Multicentre BSSVD UK Audit on screening practices in Vulval Paget's Disease

Introduction

A recent study by Van der Linden et al, 2018 (1) has brought the subject of routine screening for malignancy in those diagnosed with non-invasive primary cutaneous Paget's disease into sharp focus. It suggests that there is no statistically significant increased risk of associated breast, urological and intestinal malignancy in this cohort of patients for up to 3 years after diagnosis compared to the general population. However, this is with the exception of perianal localisation, as it has been shown to be a risk factor for intestinal/anal malignancies (40% anal cases are associated with anorectal malignancy). Patients with suspected secondary vulval Paget's disease, by definition will have an associated non-cutaneous neoplasm and therefore must continue to be screened for intestinal and urological malignancies.

Background

Vulval Paget's disease (VPD) is a rare skin condition which is most commonly seen in postmenopausal Caucasian women. It often presents with symptoms of itching or burning erythematosquamous plaques and is diagnosed when typical Paget cells are seen within the epidermis. (2)

The aetiology of Paget cells remains unknown. (2) VPD is classified according to origin into 3 main types. Type 1 is primary cutaneous origin, type 2 and type 3 are secondary to another malignancy, intestinal or urological respectively. (3) Most cases of primary disease (i.e. cutaneous) are non-invasive (type 1a). Cutaneous VPD can invade through the basal membrane (type 1b) or be seen in conjunction with a vulvar adenocarcinoma (type 1c). The difference between primary and secondary VPD cannot be made on histopathological assessment alone. (4) VPD has also been considered to be associated with malignancies of the breast. (5,6)

Interestingly, Van der Linden's 2016 (2) review of published cases demonstrated an associated risk of 3.2% breast, 2.2% intestinal and 3.9% urological malignancy compared to much higher associated risks in older publications (18% (5) and 29% (6) of associated breast cancer).

Some consider VPD secondary to intestinal or urological malignancies, a 'pagetoid spread or phenomenon' rather than a separate entity and therefore, primary non-invasive VPD as the only 'true' VPD. (7-10)

Histologically, VPD is characterized by the presence of large oval intraepithelial cells that have pale cytoplasm and large nuclei with prominent nucleoli, the so-called Paget cells. Paget cells can be visualised singly or in clusters throughout the epithelium using haematoxylin and eosin (HE) staining. Reactive changes such as acanthosis and hyperkeratosis can be seen, but in themselves are not sufficient for diagnosis. The scattered Paget cells are diagnostic, but are interspersed within the normal epithelium and can be difficult to detect. Invasive growth must be excluded, however this is challenging because it is not uncommon for VPD to extend into the adnexal structures. An additional problem is the presence of a dense infiltrate that can obscure the epithelial/stromal interface. Invasion is characterized by the presence of poorly cohesive neoplastic Paget cells infiltrating the underlying dermis or submucosa. (2)

Immunohistochemistry is employed to distinguish cutaneous VPD from histological mimics. Paget cells are usually positive for cytokeratin (CK) 7 and carcinoembryonic antigen (CEA). They do not

express markers of squamous cell differentiation (p63 and p40), which can therefore be used to exclude squamous intraepithelial lesions such as uVIN, also known as HPV-induced H-SIL with a pagetoid growth. However, VPD may over express p16 and mimic uVIN (or HPV-induced H-SIL), which strongly over express p16 as well. In addition, Paget cells do not express melanocyte markers, such as Mel-A, HMB45 or S100 which can help distinguish VPD from (in situ) melanoma. Paget cells may express androgen receptors, but in general are negative for oestrogen and progesterone receptors.

Immunohistochemistry can also be helpful in determining the primary location of an underlying adenocarcinoma. For example, pagetoid extension of urothelial cancer will likely express CK20, uroplakin-III, and GATA-3, whereas CK20, CDX2, and MUC2 positivity might indicate an underlying anorectal adenocarcinoma. It is therefore recommended that a combination of these markers be used in cases in which pagetoid extension from an underlying adenocarcinoma is suspected.

Recent findings by Van der Linden et al, 2018 (1) challenge the long-held assumption that primary cutaneous non-invasive VPD ***is*** associated with malignancy. This may assist clinicians in reassuring and allaying the concerns of patients with this diagnosis. Reassuringly, the majority of patients are at an age where they are offered screening for bowel, breast and cervical cancer in any case.

Aim

- To establish current UK practice of screening for associated malignancy in patients diagnosed with VPD.
- To identify the number and type of malignancies detected in type 1a VPD.
- To identify the number and type of malignancies identified on screening for type 2 and 3.

Methods

- Retrospective data collection of all cases of VPD, including female perianal cases, diagnosed over the past 5 years (from January 2015 to present date).
- Cases will be identified using any methods available (e.g. memory, clinic lists, histology databases). If the local information team is involved to help perform search on electronic patient record system, completion of access to patient information form/accurate ICD coding will be necessary.
- Information will be collected on age of patient, type of VPD including histology and immunohistocytochemistry, screening investigations performed and results of screening investigations including detection of any secondary malignancies.
- One proforma to be completed per patient. Clinical notes including the histopathology report will be necessary.
- The proforma should not include any identifiable patient data.
- Data collection proforma to be distributed to all departments with dedicated vulval clinics via BSSVD membership (including gynaecology/gynae-oncology clinics).
- It is recommended that the audit is registered with local hospital governance department.
- Deadline for return of completed proformas: **1st September 2020.**
- Return completed proformas to sabrina.khan@ouh.nhs.uk

End-point

Once data collection is complete in each centre **(1st September 2020),** proformas to be returned for statistical analysis. Audit data will be analysed with the intention of presenting the completed audit at the next available BSSVD meeting.

References

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