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EXTRAMAMMARY PAGET'S DISEASE OF THE PERIANAL AREA: A RARE CASE REPORT AND THE SUMMARIZING REVIEW OF LAST 5-YEAR LITERATURE

Shponka I.S., Hrytsenko P.O., Skoryk V.R. ✉ Extramammary Paget's disease of the perianal area: a case report and the summarizing review of last 5-year literature.
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ABSTRACT. Background. Extramammary Paget's disease is one of the rarest malignant skin tumors which are mostly apocrine. However, there were described some cases in non-apocrine bearing glands areas. The perianal region, as part of the anogenital site, is the place where extramammary Paget's disease could manifest. It is used to classified this disease into 2 categories: primary and secondary, where the main differentiating feature is the absence or presence of underlying carcinoma relatively. Due to extramammary Paget's disease rarity all around the world publishing information about any case could help to evaluate the situation in all. **Objective.** To report a rare case of the extramammary Paget's disease and analyze one-case-publications during last 5 years on PubMed and assessed contributions of age, sex, and localizations. **Methods.** While making a diagnosis histological, immunohistochemical studies and statistical methods were used. **Results.** The first case of primary noninvasive extramammary Paget's disease was diagnosed in the immunohistochemical laboratory of the Medical Diagnostic Center of the Medical Academy and described in this article. A 64-year-old Ukranian man suffered within 1 year from big erythematous pruritus unhealed lesion between his buttocks and came to our laboratory to verify suspicious malignant melanoma what was assumed while previous histological study. According to immunohistochemical study, this tumor had positive status with cytokeratin 7, HER-2/Neu, EGFR and p16, while cytokeratin HMW, S100, HMB-45, EBV were negative. Such immunophenotype might point to some ways of the pathogenesis of this problem. The theory about involved Toker cell and preceded Toker cell hyperplasia had both advantages and drawbacks, what we showed with the presented example. There were already published 49 cases with middle age 67,68±1,64; median 67 years, m:f ratio 1,58:1 and utterly predominant location – anogenital region. **Conclusion.** Received data have mostly corresponded to published information previously.Both clinical studies and immunophenotype gave a possibility to make an accurate diagnose.

Key words: Extramammary Paget's disease, primary, secondary type, perianal region, Toker cells, immunohistochemical study.

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Background

Extramammary Paget's disease (EMPD) is "uncustomary" epithelial origin neoplasm with both apocrine and eccrine glandular-like differentiation features. Despite the official fact of discovering and coming out EMPD like separate disease took place more than one century ago (in 1889 by Radcliff Crocker) [1], accurate its accidence is unknown owing to this tumor rarity. Up to 200 cases just have been reported in the literature to refer to Shen K et al. [2], and only several countries have looked into this problem, for instance, the USA and Japan [3, 4].

However, in the last few years, this theme is generally sensational in the scientist publishing sphere. But it should be mentioned that in most articles only single or pair of rare cases in different locations is performed and there is a lack of summarizing data [2, 5, 6]. On the other hand, given that

EMPD occurrence is so low and evident deficiency of profound researches is presented such kind of way of providing data accumulation possibility is applicable.

Few more things make difficult the statistics built-up. Firstly, different localizations of EMPD: the most often among apocrine bearing sites are vulva, perineal and perianal areas, the skin of penis and scrotum. WHO indicates EMPD is about 2% of vulva's primary tumors and other areas are significantly uncommon [7]. Secondly, taking into account the fact that the anogenital region is predominantly affected there is still a controversial point about the possibility to combine figures about unrelated sites or ought to keep its separately while assessing.

Objective

Based on exhibited information below the main purposes of this work were to present one more case of EMPD of perianal skin and wrap up the accumulated accessible published data on the Internet over 5 last years (contributions of age, sex, and localizations).

Materials and Methods

We reported about first case of EMPD what was diagnosed in the immunohistochemical laboratory of the Medical Diagnostic Center of the Medical Academy. There were used routine staining with hemotoxilin and eosin for histological study, protocols and all reagents of the TermoScientific company, the USA for IHC study.Three pathologist evaluated the staining separately. Statistical methods were included mean, arithmetic mean error and median.

