Research article

**A Clinicopathological Classification of Perianal Paget’s Disease**

Elroy Patrick Weledji

Department of Surgery, Faculty of Health Sciences, University of Buea, Buea, PO Box 63, Cameroon

Correspondence to: Prof Dr Elroy P Weledji, Pemset House, PO Box 126. Limbe, Cameroon. E-mail: elroypat@yahoo.co.uk

**Abstract**

**Background:**  Perianal Paget’s disease is exceedingly rare and a heterogenous entity. The current staging system does not take into account the paraneoplastic aspect of the disease. The author attempted to simplify the conundrum by proposing a clinicopathological classification system of perianal Paget’s disease.

**Methods**: The texts on the staging and treatment of perianal Paget’s disease have been reviewed. The clinicopathological classification has been developed from the cases reported in the literature and texts on perianal Paget’s disease.

**Results:**  The presenting author classified perianal Paget’s disease into four clinicopathological groups. In the first group (Type1), there is a high frequency of an associated distant malignancy with similar immunoprofile requiring an aggressive search for the primary. This is akin to a paraneoplastic syndrome and has the worse prognosis. In the second group (Type 2) which is the commonest presentation, perianal Paget’s disease represents a cutaneous manifestation through the intraepithelial spread of an underlying anorectal or vulvar adenocarcinoma (i.e. secondary). The third group (Type 3) represents true primary intraepithelial cutaneous apocrine adenocarcinoma. The fourth group (Type 4) represents a primary perianal Paget’s disease with an associated malignancy but with discordant immunoprofile.

**Conclusions**: Preoperative staging of perianal Paget’s disease should include the Weledji’s clinicopathological classification before deciding treatment.

**Keywords:** Perianal; Paget’s disease; staging; classification; clinicopathological

**Introduction**

Perianal Paget’s disease is extremely rare. First discovered by Paget in 1874 (figure 1) as a breast lesion (figure 2) [1], similar findings in the perianal area were reported 20 years later by Darier (figures 3, 4) [2]. Sir James Paget, who is the father of British pathology stressed the importance of bringing science into medical practice with the success base on his knowledge of pathology and physiology. These are seen in his descriptions of Paget’s disease of bone, Paget’s abscess and Paget’s disease of the nipple etc. Paget reported in 1874 a chronic eczematous disease on the skin of the nipple and the areola with associated intraductal carcinoma in 15 women [1]. The ductal carcinoma-in-situ extended along major ducts into the skin around the nipple. Paget’s disease of the nipple is thus a secondary disease. The French dermatologist, Ferdinand-Jean Darier (figure 3), a father of modern dermatology demonstrated in 1893 similar findings of perianal Paget’s disease as a cutaneous paraneoplastic syndrome (figure 4) [2]. He had demonstrated papulosquamous disorders such as acanthosis nigricans associated with gastric cancer and other cutaneous manifestations of distant malignancies such as tripe palms, palmar hyperkeratosis, acquired ichthyosis, erythema annularis, dermatofribrosarcoma etc,. A paraneoplastic syndrome is non-metastatic systemic effects that accompany malignant disease. It may consist of a set of signs and symptoms that is a consequence of cancer, but not due to local presence of cancer cells [3]. It may present as dermatoses which may precede, coincide with or follow the diagnosis of cancer. It may also be evidence of local recurrence of cancer. Generally, a paraneoplastic syndrome is often associated with a poor prognosis. The mechanism may entail humoral factors (hormones/ cytokines) excreted by tumour cells or immune response against tumour [3]. Therefore, perianal Paget’s disease is an heterogenous entity. It can present in isolation as a primary lesion of the apocrine glands, may be associated with underlying malignancy by intraepithelial spread of carcinoma of the sweat glands in vulva, perianal region, rectum, i.e. secondary as in the breast or may manifest as a cutaneous paraneoplastic syndrome [4]. ‘True’ Paget’s disease (a primary lesion of the apocrine glands) is usually a low-grade neoplastic lesion and can be distinguished from the Pagetoid spread of signet ring cells from a nearby carcinoma (a secondary lesion) by immunohistochemical studies CK7+/ CK20+/ GCDFP-15-/ lysozyme-/Leu- M1- immunophenotype [5]. The cytokeratin CK20 and GCDFP-15 are particularly useful adjuncts in distinguishing primary and secondary perianal Paget’s disease. If apocrine markers are absent in the staining pattern of perianal Paget’s, it is more likely that the lesion is associated with an underlying adenocarcinoma [5-8]. As perianal Paget’s disease is a heterogenous entity, the author proposed a clinicopathological classification system. The current staging system utilizes a tumour progression (TNM) histopathological approach which does not take into account the paraneoplastic aspect of the disease.

