Extra-mammary Paget’s Disease

Subjects: Pathology
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Extramammary Paget disease (EMPD) was first described by Crocker in 1889 in a man affected from bladder carcinoma and presented with an eczematous lesion involving the penoscrotal region, that was diagnosed as Paget disease in an extramammary site. Subsequently EMPD has been reported involving more frequently the external female genitalia and less commonly, the perianal/perineal region, groin, axilla, umbilicus, eyelids, and also external ear canal.
EMPD has been defined by World Health Organization (WHO) as an intraepithelial neoplasm of epithelial origin expressing apocrine or eccrine glandular-like features and characterized by distinctive large cells with prominent cytoplasm, referred to as Paget cells’.

estrogen receptor progesterone receptor

1. Introduction

The pathogenesis of EMPD is not fully understood; the stem cell compartment of the epidermis and hair follicle as well as Toker cells and mammary-like glands have been reported as possible sites of origin of Paget cells [6][7][8].

Over time, different attempts to classify EMPD have been made and, in particular, at the vulvar site, a histopathological classification of VPD has been conceived, distinguishing primary/cutaneous VPD (type 1) from secondary/non-cutaneous VPD [9]. In detail, cutaneous VPD (type 1) is further subdivided according to the presence or absence of dermal invasion: type 1a (intraepithelial disease arising within the epidermis and extending into the epithelium of skin appendages and less commonly arising from the skin appendages and migrate to the overlying epidermis by epidermotropism); type 1b when focal invasion can be observed; type 1c when there is a cutaneous “pagetoid spread” from an underlying vulvar adenocarcinoma of the skin appendage or subcutaneous vulvar glands.

The 5-year survival is highly variable, depending on the entity of infiltration, being, respectively, 100% and 88% for intraepithelial and micro-invasive disease (<1 mm), and only 15% when neoplastic invasion exceeds 1 mm [10].

On the other hand, secondary VPD can originate by epidermotropic metastases or by direct extension from a malignancy of the gastrointestinal tract (type 2) or the uro-genital tract (type 3) [11][12].

More recently, the WHO Classification of Tumours of Female Reproductive Organs (4th edition) considers to use the subdivision of cutaneous and non-cutaneous EMPD in routinary diagnosis [5].

Given the rarity of EMPD, data on genetic alterations are largely unexplored. Findings regarding the hormonal status including Her2/Neu amplification are probably the most studied genetic alteration, likely because of their therapeutic potential but the clinical significance of these abnormalities still remains to be fully understood [13]. Being aware that at present the need of a tailored treatment for EMPD is a critical clinical goal, but its concrete availability is still too far to achieve, we reviewed the current literature in order to study the impact of IHC expression in VPD and EMPD in both genders of biological markers that could serve as potential prognostic/therapeutic factors, including human epidermal growth factor receptor 2 (HER2/neu), Estrogen Receptor (ER), Progesterone Receptor (PR), and Androgen Receptor (AR).

2. Discussion

EMPD, also referred as in situ adenocarcinoma of the skin, is a rare malignant disorder of skin occurring on cutaneous sites with abundant apocrine sweat glands and hair follicles [1][2][3][4][5]. The most common sites of occurrence are represented by the vulvar region, perineal, perianal, scrotal, and penile skin. Axilla, buttocks, thighs, eyelids, and the external auditory canal represent other uncommon sites of occurrence [1][2][3][4][5]. Clinically, EMPD manifests as erythematous or persistent, eczema-like skin lesions [1][2][3][4][5].

The majority of primary EMPD, are confined to the epidermis, with a slow growth and exceptional metastases. However, cases with dermal invasion show an increased propensity for lymph node involvement and distant metastases [45]. In this subset of patients, imaging, ultrasound guided aspirative cytology, as well as sentinel lymph node biopsy have proven interesting results for the early detection of metastases and therapeutic management [46][47][48][49][50].

Before rendering the diagnosis of primary Paget disease, synchronous or metachronous secondary malignancies arising from the underlying dermis and adjacent or distant organs must be taken into consideration. In detail, sweat gland adenocarcinoma, colorectal carcinoma, prostatic carcinoma, endometrioid adenocarcinoma, and urothelial carcinoma represent possible etiologic factors of secondary EMPD [6][9][11][12][51].

