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EDITORIAL

Perianal Paget's Disease and Malignancies of Lower Hindgut and Anal Canal

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ABSTRACT

Perianal Paget's disease (PPD) consists of a skin neoplasia which can be either primary or secondary to an underlying internal malignancy. Treatment of perianal Paget's disease associated with primary colonic or anal adenocarcinoma is secondary to the treatment of the primary tumor and, thus, accurate clinical, pathological and immunohistochemical assessment is essential. Adenocarcinomas are estimated to be only 10% of anal cancer, and anal mucinous or colloid adenocarcinoma is an even rarer entity. We reviewed literature concerning the association between malignancies of the lower gastrointestinal tract and anal canal not associated with a chronic fistula-in-ano and perianal Paget's disease, focusing on immunohistochemical differential diagnosis and management. Immunohistochemistry is very useful in choosing the ideal treatment for perianal Paget's disease; our "immunopanel" is useful to classify perianal Paget's disease.

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Keywords: Perianal Paget's disease; Anal mucinous adenocarcinoma; Immunopanel; Pagetoid spread; Cytokeratine; PPD

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INTRODUCTION

Perianal Paget's disease (PPD) is a variant of Extramammary Paget's disease (EMPD). It represents an uncommon condition which afflicts the perianal region, consisting in a skin neoplasia which can be either primary or secondary to an underlying internal malignancy

of digestive, urothelial or genital origin. EMPD seems to be more frequently found between 50-70 years of age, PPD being more common in female gender^[1,2].

PPD is characterized by typical histological feature of large, round, clear-staining cells with large nuclei. Immunohistochemistry is very useful in differentiating primary PPD from the so called "pagetoid phenomena", skin spreads of internal malignancies. Primary PPD usually shows cytokeratine (CK) 7 positive and CK20 negative pattern whereas anal/colorectal adenocarcinomas are positive for CK20: several studies demonstrate that CK7-/CK20+ is the most common secondary PPD pattern^[3-5]. Several therapeutic options have been proposed for primary PPD, such as local excision (LE) or wide local excision (WLE), with or without flap or graft reconstruction^[6-9], YAG or CO₂ laser ablation^[10,11], radiotherapy (RT)^[12], photodynamic therapy^[13] and the more recent topical Imiquimod 5%^[14,15] whereas the treatment of Paget's disease associated with primary colonic or anal adenocarcinoma is secondary to that of the primary tumor^[2].

PERIANAL PAGET'S DISEASE

First described by Crocker in 1888 then by Darier and Couillaud in 1893, EMPD consists of several forms, of which one is PPD^[16]. PPD is often associated with underlying deep malignancies, according to Tjandra^[17], whose study reported this association in 38 of 55 (69%) patients affected by PPD: 20 were apocrine or eccrine carcinoma, 12 were rectal carcinoma, 6 anal carcinoma. The relation between PPD and malignancies hasn't been clearly understood; if Oster^[18] reported a case of colorectal carcinoma years after the diagnosis of PPD and Koashi^[19] found PPD arising after a rectal carcinoma removal, Marchesa^[9] described 3 cases of primary PPD without invasive tumor at presentation recurring with cancer. These findings justify the need of submitting all subjects found with PPD to endoscopic examination and biopsies of the area, examining them with immunohistochemistry; but it also is very important to carry out a careful and continuous follow-up either in patients diagnosed with and treated for PPD or in patients who underwent anorectal cancer removal.

Four main theories are reported to explain the different patterns of PPD presentation^[20]. Paget's cells may arise from underlying carcinoma of eccrine or apocrine glands, with a secondary epidermal involvement. Second, Paget's cells may be metastatic from underlying carcinoma cells. It could also be possible that simultaneous neoplastic changes in epidermis, apocrine structures and glandular elements of the rectum result in PPD. Another theory has been hypothesized which would explain those cases without malignancies: Paget's cells may arise from the pluripotential ectodermal basal cells as an

adenocarcinoma in situ, with a long pre-invasive phase^[6,21]. These theories explain the existence of both primary and secondary PPD.

Treatment of choice has been matter of debate for years. We reviewed literature to find cases of PPD associated with malignancies of the rectum or anal canal (Table 1).

