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Implications of Adnexal Invasions in Primary Extramammary Paget's Disease: A Systematic Review

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Abstract:- Extramammary Paget's disease (EMPD) is an erratic malignant skin disorder primarily affecting skin areas abundant with skin appendages like hair follicles. The vulva is most involved site, followed by genital areas, penoscrotal regions and axillary skin. EMPD presents as erythematous skin lesions resembling eczema, typically progressing slowly, either primary or secondary manifestations. Primary EMPD originates as an intraepithelial neoplasm of the epidermis, often leading to local lymph node metastases and distant metastases. A systematic literature search using targeted keywords across multiple databases was conducted. Studies focusing on EMPD, adnexal involvement, depth, recurrence, and prognosis were included by keeping in view the objective which is to determine the significance of adnexal involvement and depth concerning recurrence and prognosis in the primary EMPD. Adnexal involvement, especially in hair follicles and eccrine ducts, is prevalent in primary EMPD. However, its correlation with tumor progression or recurrence rates remains inconclusive. Surgical excision, including Mohs micrographic surgery, is the primary therapeutic approach, with topical agents and systemic treatments used in advanced cases. Future studies regarding understanding adnexal involvement's depth and significance are essential in designing effective targeted therapeutic approaches in EMPD.

Keywords:- *Disease of the Cutaneous Annexes, Primary EMPD, Extramammary Paget's Disease, Skin Neoplasm, Prognosis, Skin Adnexa, Adnexal Involvement.*

I. INTRODUCTION

First reported by Crocker in 1889, EMPD is a rare malignant skin disorder that affects apocrine rich skin sites with an abundance of hair follicles. [1, 2] The vulva is the most often occurring site; perineal, perianal, scrotal, and penile skin are next in frequency. The axilla, buttocks, thighs, eyelids, and external auditory canal are additional, less common locations. Typically, erythematous or persistent skin lesions resembling eczema are the first sign of EMPD. [3] Another name for EMPD is skin in situ adenocarcinoma. The tumor is limited to the epidermis, grows slowly, and rarely spreads to other areas of the body. There are two types of EMPD manifestations: primary and secondary. Secondary EMPD involves the direct extension of an underlying internal neoplasm or the epidermotropic spread of malignant cells, whereas primary EMPD originates as an intraepithelial neoplasm of the epidermis [4], while some theory suggesting infiltration via adnexal structures (Figure 1). Predominant cases of EMPD are identified as carcinoma *In Situ*, which typically progresses slowly. However, local lymph node (LN) metastases and non-local metastases often occur once Paget cells penetrate deeply into the dermis [5]. Due to the limited effectiveness of conventional chemotherapies, which are typically used to treat EMPD, cases with distant metastases with multiple lesions have a poor prognosis. Here, we review EMPD, covering its diagnosis, pathogenesis, and treatment, with an emphasis on recent developments.

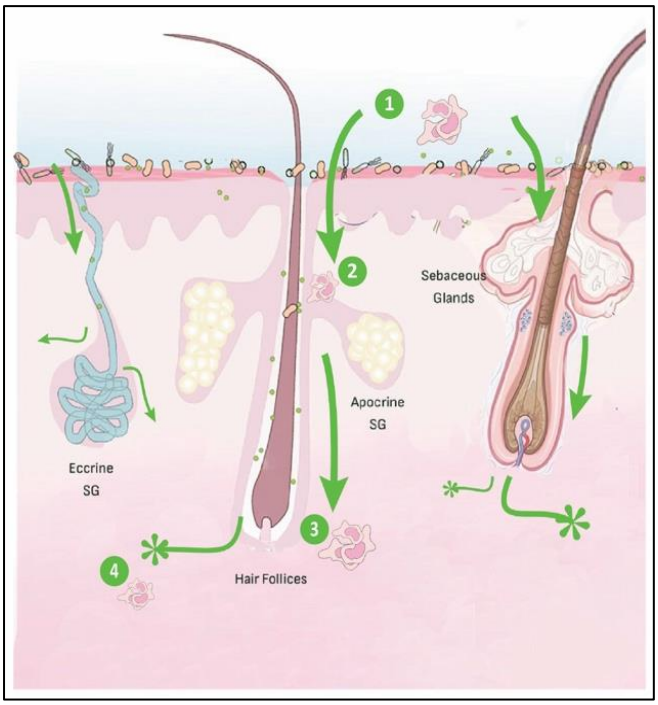

Fig 1 Adnexal Proliferation in Primary EMPD Showing Pagetoid Cells Infiltrating the Dermal Layer via Adnexal Structures