**Methods**: The texts on the staging and treatment of perianal Paget’s disease have been reviewed. Electronic searches of the medline (PubMed) database, Cochrane library, and science citation index were performed to identify original published studies on perianal Paget’s disease. The clinicopathological classification of perianal Paget’s disease was developed from the cases reported in the literature and from relevant chapters in specialized texts.

**Results**

100 cases were reported between 1893 -1990, 193 cases between 1990-2008 and 10 cases between 2009-2017. It is more common in white - skinned races, women greater than men and in the 50-80 years range [6]. The staging and treatment of perianal Paget’s disease (1990) is illustrated in table 1 [9]. Stage 1 is Paget’s cells found in peranal epidermis (in situ) and adnexa without primary carcinoma. This will require wide local excision. Stage IIA is cutaneous Paget’s disease without adnexal carcinoma (primary) in which a wide local excision with flap reconstruction would suffice. Stage IIB is cutaneous Paget’s disease with associated anorectal carcinoma. This would require an abdominoperineal resection. Stage III is peranal Paget’s disease in which the associated anorectal carcinoma has spread to the regional inguinal nodes. This would require abdominoperineal resection with inguinal node dissection. Stage IV is perianal Paget’s disease with distant metastases of associated carcinoma. This would require chemotherapy, radiotherapy and local palliative treatment. The presenting author classifies perianal Paget’s disease into four clinicopathological groups. In the first group (Type1), there is a high frequency of an associated distant malignancy with similar immunoprofile ( lysozyme /leu1-M1) requiring an aggressive search for the primary. This is akin to a paraneoplastic syndrome and has the worse prognosis [8, 10-12]. Regression of perianal Paget’s disease (type 1) has been observed following removal of an associated sigmoid colon carcinoma [13]. In the second group (Type 2) which is the commonest presentation, perianal Paget’s disease represents a cutaneous manifestation through the intraepithelial spread of an underlying anorectal or vulvar adenocarcinoma (i.e. secondary just like Paget’s of the breast) [4, 13-17]. This type may be made latent by neoadjuvant and adjuvant chemotherapy to slowly re-emerge as the evidence of local recurrenceafter anterior resection (figure 1) [4] The third group (Type 3) represents true primary intraepithelial cutaneous apocrine adenocarcinoma which is usually a low - grade neoplastic lesion [7, 18-20]. The fourth group (Type 4) represents a primary perianal Paget’s disease with an associated malignancy but with discordant immunoprofile [21, 22].

Table 1: Staging and treatment of perianal Paget’s disease [9]

|  |  |
| --- | --- |
| STAGE | THERAPY |
| **I.Paget’s cells found in perianal epidermis *(in situ)* and adnexa without primary carcinoma** | **Wide local excision** |
| **IIA. Cutaneous Paget’s disease without associated adnexal carcinoma *(primary)*** | **Wide local excision (Flap reconstruction)** |
| IIB. Cutaneous Paget’s disease with associated anorectal carcinoma *(secondary)* | **Abdominoperineal excision** |
| III. Paget’s disease in which associated anorectal carcinoma has spread to regional nodes *(secondary with locoregional spread)*  IV. Paget’s disease with distant metastases of associated carcinoma | **Inguinal node dissection**  **Abdominoperineal excision**  **Chemotherapy, radiotherapy**  **Local palliative treatment** |

**Table 2: Weledji’s Clinicopathological Classification of Perianal Paget’s disease.**

|  |  |
| --- | --- |
| Type 1 | * **Cutaneous paraneoplastic syndrome -underlying adenocarcinoma may be in a distant organ, with similar immunoprofile (*lysozyme/leu1-M1)*** * **aggressive search for the distant primary, poor prognosis** |
| Type 2 | * **50-80%** * **cutaneous manifestation via intraepithelial spread of an underlying anorectal or vulva adenocarcinoma (i.e. secondary -just like Paget’s of the breast)** * **necessitating an abdomino-perineal excision** |
| Type 3 | * **‘True’ perianal Paget’s disease affecting the apocrine glands only i.e. primary** * **Rare, indolent but often recurs** * **low- grade neoplasia when unassociated with adenocarcinoma elsewhere 50-70yrs, M=F** |
| Type 4 | * **Primary perianal Paget’s disease with an associated malignancy but with discordant immunoprofile ( *indicating different origin*)** |