Our literature review showed an association of PPD and rectal or anal adenocarcinoma in 40 patients (1 patient with 2 sigmoid adenocarcinomas) with only 5 cases of mucinous adenocarcinoma (12.5%). We found this association more frequent in male gender (M:F=17:8). Procedures outcomes are summarized in table 2. Adenocarcinomas are estimated to be only 10% of anal cancer, with approximately 100 case/year of anal adenocarcinoma cancer in the United States^[22]. Anal mucinous or colloid adenocarcinoma is an even rarer entity which is often associated to a story of chronic fistula-in-ano, but several cases are today known to occur without; metastases typically occur to the inguinal lymph nodes, and treatment of choice is chemo-radiotherapy followed by excision (for early intercepted lesions) or APR with or without node dissection and adjuvant chemo-radiation therapy^[20,23-25]. We previously reported the case of a lady with uterine procidentia presenting with a perianal intra-epidermal pagetoid spread of the anal mucinous adenocarcinoma^[26], we decided to perform an APR without neoadjuvant therapies because their utility has not been demonstrated and they are not routinely recommended in literature, further studies being necessary^[25,27], moreover irradiation of carcinomas with concomitant uterine prolapse has been associated with high morbidity^[28,29].

Shutze's PPD staging (Table 3)^[30], is useful in classifying lesions and in planning the most appropriate treatment strategy. The treatment of Paget's disease associated with primary colonic or anal adenocarcinoma is secondary to the treatment of the primary tumor, depending on the underlying cause and, thus, accurate clinical, pathological and immunohistochemical assessment is essential^[2].

Several publications focused on distinguishing primary from secondary agreed in defining an "immunopanel" for Paget's disease. CK7 positivity is always present in Paget's disease lesion, CK20 and Gross Cystic Fluid Protein (GCFP) are helpful to identify secondary PPD. Rectal carcinomas often are CK7-/CK20+: PPD showing CK7-/CK20+ pattern is the most frequently associated with it^[31]. On the other hand, mucinous anal canal adenocarcinoma is characterized by a different pattern, showing both CK7 and CK20 positivity^[32]; that's the reason why GCFP test association can be useful. GCFP is always positive in primary PPD cases^[2,5,33]. Recently, the evaluation of tissue mucine genes (apomucine MUC1, MUC2 and MUC5AC) expression has been advocated as a useful tool in indentifying primary and secondary PPD, MUC1 always being present in case of primary PPD, whereas MUC2 is always found in secondary perianal PPD^[26]. However, further studies are needed^[34,35]. We recently proposed an immunopanel which could be useful in distinguishing between primary and secondary PPD (Table 4): this has the advantage of being easily reproducible, allowing a more reliable differentiation and increasing the possibility of choosing the right treatment^[26].

Table 1 Literature review.

YEAR	FIRST AUTHOR	N	mAGE	SEX	ASSOCIATED CANCER	TREATMENT	OUTCOME
1925	Artz ^[37]	1	74	F	rectal adenoK	APR	-
1939	Pinkus ^[38]	1	57	M	rectal adenoK	RT	Died
1952	Dockerty ^[39]	1	72	M	rectal adenoK	APR	-
1964	Straus ^[40]	2	67	1 M	2 rectal adenoK	1 LE1 /1APR	Died after 24/26 mo.
1976	Beahrs ^[1]	4	-	-	adenoK	APR	Dead at 60th mo.
1976	Williams ^[41]	1	66	M	rectal mucinous adenoK	APR	Alive at 23th mo.
1977	Grow ^[42]	1	67	M	rectal adenoK	APR	Alive at 12th mo.
1981	Subbuswamy ^[43]	1	68	F	rectum-anal canal cloacogenic K	APR + RT	Died after 7 mo.
1988	Tjandra ^[17]	1	76	M	rectal K	APR	Alive at 12th mo.
1985	Giltman ^[44]	1	75	M	anal canal mucoepidemoid K	APR	-
1991	Lertprasertsuke ^[45]	2	79.5	M	2 anal canal adenoK	1 LE/1 APR	Died after 30/52 mo.
1992	Goldman ^[46]	2	58	1 M	1 rectal adenoK/1 anal canal adenoK 2 rectal adenoK	RT + APR/APR APR	Alive after 3/17mo.
1996	Marchesa ^[9]	4	-	-	1 anal canal apokrineK with dm 1 anal canal adenoK with dm anal canal mucinous adenoK	LE + RT LE + RT APR	All dead at 10th mo. Alive after 12 mo.
1997	Wong ^[28]	1	73	M	rectum-anal canal adenoK	APR	Alive at 15th mo.
1998	Kubota ^[47]	1	58	M	1 rectal adenoK 1 anal canal mucinous adenoK + 1 rectal adenoK	APR + CT R + CT	Died after 11 mo. Died after 18 mo.
1998	Nowak ^[33]	3	64	M	1 anal canal mucinous adenoK 1 anal canal mucinous adenoK	RT + CT	Died after 51 mo.
2003	Mc Carter ^[48]	7	-	-	4 anal K 3 rectal K	5 APR 2 WLE ± graft	1/5 dead at 60th mo. 2/2 dead at 60th mo
2004	de la Portilla ^[49]	1	68	F	anal canal adenoK	APR	Alive after 24 mo.
2004	Delaunoi ^[50]	1	71	M	rectum-anal canal adenoK	APR + WLE	PPD relapse -> LE
2004	Le Fur ^[5]	1	69	F	2 sigmoid adenoK	LHC + 5FUc	Alive
2004	St Peter ^[51]	1	-	-	anal gland K	WLE + graft	Alive after 42 mo. Incomplete PPD Removal -> WLE
2006	Suenaga ^[52]	1	70	M	anal canal adenoK	TLE	Removal -> WLE
2010	Selvaggi ^[26]	1	78	F	anal mucinous adenoK	APR	Alive after 28 mo.