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II. MATERIALS AND METHODOLOGY

A. Study Design

➢ *Research Question:*

The primary research question driving this systematic review is: "What is the significance of adnexal involvement and depth concerning recurrence and prognosis in primary extramammary Paget's disease (EMPD)?"

➢ *Statement of Aims:*

This systematic review aims to comprehensively evaluate the significance of adnexal involvement and depth in primary extramammary Paget's disease (EMPD) concerning recurrence and prognosis. The review aims to consolidate existing research to investigate the role and depth of adnexal structures in primary EMPD, and how they correlate with tumor progression, recurrence rates, survival rates, and overall patient prognosis.

➢ *Search Strategy:*

The literature search methodology involved systematic techniques utilizing targeted keywords across several databases, including PubMed, Google Scholar, ProQuest, ScienceDirect, and the university's linked library databases such as ISI Web of Science. The search strategy incorporated a blend of MeSH terms and keywords focusing on extramammary Paget disease, Paget, adnexal involvement, depth, recurrence, and prognosis by keeping in view the study's objective.

Moreover, a manual search is performed for relevant articles in the journal's bibliography list and included studies. Unpublished studies/gray literature are manually searched in Google Scholar and gray literature databases using study keywords. This review follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

B. Study Selection Process

The first step was identifying and retrieving articles based on inclusion and exclusion criteria (shown in Figure 2).

➢ *Inclusion Criteria*

- Studies focused on primary extramammary Paget's disease (EMPD), including its diagnosis, pathogenesis, treatment, and outcomes related to adnexal involvement and depth.
- English-language publications were included to ensure comprehensive understanding and analysis.
- Studies reporting outcomes related to adnexal involvement and depth concerning recurrence rates, prognosis, therapeutic approaches, and advancements in EMPD management.

➢ *Exclusion Criteria*

- Studies published in languages other than English were excluded due to potential limitations in comprehension and analysis.
- Literature lacking empirical evidence, including conceptual papers, reviews lacking original research, case reports, case series, conference abstracts, or theoretical discussions without practical implications, were excluded.
- Studies not specifically detailing adnexal involvement and depth in primary EMPD or not directly related to the research questions were excluded.