**Discussion**

It is important to compare Paget’s disease of the breast with perianal Paget’s disease histopathologically. Paget’s disease of the breast is always accompanied by intraduct carcinoma, and direct continuity at the nipple can usually be demonstrated [1, 3]. The affected skin shows reactive changes in the dermis, with exudation, formation of vascular fibrous tissue, and infiltration with lymphocytes and plasma cells. These changes produce a characteristic eczematous condition of the nipple and areola named Paget’s disease of the breast (figure 2). The cancer cells are larger than those of the epidermis, with pale cytoplasm and a large vesicular, hyperchromatic nucleus and prominent nucleolus (Pagetoid cells) (figure 5). In some patients, intraduct cancer has already invaded the breast stroma but in others, it is still contained within the duct system. In either case, mastectomy is essential. Similarly, extramammary Paget’s disease of the skin may occur at the vulva, parianal region, axilla, etc., by intraepithelial spread of carcinoma of the sweat glands in these sites [20, 23]. As Paget’s cells are probably of apocrine origin, corroborated by the breast itself being a modified sweat gland, these are ‘true’ Paget’s disease (figure 6) with usually low-grade neoplasia when unassociated with adenocarcinoma elsewhere (Type 3)[7]. The immunophenotype is favourable with an excellent prognosis if adequately resected [5]. In most cases of perianal Paget’s disease (50-80%), there is an underlying adenocarcinoma usually of the rectum or vulva (figure 7) (Type 2) although the lesion may rarely be in a distant organ (Type 1) [8, 13-17, 23]. Clinically occult Paget’s disease may be found on histologically examination following rectal excision for carcinoma (Type 2) [13, 14, 17]. Perianal Paget’s disease has occurred 4 years after anterior resection of rectal carcinoma associated with local recurrence of rectal carcinoma, necessitating an abdominoperineal excision (Type 2) [4]. Latent perianal Paget’s disease from contiguous spread have appeared several years following excision of rectal carcinoma (Type 2) [24]. Conversely, Paget’s disease with no apparent associated malignancy may be followed several years later by the development of an adenocarcinoma (Type 2) [13, 14, 17]. The stage 11b and stage III of the current staging system is equivalent to the Type 2 of the clinicopathological classification. Type 4 consists of primary perianal Paget’s disease with an associated malignancy but with discordant immunoprofile which may indicate a different origin [12, 21, 22]. Although a typical macroscopic appearance of perianal Paget’s disease shows a variegated darkly reddened skin and distorsion of the anus (figure 4), the differential diagnosis of perianal Paget’s disease is wide. It includes intraepithelial squamous cell carcinoma (Bowen’s disease), squamous cell carcinoma, dermatitis, lichen planus, melanoma, psoriasis, hidradenitis suppurativa, and eczema [25]. Thus, the diagnosis must be confirmed from several full-thickness biopsies around the periphery of the lesion under general anaesthesia (figure 8) [26, 27]. The staging system is the basis for deciding appropriate treatment of perianal Paget’s disease as shown in table 1 [9]. However, there are limitations of the current staging system because it is based simply on tumour progression (TNM) and not on the clinicopathological aspect of the disease. For example the stage I or stage IIa in the current staging system with apparently no associated primary or adnexal carcinoma histopathologically may clinicopathologically be a Type 1 where a distant primary should be sought, and, it is indeed most sinister as being part of a paraneoplastic syndrome. Stage IIa defining cutaneous perianal Paget’s disease without an adnexal carcinoma may be a ‘true’ primary Paget’s equivalent to Type 3 of the Weledji’s clinicopathological classification system. This has a good prognosis as being a low grade lesion which is successfully treated by wide local excision. In addition, the staging system excluded concomitant cancers with discordant immunoprofile (Type 4).

Clinicians and pathologists should carefully examine the perianal epidermis in anorectal carcinoma and vice versa if the anorectal tumour shows intraepithelioid pagetoid (signet ring) cells. Preoperative staging of perianal Paget’s disease should include the Weledji’s clinicopathological classification before deciding treatment. Long-term follow-up after definitive treatment is required as local recurrence may occur many years later with the risk of metastatic spread.

**DECLARATIONS**

**Acknowledgement**

The author would like to acknowledge his clinical fellowship award on pelvic floor surgery granted by the European Society of Coloproctology to Kantonsspital St Gallen, Switzerland, where my study on perianal Paget's disease evolved. I acknowledge Dr. Lukas Marti and Dr. Walter Brunner of the coloproctology unit at Kantonsspital St Gallen.