Results and discussion

Case report. We reported about 64-year-old Ukranian man who suffered from the incurable erythematous patch (diameter approximately 7cm) with "weeping" central part on the internal buttocks surface (closely to the perianal area) within one year. Focal brownish pigmentation was noted. During this time, his problem was suggested as fungal infection, autoimmune disease (eczema), therefore he was treated with baby powder, steroids and antifungals unsuccessfully. Since he noticed the problem firstly, it has risen its size on 2 cm in diameter.

On physical examination, no other skin lesions (on both apocrine and non-apocrine sites) were found. Medical history announced chronic heart failure, II functional class on medication and chronic prostatitis. To verify another malignancy check's list included punch biopsy, colonoscopy, esophagogastroduodenoscopy, intravenous urogram on account of urethral stricture due to chronic prostatitis. Apart from histology result there were no other findings.

Histologically, the round, large, pale cells predominantly in the lower and middle third of epidermis were described, but the entire thickness of the epithelium was involved. The tumor's cells had round,sometimes eccentric, vesicular nuclei with prominent nucleoli. There were marked nuclear atypia among tumor cells and mitoses (around 3-4 on 5 field of view)(Fig. 1). Also, focally it was noticed that tumor cells contained intracytoplasmic melanin. The suspicious diagnosis was superficial spreading melanoma in situ.

Nevertheless, IHC study revealed next phenotype: "CK7+/CKHMW-/S100-/HMB-45-/HER-2/NEU(3+)/Ki-67 34%" and confirmed diagnose noninvasive EMPD.

After this, we additionally studied several markers: "EGFR+/p16±/EBV-" (Fig. 2). Both phenotype and underlying malignancy absence testified to primary EMPD.

There were two main problems, that confused pathologists previously. First of all, focally contained intracellular brown pigment what was suggested like melanin. And secondly, the contribution of the tumor cells where the predominance was on the bottom of the squamous epithelial thickness.

The patient has been getting complete remission after two courses of radiation therapy without preceded operation for 18 months. The decision to treat without surgical operation was confirmed by 6 doctors of different oncological specializations and was possible owing to lack of summarizing information about treatment that disease with different clinical manifestations.

EMPD is one of the rarest malignant tumors without accurate epidemiological data. There are some studies with numbers of cases from 100 up to 200 [2, 8], but a predominance of published data is devoted just case report. We analyzed and summarized reported information about all published in PubMed (https://www.ncbi. nlm.nih.gov/pubmed/) cases of EMPD for 5 years since 2015 up to 2019. It could be announced that the received results are utterly expected.

First of all, it was found 49 cases of a different locations. Where the absolute predominance had the perineal region in both men and women with a general sum of 31 cases (63,26%), whereas the perianal region took second place – 13 cases (26,53%). The oral cavity was performed as an EMPD site two times (4,08%) and non-apocrine locations (esophagus, right lower back and right thigh) were noticed once (each took 2,04%). Fundamental book and some authors show us a close distribution of epidemiology [9, 10]. But in two times penoscrotal localization was more than vulvar one when Haijun Y. et al. [11]mentioned the opposite situation.

Secondly, the usually affected age is considered a 6th-7th decade [1-6]. As a witness, we found only 5 cases (10,2%) with age less than 60: mean 67,68±1,64; median 67 years.

Next important point is the provocation factors for EMPD are not recognized [7]. There are two main groups of EMPD (primary and secondary) and several development theories for both. In the presented case it was diagnosed primary type without any underlying malignancy, despite statistics data where perianal EMPD is associated with adnexal or

visceral carcinoma in 80% [9]. That was a reason to check additional markers: EGFR, p16, EBV because of the theory anal canal cancer is in roughly 90% cases associated with HPV infection and could be divided into 2 groups depending on EGFR status [12]. Some authors mentioned a connection with EBV infection [13]. Moreover, we could add "CK7+/CKHMW-" status what the most likely excluded urothelial and colon carcinoma to the IHC-confirmation of the "primacy" of the presented case.