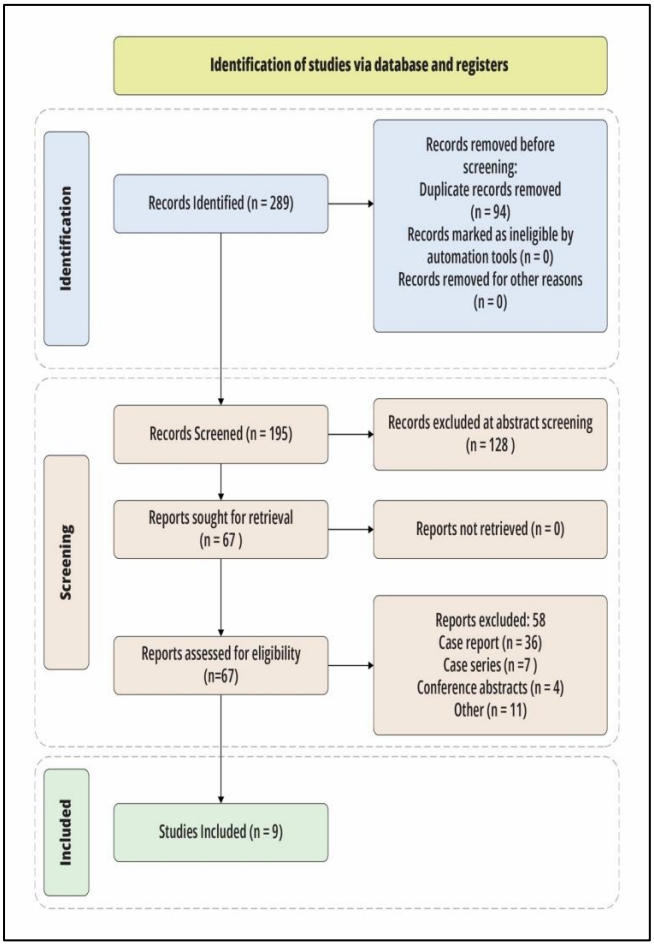

Fig 2 PRISMA Flow Chart Showing the Selection of Included Studies

III. RESULTS

The initial search identified a total of 289 citations, 94 of which were duplicated. Total articles retrieved after removing duplication is 195. The next step of the process involved reading the abstracts in more detail and narrowing down the larger set of articles to those that specifically addressed adnexal involvement in extramammary Paget disease. Title and abstract screening of the remaining 195 citations resulted in the inclusion of 67 citations for further review. After examination of full-text articles, 9 articles were identified as being eligible.

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IV. DISCUSSION

Intraepidermal adenocarcinomas are the term used to describe both extramammary and mammary Paget disease. EMPD is more frequently a primary intraepidermal lesion than mammary Paget's disease; only 20% of cases show evidence of a dermal invasive component. [6] A disease is deemed minimally invasive if the invasive component is less than 1.0 mm in depth, and full excision is typically curative. [7] An underlying cutaneous adnexal carcinoma, typically an apocrine adenocarcinoma, may also be linked to EMPD. Up to 30% of cases indicate the spread of metastatic cancer from a regional visceral malignancy, such as rectal, cervical, prostate, or transitional cell carcinoma. In these cases, the tumor cells show positive profiles for CK 7 and potentially GCDFP-15, but they also exhibit immunohistochemical profiles that are similar to the original carcinoma, such as positive for prostate-specific antigen in prostate cancer or CK 20 or CA19.9 in genitourinary or gastrointestinal carcinomas. [8] Crude prevalence of EMPD in mainland China was estimated to be 0.4 per 100,000 people in a recent study by Yin et al. With the peak incidence at 66 years during first diagnosis, the majority of people are between 50 and 80 years old. [9]

Ghazawi et al. report that the vulva in females and the scrotum and penis in males are the primary sites of EMPD development, though perianal, axillar, or umbilicus regions may also occasionally be affected [10]. Multifocal EPMD is possible, and instances of double, triple, or synchronous EMPD—EMPD that developed in more than two apocrine gland-bearing areas—have also been documented. [11] There have also been cases reported where hypopigmentation was the primary clinical presentation; these cases are challenging to diagnose as EMPD. [12] There may also be crust, scale, or erosion on the erythematous lesions. These lesions can resemble several different skin conditions, including psoriasis, eczema, and fungal infections. Deep ulcers or nodules may appear in the later stages. 10% of patients with EMPD are asymptomatic, despite the possibility of developing related symptoms like pruritus and tenderness. [13] The dermoscopic characteristics of EMPD lesions have also been studied recently. [14] Mun et al. compared the dermoscopic characteristics of EMPD lesions with those of other skin lesions, such as eczema, fungal infection, and Bowen disease, the gross findings such as milky-red areas, dotted vessels, glomerular vessels, polymorphous vessels, surface scales, and linear irregular vessels may be comparable to EMPD. [15]

Although the histogenesis of EPD is still unknown, several theories point to pluripotent epidermal stem cells, intraepidermal "Toker cells," apocrine glands, or both as possible sources. Mucin core proteins, androgen receptors, Her-2 neu, gross cystic disease fluid protein-15, and intermediate filaments of the cytokeratin (CK) type15—specifically, CK7 and CK20—are all expressed by Paget cells. [16] Progeny from follicular stem cells can differentiate into sebocytes, sweat glands, epidermis, and hair follicle lineages. The bulge region's follicular stem cells are distinguished by the expression of CK15 and CK19. Both CK15 and CK19 are thought to be indicators of derivation from follicular stem cells of the upper hair follicle and are expressed in trichogenic tumors. [17] A follicular origin of Paget cells is further supported by CK20 positivity in EPD without associated rectal carcinoma, as the hair follicle stem cell niche is co-occupied by CK20+ Merkel cells and pluripotent neuroendocrine stem cells. [18] Furthermore, Tanaka et al. found that HER2 overexpression and ERBB2 gene amplification did not differ between primary lesions and lymph node (LN) metastasis in about 90% of EMPD patients, suggesting that HER2 targeting therapies could be useful for treating both primary and metastatic lesions. [19]

