was free. Immunocytochemistry showed strong positivity for CK7 [Fig. C](#) and CEA signifying primary cutaneous VPD. HMB45 was negative ruling out in situ melanoma [Fig. D](#). Negative CK20 eliminated gastro-intestinal and urothelial secondaries. Considering the high risk of local invasion in Paget's disease decision was taken to perform radical vulvectomy with bilateral inguino-femoral lymph node dissection but she was not cleared from cardiology side due to unstable coronary artery disease. Radiotherapy was planned and she received intensity modulated radiation (IMRT) of 50 Gy in 28 fractions to the groin, bilateral inguino-femoral and pelvic lymph nodes. She is currently under close follow-up at 3 monthly intervals. At 18-month post radiotherapy, there is no residual disease both clinically and radiologically. On clinical examination, no groin lymph nodes are palpable.

3. Discussion and literature review

VPD generally manifests in the form of irritation, itching and burning. 5–15% patients may be asymptomatic ([Willman et al., 2005](#)). Examination reveals erythematous plaque like lesions with typical white scaling known as “cake-icing”, with ulceration and crust formation over the surface. It is often referred to as a clinical chameleon ([Gunn and Gallager, 1980](#)). A plethora of differentials may arise in the form of melanoma, hidradenitis suppurativa, contact dermatitis, psoriasis, lichen sclerosus, fungal infections, vulval intraepithelial neoplasms and occasionally condyloma accuminata ([Vincent and Taube, 2011](#)). Thus, biopsy forms the mainstay of diagnosis.

Immunohistochemical markers have emerged as newer modality for confirming the diagnosis. In our case, immunohistochemistry proved quite informative ([Vincent and Taube, 2011](#)). Positivity for CK7 and CEA stains pointed towards primary cutaneous origin of the neoplasm.

Negative CK20 ruled out urothelial and gastro-intestinal secondaries while negative HMB45 helped to exclude the diagnosis of a melanoma. P53, although not done in the index case, can help to differentiate from Bowen's disease.

Most studies do not define ‘invasive VPD’. Lee et al defined invasion as involvement of the underlying apocrine sweat glands ([Delpert, 2013](#)). Curtin et al and few other authors have however defined dermal invasion as ‘invasion > 1 mm’ ([Curtin et al., 1990](#)). Paget's cells are known to spread microscopically through the epidermis ([Chan et al., 2012](#)). This makes it difficult to determine the extent of spread. Gunn et al have examined specimens from affected vulvas and found that the histological presence of this neoplasm extended far beyond the visible lesion ([Gunn and Gallager, 1980](#)). This may contribute to the difficulties in obtaining a clear margin. As there is no clear definition of surgical margin, so wide local excision remains a challenging task. Wide surgical excision may be a therapeutic approach for non-invasive VPD although this may not always demonstrate acceptable rates of local control ([Gunn and Gallager, 1980](#)). Since Paget's cells are present in hair follicles and bulbs situated deeper into the adipose tissues of the dermis, hence a superficial skinning vulvectomy even in non-invasive VPD may leave diseased hair bulbs leading to local recurrence. So, depth of excision must include the dermis as well ([Gunn and Gallager, 1980](#)). But in case of invasive Paget's disease, margins are often irregular and involvement of microscopic margins occur in approximately 40–75% of patients following surgical excision ([Chan et al., 2012](#)). Recurrence rates are reported to be greater than 50% in invasive VPD after a wide local excision ([Chan et al., 2012](#)). In primary non-invasive disease with clinical negative lymph nodes, risk of lymphatic metastasis is <n 1% but in case of invasive disease risk may increase upto 8% ([Chan et al., 2012](#)). So, radical vulvectomy with bilateral inguino-femoral lymph node dissection is recommended in case of invasive VPD. There is no clear consensus on extent of surgical margin of vulvectomy specimen in an invasive VPD ([Chan et al., 2012](#)). Even frozen section examination is inconclusive for Paget's disease.

Radiotherapy (RT) is an option in the presence of risk factors associated with local recurrence like dermal invasion, positive surgical margins, lymph node metastasis, perineal large tumor diameter, multifocal lesions, coexisting histology of adenocarcinoma, high Ki-67, adnexal involvement or overexpression of Her-2/neu (Moreno-Arias et al., 2001). RT has been used both as definitive and adjuvant modality of treatment in invasive VPD (Hata et al., 2011). It can be used to treat recurrences also (Tolia et al., 2016). Recent Cochrane review in 2019 has found that RT has been used as primary modality of treatment in 14 patients till date (Edey KA, Allan E, Murdoch JB, et al. Interventions for the treatment of Paget's disease of the vulva. Cochrane Database of Systematic Reviews., 2019). 12 women were reported by Parker et al in 2000. There was no documentation of treatment regimens and whether doses used were of palliative or radical levels (Parker et al., 2000).

2 more cases were reported from by Pierie et al in 2003 (Pierie et al., 2003). RT doses of 45–64.8 Gy in fields encompassing 2–3 cm radially around the clinical or excised margin has shown local progression free rates of 91% at 2-year follow-up (Pierie et al., 2003). None of the patients who received RT to the local lymph node regions developed a recurrence after 5 years suggesting that inclusion of the draining groin lymph nodes into the RT field might be important in optimizing treatment outcomes (Parker et al., 2000). In our case, the maximum depth of dermal invasion was 4 mm, thus necessitating the need for radical vulvectomy and bilateral inguino-femoral lymph node dissection. But poor medical condition of the patient did not allow us to do complete surgery. Hence, we decided to go for radiotherapy as an alternative mode of treatment. RT is generally associated with minimal side effects like transient acute confluent wet desquamation in the treated area. Also, recurrence rates are minimum (Son et al., 2005). With these small number of cases, it is still not possible to form any conclusion as to the effectivity of RT as a treatment modality in invasive VPD. Moreover, no adequate information is present regarding long term follow-up of these patients.

The overall 5-year survival of VPD is around 75–91% (Edey et al., 2019). Invasive disease is associated with lower survival rates. Patients with high initial CEA, deeper depths of invasion, lymph node metastasis and nodular lesions are found to have shorter survival than those with intra-epidermal and micro-invasive disease (Edey et al., 2019).

4. Conclusion

VPD is a rare malignancy of the skin in elderly population. Vulvectomy remains the treatment of choice. Bilateral inguino-femoral lymphadenectomy is preferred if the depth of invasion is more than 1 mm. Risk of recurrence is upto 35% for non-invasive and 51–74% for invasive VPD. Role of radiotherapy as a primary modality of treatment still remains debatable as there are only handful of case reports available in literature so far. Reporting of more such cases as ours can be a great help to medical fraternity to assess its role as an upfront treatment strategy in near future.

5. Ethical clearance

Since it is a case report so no ethical clearance is required

6. Financial support

Nil.

This case has not been previously published in any journal Written consent has been obtained from the patient

Declaration of Competing Interest

None

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