In the present review and meta-analysis, we mainly focused on the hormonal environment and HER2 status in EMPD. Surprisingly, all papers before 2000 failed to demonstrate ER, PR, and AR expression, while, starting from 2000, we noted a hormonal background in EMPD mainly dominated by AR (Table 1). In detail, the observed expression rates for ER, PR, and AR were 13%, 9%, and 40%, respectively. Considering the patients' sex, our results, in a total set of 4 studies involving 95 patients, have shown that the expression of ER was 12% (95% CI = 0.03–0.36) in female and 9% (95% CI= 0.00–0.68) in male patients and that the expression of PR was 9% (95% CI = 0.03–0.25) in female patients, and 2% in male patients. On the other hand, in a set of seven studies involving a total of 227 patients, higher expression rates of AR were detected both in female (40%; 95% CI = 0.34–0.47) and

male (40%; 95% CI = 0.32–0.48) patients. According to these findings, anti-androgen target therapy seems promising tool in the management of EMPD [52].

Table 1. Characteristics of Included Studies in the Meta-Analysis.

Author	Year	Country	Age (Mean or Median)	Se X(% female)	Total Cases	Micro-Invasive/ Invasive Cases (%)	Positive Expression In Microinvasive/INVASIVE Cases (%)	Marker	Positive ihc Espression (%)	Her2 Amplificatin Status (%)
Aoyagi, et al.	2008	Japan	70.6	34.7	23	6/23 (26)	4/6 (66.6)	HER2	F: 7/8 (87.5) M: 10/15 (66.6)	N/A
Bianco, et al.	2006	USA	75	100	15	N/A	N/A	HER2	6/15 (40)	1/15 (7)
Brummer, et al.	2004	Germany	N/A	100	10	2/10 (20)	2/2 100	HER2	8/10 (80)	N/A
Diaz de Leon, et al.	2000	USA	64.5	82	28	N/A	N/A	AR PR ER	F: 12/23 (52.2) M: 3/5 (60) 0/28 0/28	
Fujimoto, et al.	2000	Japan	67	26.6	30	13/30 (43.3)	9/13 (26.6)	AR	F: 8/8 (100) M: 16/22 (72.7)	
Garganese, et al.	2019	Italy	67	100	41	11/41 (26.8)	HER2 4/11 (36.3) AR 10/11 (90.9) PR 2/11 (18) ER 8/11 (72.7)	HER2 AR PR ER	10/41 (24.4) 33/41 (80.5) 9/41 (22) 29/41 (70.7)	10/41 (24.4)
Gatalica, et al.	2020	USA	61	72.2	18	15/18 (83.3)	AR 9/15(60) ER (4)/15 (26.6)	AR ER	F: 9/13 (69.2) M: 3/5 (60) F: 2/13 (15.3) M: 2/5 (40)	

Author	Year	Country	Age (Mean or Median)	Se X(% female)	Total Cases	Micro-Invasive/ Invasive Cases (%)	Positive Expression In Microinvasive/INVASIVE Cases (%)	Marker	Positive ihc Espression (%)	Her2 Amplificatin Status (%)
Hanna, et al.	2003	Canada	N/A	100	20	N/A	N/A	HER2	1/20 (5)	0/19
Hikita, et al.	2012	Japan	70.47	64.70	17	23.5	ER 0/2 PR 0/2 HER2 8/8 4/4(100)	HER2	F: 9/11 (81.8) M: 3/6 (50)	0/8
Horn, et al.	2008	Germany	N/A	100	8	N/A	N/A	HER2 ER PR	8/8 (100) 1/8 (12.5) 1/8 (12.5)	N/A
Inoguchi, et al.	2006	Japan	71.7	17.6	34	N/A	N/A	AR	F: 1/6 (16.6) M: 14/23 (60.8)	
Kasashima, et al.	2010	Japan	71.5	44.8	58	16/58 (27.5)	9/16 (56.2)	AR	F: 12/26 (46) M: 21/32 (65.6)	
Liegl, et al.	2005	Germany	N/A	100	23	N/A	N/A	HER2 AR PR ER	12/23 (52) 18/23 (78) 0/23 (0) 1/23 (4)	N/A
Liu, et al.	2009	USA	69	71.4	14	N/A	N/A	HER2	5/14 (35.7)	N/A
Lu, et al.	2018	China	63	0	11	N/A	N/A	HER2	3/11 (27.2)	2 (FISH+) + 1(genetic heterogeneity)/11
Masuguchi, et al.	2011	Japan	N/A	41.9	31	11/31 (35.4)	10/11 (90.9)	HER-2	F: 7/13 (53.8) M: 12/18 (66.6)	N/A
Miyamoto, et al.	2010	Japan	74	43.7	32	19/32 (59.3)	13/19 (68)	HER2	F: 7/14 (50) M: 13/18 (72)	2/5 (40)
Morbeck, et al.	2016	Brazil	66.8	100	11	2/11 (18)	2/2 (100)	HER2	6/11 (54.5)	2/6 (33.3)