The relationship between adnexal involvement and tumor progression has not been thoroughly studied, even though it was a common finding in the Shaco-Levy et al. report and did not impact the recurrence rate. In a study, comedone necrosis was found in 6 cases (11.3%) and adnexal involvement in 46 cases (86.7%). There was no statistically significant difference in the percentage of cases with adnexal involvement displaying a score of 2 between invasive EMPD (77.8%) and in situ EMPD (57.7%). These findings imply that comedon necrosis and the extent of adnexal involvement are not linked to the progression of EMPD. [20] Preti et al. examined 122 patients with vulvar primary EMPD and found that, for intraepithelial and microinvasive (≤ 1 mm) vulvar primary EMPD, the cancer-specific survival at 120 months was 100%, while for invasive (>1 mm) vulvar primary EMPD, it was 31%. [21] Similar to this, van der Linden et al. examined 113 patients with vulvar primary EMPD and found that while the 5-year disease-specific survival rate was only 50% and significantly worse in invasive primary EMPD, it was more than 98% in noninvasive and micro-invasive EMPD. Thus, microinvasion might not have a major impact on EMPD patients' prognosis. [22]

In 1993, the Japanese Skin Cancer Society proposed a TNM staging system preliminary for primary EMPD. This system classified the primary tumor category based on lymphovascular invasion depth, the lymph node category based on metastasis site (unilateral or bilateral inguinal nodes), and the term "distant metastasis" was defined as metastasis in a lymph node that was outside of the regional lymphatic basin or in a distant organ. This staging system was used in a cohort study by Hatta et al., who demonstrated its usefulness with 76 patients. [23] Regarding the prognostic factors associated with primary EMPD, Ito et al. retrospectively analyzed 35 patients and found that the degree of tumor invasion, lymph node metastases, clinically palpable lymph nodes, and the presence of a nodule on the primary lesion were significant prognostic factors. [24-26] A recent study found that while invasion level and perianal location were not significantly associated with a worse prognosis, tumor thickness, and lymphovascular invasion were. In terms of node status, it was discovered that patients who had two or more node metastases fared worse in terms of survival than those who only had one. Metastatic lymph

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node distribution on both sides did not significantly affect prognosis. [5]

According to conventional wisdom, Paget's disease is a form of skin in-situ adenocarcinoma. Because EMPD progresses slowly and typically affects only the epidermis and cutaneous adnexal structures, most patients have a good prognosis. [27] The adnexa may act as a conduit for carcinoma to spread to deeper tissues where local therapeutic agents are less likely to be effective, as evidenced by earlier case reports and case series. [28-30] According to a study, adnexal involvement is a highly prevalent feature in over 90% of cases of primary EMPD. The most often affected anatomical structures by Paget cells are hair follicles and eccrine ducts. The most profound involvement in this investigation was 3.6 mm, and the median for each adnexal structure was between 0.93 mm (eccrine ducts) and 2.55 mm (eccrine secretory coils). [31]

Future development of new local treatment modalities or planning of topical nonsurgical treatment should consider this information. Imiquimod, 5-fluorouracil, and retinoic acid are currently used to treat primary EMPD to replace more invasive, frequently disfiguring surgical methods. Additional cutting-edge therapies under investigation include photodynamic therapy, trastuzumab, either alone or in conjunction with chemotherapy, and CO2 laser. [32, 33] Although the aforementioned treatment modalities have different mechanisms of action, understanding the depths of tumor deposits and the depth of skin penetration are undoubtedly crucial for designing an effective treatment plan. While 5-fluorouracil is said to penetrate the skin to a depth of 1-2 mm, we were unable to ascertain the potential depth of imiquimod's skin penetration based on our review of the literature. [34]