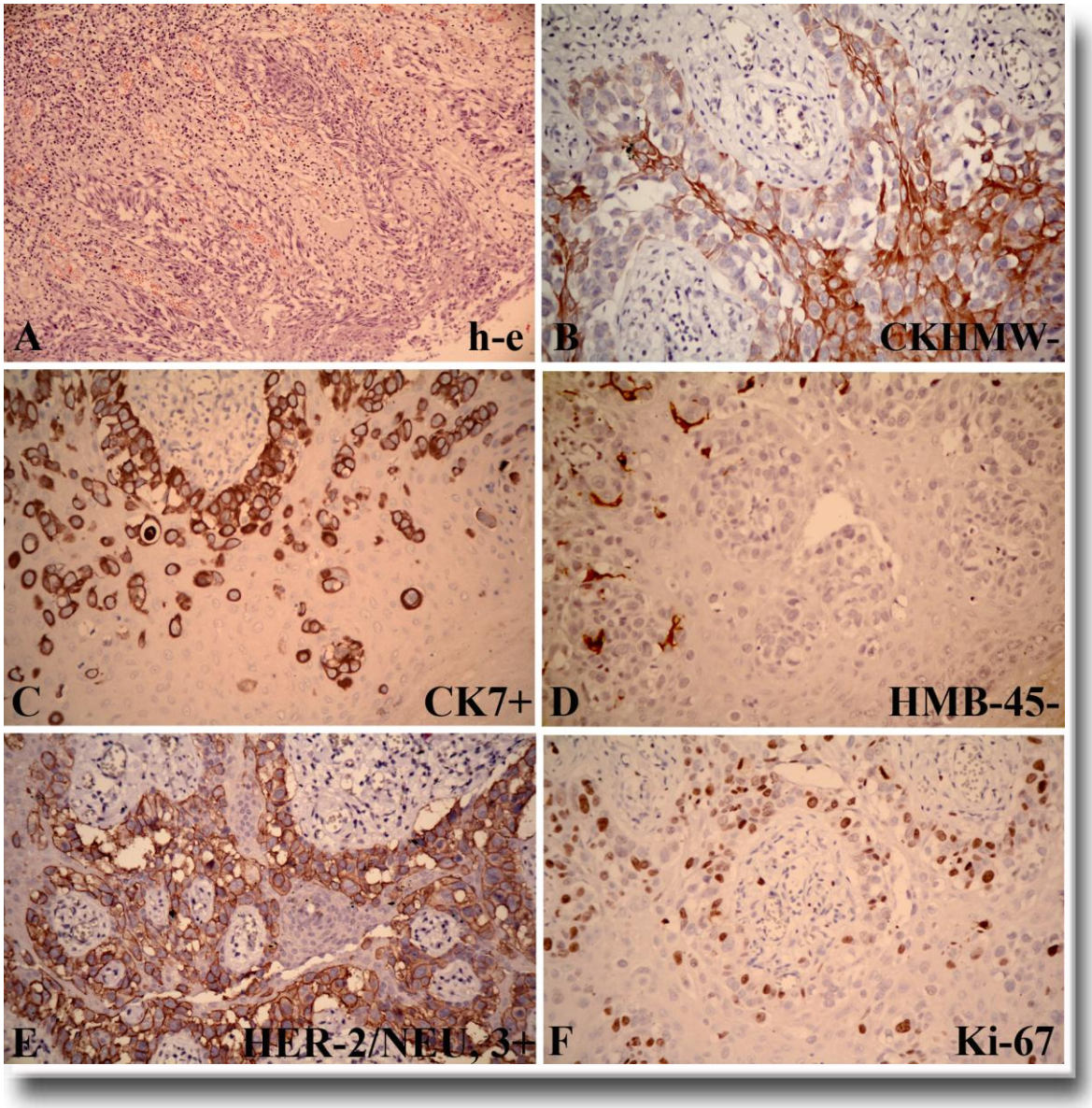

Figure 1. EMPD case, IHC staining, additional staining with hematoxylin, ×400. A. Big tumor cells with abundant pale cytoplasm, with prominent atypia, mitoses, what are arranged mostly in small clusters or more rarelysingularly, staining with hematoxylin and eosin, ×200. B. Tumor cells showed negative reaction with squamous cell marker. C. Tumor cells showed positive reaction with cytokeratin 7. D. There is a positive staining with occasional epidermal basal layer melanocytes. E. Intense full-membranous reaction with aproximately 100% tumor cells. F. Proliferative level marker showed relatively high expression, around 35%.

Anyway, there is still a question about possible carcinogenetic links of Toker cell and primary EMPD. Hashemi P. et al. [11] hypothesized this starts with Toker cell hyperplasia and can potentially evolve to carcinoma in the genital region. On the one hand, presence of the vast majority of tumor cells in the bottom and middle part of the epithelium, as a mark of spreading beginning, and "CK7+/CKHMW-" status may confirm this theory in our case. On the other hand, Toker cell hyperplasia (TCH) is an ultimate rare diagnosis, there are just 2 described cases out of 340 in Toker's original series [14], and there was not performed data TCH origin in non-apocrine regions.