**Authors’ contributions**

The author contributed solely to the article

Availability of Data and Materials

Not applicable

Financial support and sponsorship

None

Conflict of Interest

Author state no conflict of interest

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

**References**

1. Paget, J. (1874) On disease of the mammary areola preceding cancer of the mammary gland St Bartholomew Hosp Res Lond 10:87–9
2. Darier, J., and Couillard, P. (1893) On a case of Paget's disease of the perineo-anal scrotal region Soc Franc Dermatol Syph 4:25–31
3. Anderson, J. R. (2005) Tumours: 1. General features, types and examples. In: Muir’s Textbook of Pathology; Ed J.R. Anderson 12thEd; Taylor and Francis publisher
4. Weledji, E. P., Hummel, B., Marti, L., Gruenert, J., Malkert, E., and Brunner, W.(2016). Perianal Paget's disease: Is it a primary or secondary disease? World J Colorectal Dis 6:1
5. Nowak, M. A., Guerriiere-Kovach, P., Pathan, A., Campbell, T. E., and Deppisch, L. M. (1998). Perianal Paget’s disease: distinguishing primary and secondary lesions using immunohistochemical studies including gross cystic disease fluid protein-15 and cytokeratin 20 expression. Arch Pathol lab Med 122(12):1077-81
6. Carbotta, G., Sallustio, P., Prestera, A., Laforgia, R., Lobascio, P., and Palasciano, N. (2016) Perineal Paget's disease: A rare disorder and review of literature Ann Med Surg (Lond) 9:50–2
7. Merot, Y., Mazoujian, G., Pinkus, G., Momtaz, T. K., and Murphy, G.F. (1985) Extramammary Paget's disease of the perianal and perineal regions. Evidence of apocrine derivation Arch Dermatol 121:750–2
8. Le Fur, R., Mears, L., and Dannawi, Z. (2004). A peri-anal extramammary Paget's disease associated with two well-differentiated invasive intramucosal sigmoid carcinomas, a very rare case: An immunohistochemical and clinical review of extramammary Paget's disease Ann R Coll Surg Engl , 86:W26–31
9. Shutze, W. P., Gleysteen, J. J. (1990) Perianal Paget's disease. Classification and review of management: report of two cases. Dis. Colon. Rectum33(6):502-7.
10. Shimizu, S., Kobayashi, H., and Suchi T., et al**.** (1991)Extramammary Paget’s disease arising in mature cystic teratoma of the ovary. Am J Surg Pathol 5:1002-6
11. Stephenson, T. J., Cotton, D.W. (1987) Paget’s disease in an epidermal cyst. Dermatologica 174:186-90
12. Neumann, R. (1986) Extramammary Paget’s disease associated with stomach cancer. Hautarzt 37:566-570
13. Lertprasertsuke, N., and Tsutsumi, Y. (1991) Latent perianal Paget's disease associated with mucin-producing rectal adenocarcinoma.Report of two cases Acta Pathol Jpn 41:386–93
14. Kubota, K., Akasu, T., Nakanishi, Y., Sugihara, K., Fujita, S., and Moriya, Y. (1998) Perianal Paget's disease associated with rectal carcinoma: A case report Jpn J Clin Oncol 28:347–50
15. Louis-Sylvestre, C., Haddad, B., and Paniel, B.J.(2001) Paget's disease of the vulva: Results of different conservative treatments Eur J Obstet Gynecol Reprod Biol 99:253–5
16. Kim, N. R., Cho, H. Y., Baek, J. H., Jeong, J., Ha, S.Y., and Seok, J. Y., et al. (2016) Rare case of anal canal signet ring cell carcinoma associated with perianal and vulvar pagetoid spread J Pathol Transl Med 50:231–7
17. Sasaki, M., Terada, T., Nakanuma, Y., Kono, N., Kasahara, Y., and Watanabe, K. (1990). Anorectal mucinous adenocarcinoma associated with latent perianal Paget's disease Am J Gastroenterol 85:199–202
18. Northover, J. (1997) Malignant tumors: Anal and Perianal disease; In: Surgery of the Colon and Rectum. Eds: R John Nicholls, Roger R, Dozois Ist Edn 1997. Churchill Livingstone
19. Clark, M. E., Schlussel, A. T and Gagliano, R. A. Jr. (2013) Management of adenocarcinoma in the setting of recently operated perianal Paget's disease Case Rep Surg 2013:510813
20. Goldblum, J. R., and Hart, W. R. (2009). Perianal Paget's diseases: A histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma Int J Surg Pathol. 17:42–5
21. Chanjuan, S., and Argani, P. (2014). Synchronous primary perianal Paget's diseases and rectal adenocarcinoma: Report of a hitherto undescribed phenomenon Dis Colon Rectum. 57:747–51
22. Liao, X., Mao, W., and Lin, A. (2014) Perianal Paget's disease co-associated with anorectal adenocarcinoma: Primary or secondary disease? Case Rep Gastroenterol. 8:186–92
23. Armitage, N .C., Jass, J. R., Richman, P. I., Thomson, J. P. and Phillips, R. K. 1989. Paget's disease of the anus: A clinicopathological study Br J Surg. 76:60–3
24. Koashi, Y., Kitajima, S., Schwartz, R. A., and Tsuji, T. ( 1997) Perianal Paget's disease years after rectal adenocarcinoma removal. Dermatol Surg. 123:1032–4
25. Devine, R. M. (1997) Perianal dermatology; In: Surgery of the Colon and Rectum. Eds: R John Nicholls, Roger R, Dozois Ist Edn. Churchill Livingstone
26. Jabir, S., Khatib, M., Ali, S., and Niranjan, N. (2013) Perianal Paget's disease: A diagnostic dilemma.BMJ Case Rep 2013;2013 pii: Bcr2013200504
27. Wielfeldt, E. D., and Thiele, J. (2009). Malignancies of the anal margin and perianal skin. Clin Colon Rectal Surg 22(2): 127-135