The principal therapeutic approach entails a broad local surgical excision of the affected area. In comparison to the standard treatment (wide local excision), Mohs micrographic surgery resulted in an over 10-fold reduction in the risk of positive margins. [35] A study by Long et al. with 154 cases of EMPD found that females were more likely than males to have a positive margin. They also concluded that patients with positive pathologic margins had a 3.5-fold higher chance of recurrence than patients with negative margins. [36] A study conducted between 1998 and 2012 by Fujisawa et al. with 151 patients examined the function of sentinel lymph node biopsy in EMPD. 107 patients in this cohort did not exhibit any clinically noticeable lymphadenopathy, and all of them had sentinel biopsies performed. Finally, it was discovered that 15% of these clinically negative patients had lymph node metastases. This was linked to the primary specimen's lymphovascular and deeper levels of invasion. This indicates that, in the absence of clinically noticeable lymphadenopathy, patients with invasive disease should seek sentinel lymph node biopsy. Hence, patients with early-stage lymph node metastases may have a better prognosis if they receive early detection and lymph node dissection. [5]

The 5-year overall survival rate for metastatic disease is less than 10%. For these patients, there isn't yet a standard systemic treatment plan. [37, 38] 5-FU and cisplatin (FP therapy), 5-FU, epirubicin, carboplatin, vincristine, and mitomycin C (FECOM therapy), cisplatin, epirubicin, and paclitaxel (PET therapy), or combination S-1 (tegafur, 5-FU, and 5-chloro-2-4-dihydroxypyridine) and docetaxel, S-1 monotherapy, or docetaxel monotherapy are among the available combination therapies. [39] Patients on FP and FECOM regimens have shown a median progression-free survival of 5.2 months and 6.5 months, respectively, even though the overall median survival is less than a year. [40]

Future directions in the field of primary EMPD with adnexal involvement hold immense promise for advancing diagnosis, treatment, and patient outcomes. One critical area of focus is the development of targeted therapies that specifically address the mechanisms underlying adnexal infiltration and disease progression. This includes investigating molecular markers associated with adnexal involvement, such as cell adhesion molecules, growth factors, and signaling pathways implicated in tumor cell survival and proliferation within adnexal structures. By elucidating these molecular mechanisms, researchers can identify potential therapeutic targets for novel drug development. In addition to molecular and microenvironmental studies, future diagnostic modalities should aim for greater precision in detecting adnexal involvement in primary EMPD. Advanced imaging techniques, such as high-resolution MRI and molecular imaging approaches, could enhance our ability to visualize tumor extent and accurately assess adnexal infiltration. Integration of imaging data with histopathological findings and biomarker analysis may enable more personalized treatment strategies tailored to individual patients based on the degree of adnexal involvement and disease aggressiveness.

V. CONCLUSION

The prognosis and recurrence of primary EMPD are closely linked with the extent of adnexal involvement. Over 90% of primary EMPD cases exhibit adnexal involvement, predominantly in hair follicles and eccrine ducts. Although this involvement has not been definitively linked to tumor progression or higher recurrence rates, it plays a crucial role by potentially facilitating deeper tissue infiltration, thus highlighting its clinical importance.

Therapeutic options for primary EMPD range from topical treatments like imiquimod and 5-fluorouracil to surgical excision. Among surgical methods, Mohs micrographic surgery is preferred for its enhanced margin control. The efficacy of topical agents depends significantly on the depth of Paget cell invasion within these adnexal structures, illustrating the need to thoroughly understand the pattern and extent of this invasion to optimize patient management strategies.

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Given these insights, it is essential to refine current diagnostic and treatment protocols to better address the intricacies of adnexal proliferation in primary EMPD.

➢ *Conflict of Interest Statement*

The authors have no conflicts of interest to declare.

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➢ *Author Contributions*

All authors have participated sufficiently in the intellectual content, conception, and design of this study. All authors agree to be accountable for all aspects of the manuscript.

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