APR: abdominoperineal resection; RT: radiotherapy; LE: local excision; CT: chemotherapy; WLE: wide local excision; LHC: left hemicolectomy; 5FUc: 5fluorouracil cream; TLE: transanal local excision.

Table 2 Procedures outcomes. We evaluated only cases with available outcome.

PROCEDURE	N	ALIVE AT 12 th MONTH	ALIVE AT 24 th MONTH	ALIVE AT 60 th MONTH
APR	20	18	13	4+1 doubtful
WLE+graft	3	3	1+2 doubtful	1 doubtful
LE±RT	4	2	1	0
RT+CT	2	2	1	0

N: number of patients; APR: abdominoperineal resection; RT: radiotherapy ; LE: local excision; CT: chemotherapy; WLE: wide local excision.

Table 3 PPD staging (Shutze *et al*^[30]) and outcome.

STAGE	DESCRIPTION	THERAPY	SURVIVAL DATA (literature review)
I	Paget's cells found in perianal epidermis and adnexae without primary carcinoma	Wide local excision	23/32
IIA	Cutaneous Paget's disease with associated adnexae carcinoma	Wide local excision	6/7
IIB	Cutaneous Paget's disease with associated anorectal carcinoma	Abdominoperineal resection	7/10
III	Paget's disease in which associated carcinoma has spread to regional nodes	Inguinal node dissection Included with resection	0/10
IV	Paget's disease with distant metastases of associated carcinoma	Chemotherapy±radiotherapy; Local palliative management	0/2

Table 4 Immunopanel for perianal Paget's disease^[26].

PPD	CK7	CK20	GCDPF-15	MUC1	MUC2
Primary (apocrine type)	+	-	+	+	-
Secondary to rectal/ sigmoid/colonic adenocarcinoma	±	+	-	±	+
Secondary to anal canal adenocarcinoma:	+	±	-	±	+
- anal gland adenoK	+	-	-	±	+
- mucinous adenoK	+	+	-	±	+
- rectal type adenoK	-	+	-	±	+

PPD: perianal Paget's disease; CK: cytokeratin; GCFP: Gross Cystic Fluid Protein; MUC: apomucin.

Le Fur^[5] reported the regression of PPD lesion after adenocarcinoma removals applying a 5FU cream for 6 weeks, and Ye^[36] found 5FU cream associated with Imiquimod 5% and retinoic acid effective in a case unresponsive to surgery and Imiquimod alone.

Inguinal node dissection is another issue. Positron emission tomography (PET) examination could be useful in identifying patients who could benefit from such an aggressive approach, however literature survival data show no difference between patients undergoing nodes dissection and patients not receiving this procedure in individuals affected by PPD and anorectal carcinoma^[30]. Moreover, several reports are highly critical about groin dissection because of its high morbidity, remarking it is an unnecessary operation in the vast majority of patients; interval radical groin dissection should be considered if metastatic inguinal nodes persist or subsequently develop following chemoradiation therapy^[20].

Follow-up of patients affected by PPD and malignancies hasn't been clearly set; we believe it is an important part of the management for the reasons previously stated. Biopsies probably have a role, considering that Beck and Fazio recommended to take routine biopsy samples 1 cm from the edge of the lesion and in all four quadrants of the perineum^[6].

CONCLUSIONS

The association between adenocarcinomas of the anal canal without

a chronic fistula-in-ano and a cutaneous pagetoid spread is poorly in literature. Distinguishing primary from secondary PPD (pagetoid phenomenon) can be very difficult and surely needs further and wider analyses; as evident, the treatment is markedly different and the achieving of satisfactory results could be improved. Nevertheless, we believe that both primary and secondary PPD are similar in needing a rigorous follow-up, with clinical/instrumental examination, selecting patients requiring periodical biopsies.

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