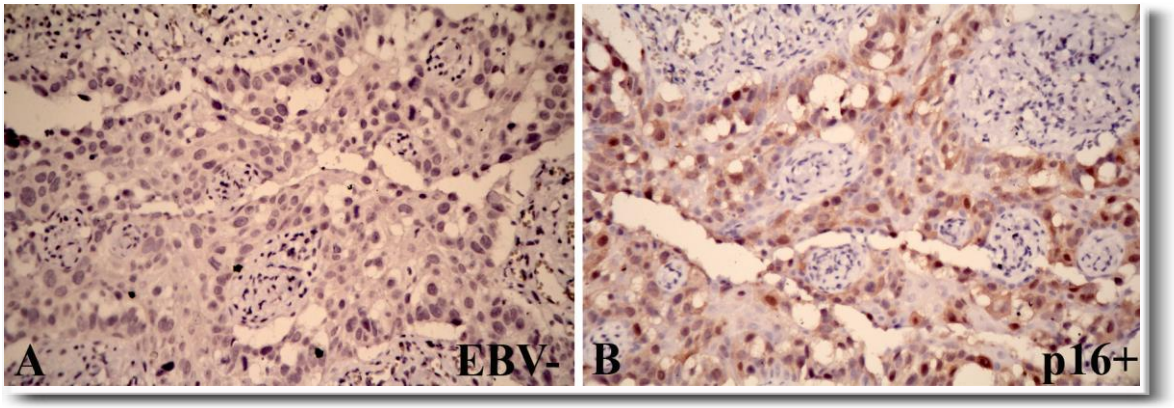

Figure 2. EMPD case, IHC staining, additional staining with hematoxylin, ×400. A. Tumor cells showed negative reaction with EBV. B. Tumor cells showed positive nuclear staining in more than 50% of them with p16.

Nevertheless, we may think two possible way of transformation TCH in EMPD over. One of them is HER2 gene amplification and another one is an association with HPV infections. The credibility of the first one could be verified by the acquisition of HER-2/Neu 3+ expression (Fig.1), absence of what is one of the differentiating features between TCH and Paget's disease [7, 9]. Potential connection EMPD with HPV infection in our case could be confirmed by p16 expression (Fig.2). Though the greatest number of the tumor cells nuclei were stained with p16, not all were. Some of them had just cytoplasmic staining. On the other hand, it is well known, that p16+ status malignant tumor without HPV-association could have. However, Zhang G et al. [15] stated that primary EMPD is so often p16+ and, moreover, noninvasive EMPD is more characterized by predominant cytoplasmic staining, where mostly nuclear reaction testified to invasive one. Also, it might confirm the HPV or/and HER-2/Neu pathogenesis theories of the EMPD that one of the newest exome analysis has identified modern genomic alterations in several genes such as TP53, PIK3CA and ERBB2, [16].

Conclusion

To sum up, some conclusions are needed to be mentioned.

First of all, it is principal to suspect diagnose EMPD when there is non-healing skin lesion in the apocrine area, especially in the anogenital region.

Secondly, it is needed a summarizing data publications in all spheres of the discussed problem: epidemiology, etiology and pathogenesis, treatment.

Finally, it is confirmed the usefulness of IHC for both diagnosing process and finding out pathogenesis ways.

Prospects for further investigations

The above data indicate the need to continue the search for indicators that are statistically validly considered to be "launcher" in pathogenesis of EMPD.

Information about conflicts of interest

Potential or explicit conflicts of interest related to this manuscript do not exist and are not foreseen at the time of publication.

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Шпонька І.С., Гриценко П.О., Скорик В.Р. Позамаммарна хвороба Педжета перианальної ділянки: опис випадку та огляд літератури за останні5-років.