Author	Year	Country	Age (Mean or Median)	Se X(% female)	Total Cases	Micro-Invasive/ Invasive Cases (%)	Positive Expression In Microinvasive/INVASIVE Cases (%)	Marker	Positive ihc Espression (%)	Her2 Amplificatin Status (%)
Ogawa, et al.	2005	Japan	68.5	14.7	34	16/34 (47) 18/34 (52.9)	5/18 (27.7)	HER2	F: 1/5 (20) M: 6/29 (20.6)	3/7 (42.8)
Plaza, et al.	2009	USA	66	70.2	47	2/47 (4.2)	0/2 (0)	HER2	F: 14/33 (42.4) M: 1/14 (7)	N/A
Reich, et al.	2005	Austria	63	100	6	N/A	N/A	HER2	4/6 (66.6)	4/6 (66.6)
Richter, et al.	2010	USA	68.5	100	33/39 *	7/33 (21)	5/7 (71)	HER2	19/33 (57.5)	N/A
Sekiguchi, et al.	2020	Japan	71	50	4	N/A	N/A	HER2	F: 2/2 (100) M: 2/2 (100)	2 amplified 2 polysomic
Tanaka, et al.	2016	Japan	72	15.3	26	26/26 (100)	6/26 (23.07)	HER2	F: 2/4 (50%) M: 4/22 (18)	5/6 (83.3)
Tanaka, et al.	2013	Japan	71.1	33.6	104	73/104 (36.5)	10/73 (13.7)	HER2	F: 5/35 (14.2) M: 7/69 (10)	12/16 (75)
Tanskanen, et al.	2003	Finland	65.47	60.8	23	3/23 (13.04)	1/3 (33.3)	HER2	F: 12/23 (52) M: 4/9 (44.44)	10/23 (43.47)
Zhang, et al.	2015	China	61.5	0	2	1/2 (50)	1/2 (50)	HER2	1/2 (50)	N/A

* Tissue specimens available for Her-2/neu testing.

Regarding ER and PR expression in EMPD, limited and conflicting results are still available. However, a recent study by Garganese et al., reported a remarkably high percentage of ER-positive EMPD (at least 70%), which may provide novel insights in the future hormonal treatment of this disease [19].

Regarding HER2 status, our results indicated that, in a highly heterogeneous set of 27 studies, the overall rate of HER2/neu expression was 30% (95% CI = 0.25–0.36; Q = 34.47; I^2 = 39.08). Considering the patients' sex, the performed analyses have also indicated that the expression of HER2/neu in female and male patients was 32% (95% CI = 0.27–0.38) and 26% (95% CI=0.18–0.36), respectively. Moreover, some authors highlighted a possible correlation between HER2 overexpression and disease recurrence, dermal invasion, and lymph-node metastases [33][34][35][36].

Few studies have also analyzed HER2 overexpression and gene amplification in metastatic patients. Ogawa et al. have found HER2 overexpression in 19.4% of the lesions, three of which with HER2 amplification by CISH [32]. Tanaka et al. reported that the ERBB2 gene was amplified in all cases with a HER2 score of 3+ [37]. Other authors detected by CISH HER2 gene amplification in 43% of the lesions. HER2 protein overexpression (score 3+ by IHC) was found in 12 tumors (52%), including all 10 tumors with gene amplification [39].

A good overall concordance between HER2 status in primary tumors and in the corresponding metastatic sites has also been described in EMPD [37]. This finding contrasts with the reported discordance rates of HER2 expression between primary and metastatic lesions reported for breast and gastric cancer [53].

According to these results, we can conclude that HER2/neu overexpression is found in at least one-third of EMPD lesions, probably characterized by poor outcome related to deep invasion, recurrence, and node metastases. However, therapies targeting HER2 may be useful in treating HER2 positive advanced and/or metastatic patients [28][36].

Moreover, several studies in the field of epigenetics have documented the pathogenic role of MicroRNAs (miRNAs) in different solid tumors, including HER2 positive breast cancer [54][55][56]. MiRNAs are small endogenous non-coding RNAs with a wide range of cellular functions. In breast cancer, both oncogenic and tumor suppressor properties have been related to specific miRNAs. In detail, miRNAs are involved in different stages of breast cancer progression, such as tumor growth, apoptosis, differentiation, angiogenesis, metastasis, and drug resistance [54][55][56]. Importantly, the tumor suppressor role of miRNAs has been recently highlighted also in HER2-overexpressing breast cancer where they mediate the downstream signaling of HER2, suppress the expression of HER2 and affect responses to anti-HER2 therapies [55].

In this regard, understanding the role of miRNAs in HER2-positive tumors is of great importance for the future development of novel and individualized target-therapies.

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