**Figure Legends**

Figure 1: Sir James Paget (1870)



Figure 2: Paget’s disease of the breast



Figure 3: Ferdinand-Jean Darier (1856-1938)



Figure 4: Perianal Paget’s disease



Figure 5: Cutaneous Paget’s *(showing Pagetoid cells and reactive changes in the dermis)* with adnexal carcinoma

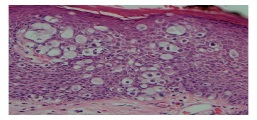


Figure 6: ‘True’ Paget’s disease (a primary lesion of the apocrine glands)

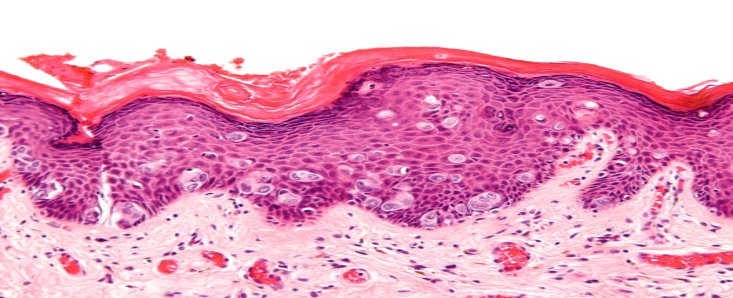


Figure 7: Pagetoid spread of signet ring cells from a nearby carcinoma (a secondary lesion) by immunohistochemical studies (CK7+/CK20+/GCDFP-15-/lysozyme-/Leu-M1-immunophenotype

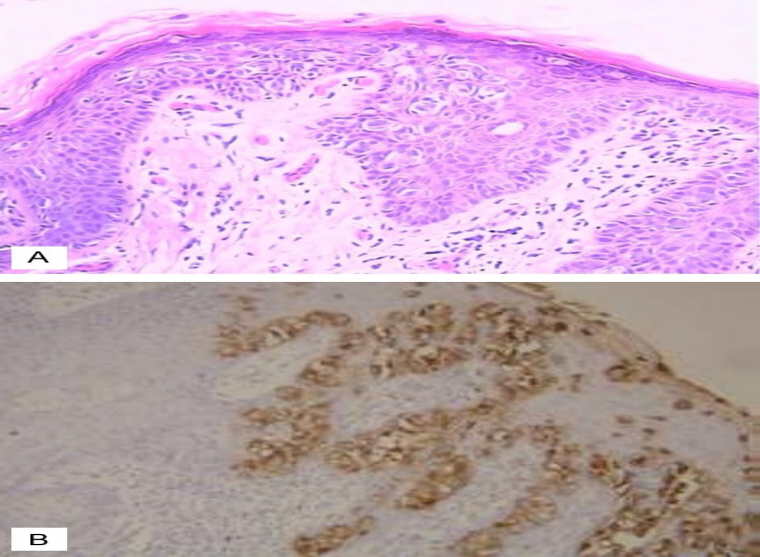


Figure 8: Perianal mappingof the lesion under general anaesthesia