РЕФЕРАТ. Актуальність. Позамаммарна хвороба Педжета- одна з найрідкісніших злоякісних пухлин шкіри переважно апокринового походження, проте описані випадки ураження неапокринових ділянок. Перианальна область, як частина аногенітальної ділянки, є місцем, де може маніфестуватизазначене новоутворення. Воно класифікується на 2 категорії: первинну та вторинну, що їх відрізняєнаявність асоціації із аденокарциномою прилеглих органів. Через низьку у всьому світі поширеність позамаммарної хвороби Педжета публікація інформації стосовно будь-якого випадку може допомогти оцінити ситуацію в цілому. **Мета.** Повідомити про рідкісний випадок позамаммарної хвороби Педжета та проаналізувати представлені на PubMed за 5 років клінічні випадки, оцінивши вік, стать та локалізацію патології. **Методи.** Під час встановлення діагнозу та аналізу були використані гістологічні, імуногістохімічні дослідження та статистичні методи. **Результати.** Перший випадок первинної неінвазивної позамаммарної хвороби Педжета діагностовано в імуногістохімічній лабораторії лікувально-діагностичного центру Медичної академії. 64-річний громадянин України скаржився протягом 1 року на велику еритематозну пляму між сідницями, що не загоювалась,не зважаючи на лікування. Вінзвернувся до нашої лабораторії, щоб підтвердити діагнозмеланоми, який було встановлено під час попереднього гістологічного дослідження. За даними імуногістохімічного дослідження, ця пухлина мала «+»-статус за цитокератином 7, HER-2/NEU, EGFR та p16, тоді як цитокератин HMW, S100, HMB-45, EBV були негативними. Такий імунофенотип може вказувати на деякі шляхи патогенезу цієї проблеми. Теорія про залучення клітин Токера та попередню їх гіперплазію мала перевагиі недоліки, що ми показали їх на представленому прикладі. Протягом останніх 5 років вже було опубліковано 49 випадків: середній вік 67,68±1,64; медіана 67 років, співвідношення Ч:Ж=1,58:1, переважна ділянка розташування-аногенітальна область. **Висновки.** Отримані дані здебільшого відповідали опублікованій раніше інформації. Тільки комплекс клінічних досліджень та визначенняімунофенотипу дали можливість верифікувати діагноз.

Ключові слова: позамаммарна хвороба Педжета, первинний, вторинний тип, перианальна область, клітини Токера, імуногістохімічне дослідження.

Шпонька И.С., Гриценко П.А., Скорик В.Р. Экстрамаммарная болезнь Педжета в перианальной области: описание случая и обзор литературы за последние 5 лет.

РЕФЕРАТ. Актуальность. Экстрамаммарная болезнь Педжета - одна из самых редких злокачественных опухолей кожи преимущественно апокринового происхождения, однако описаны случаи поражения неапокриновых участков. Перианальная область, как часть аногенитального участка, является местом, где также может манифестировать данное новообразование. Из-за низкой во всем мире встречаемости экстрамаммарной болезни Педжета публикация информации о любом случае может помочь оценить ситуацию в целом. **Цель.** Сообщить о редком случае экстрамаммарной болезни Педжета и проанализировать представленные на PubMed за 5 лет клинические случаи, оценив возраст, пол пациентов и локализацию патологии. **Методы.** Во время постановки диагноза и анализа опубликованных были использованы гистологические, иммуногистохимические исследования и статистические методы. **Результаты.** Первый случай первичной неинвазивной экстрамаммарной болезни Педжета диагностирован в иммуногистохимической лаборатории лечебно-диагностического центра Медицинской академии. 64-летний гражданин Украины жаловался в течение 1 года на большое эритематозное пятно между ягодицами, которое не заживало, несмотря на лечение. Он обратился в нашу лабораторию, чтобы подтвердить диагноз меланомы, который был установлен в ходе предварительного гистологического исследования. По данным иммуногистохимического исследования, эта опухоль имела «+»-статус по цитокератину 7, HER-2/NEU, EGFR и p16, тогда как цитокератин HMW, S100, HMB-45, EBV были отрицательными. Такой иммунофенотип может указывать на некоторые пути патогенеза этой проблемы. Теория о привлечении клеток Токера и предварительную их гиперплазию имела преимущества и недостатки, мы показали их на представленном примере. В течение последних 5 лет уже было опубликовано 49 случаев: средний возраст 67,68 ± 1,64; медиана 67 лет, соотношение М: Ж = 1,58: 1, подавляющее участок расположения - аногенитальной области. **Выводы.** Полученные данные преимущественно соответствовали опубликованной ранее информации. Только комплекс клинических иимуногистохимическогоисследований позволили верифицировать диагноз.

Ключевые слова: экстрамаммарная болезнь Педжета, первичный, вторичный тип, перианальная область, клетки Токера, иммуногистохимическое исследование.