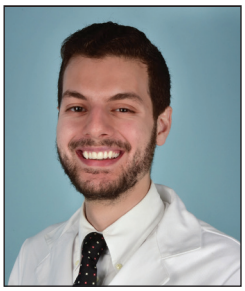
PD-1 Signaling in Extramammary Paget Disease



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RESIDENT **PEARLS**

- Primary extramammary Paget disease (EMPD) is an adnexal carcinoma of the apocrine gland ducts, while secondary EMPD is an extension of malignant cells from an underlying internal neoplasm.
- Surgical margin clearance in EMPD often is problematic, with high recurrence rates indicating the need for additional treatment modalities.
- Programmed cell death receptor 1 (PD-1) signaling can serve as a potential target in EMPD. Further studies and clinical trials are needed to test the efficacy of PD-1 inhibitors in unresectable or invasive/metastatic EMPD.

Primary extramammary Paget disease (EMPD) is an intraepidermal adnexal carcinoma of the apocrine gland ducts with the potential to become invasive or metastatic. The pathogenesis of primary EMPD remains unclear; however, there have been recent studies investigating the genetic characteristics of EMPD lesions. The interaction between the programmed cell death receptor 1 (PD-1) and its ligand is one of the pathways recently reported to be a potential target in EMPD. Given the advances of immunotherapy in the field of oncology and the paucity of effective agents to treat EMPD, this article serves to shed light on recent data studying PD-1 signaling in EMPD and highlights the potential clinical use of immunotherapy for EMPD.

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Primary extramammary Paget disease (EMPD) is an adnexal carcinoma of the apocrine gland ducts that presents as an erythematous patch on cutaneous sites rich with apocrine glands.[1] Primary EMPD can be in situ or invasive with the potential to become metastatic.[2] Treatment of primary EMPD is challenging due to the difficulty of achieving clear surgical margins, as the tumor has microscopic spread throughout the epidermis in a skipping fashion.[3] Mohs micrographic surgery is the treatment of choice; however, there is a clinical need to identify additional treatment modalities, especially for patients with unresectable, invasive, or metastatic primary EMPD,[4] which partly is due to lack of data to understand the pathogenesis of primary EMPD. Recently, there have been studies investigating the genetic characteristics of EMPD tumors. The interaction between the programmed cell death receptor 1 (PD-1) and its ligand (PD-L1) is one of the pathways recently studied and has been reported to be a potential target in EMPD.[5-7] Programmed cell death receptor 1 signaling constitutes an immune checkpoint pathway that regulates the activation of tumor-specific T cells.[8] In several malignancies, cancer cells express PD-L1 on their surface to activate PD-1 signaling in T cells as a mechanism to dampen the tumor-specific immune response and evade antitumor immunity.[9] Thus, blocking PD-1 signaling widely is used to activate tumor-specific T cells and decrease tumor burden.[10] Given the advances of immunotherapy in many neoplasms and the paucity of effective agents to treat EMPD, this article serves to shed light on recent data studying PD-1 signaling in EMPD and highlights the potential clinical use of immunotherapy for EMPD.

EMPD and Its Subtypes

Extramammary Paget disease is a rare adenocarcinoma typically affecting older patients (age >60 years) in cutaneous sites with abundant apocrine glands such as the genital and perianal skin.[3] Extramammary Paget disease presents as an erythematous patch and frequently is treated initially as a skin dermatosis, resulting in a delay

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in diagnosis. Histologically, EMPD is characterized by the presence of single cells or a nest of cells having abundant pale cytoplasm and large vesicular nuclei distributed in the epidermis in a pagetoid fashion.[11]

Extramammary Paget disease can be primary or secondary; the 2 subtypes behave differently both clinically and prognostically. Although primary EMPD is considered to be an adnexal carcinoma of the apocrine gland ducts, secondary EMPD is considered to be an intraepithelial extension of malignant cells from an underlying internal neoplasm.[12] The underlying malignancies usually are located within dermal adnexal glands or organs in the vicinity of the cutaneous lesion, such as the colon in the case of perianal EMPD. Histologically, primary and secondary EMPD can be differentiated based on their immunophenotypic staining profiles. Although all cases of EMPD show positive immunohistochemistry staining for cytokeratin 7, carcinoembryonic antigen, and epithelial membrane antigen, only primary EMPD will additionally stain for GCDFP-15 (gross cystic disease fluid protein 15) and GATA.[11] Regardless of the immunohistochemistry stains, every patient newly diagnosed with EMPD deserves a full workup for malignancy screening, including a colonoscopy, cystoscopy, mammography and Papanicolaou test in women, pelvic ultrasound, and computed tomography of the abdomen and pelvis.[13]

The first-line treatment of EMPD is surgery; however, obtaining clear surgical margins can be a challenge, with high recurrence rates due to the microscopic spread of the disease throughout the epidermis.[4] In addition, anatomic location affects the surgical approach and patient survival. Recent studies on EMPD mortality outcomes in women show that mortality is higher in patients with vaginal EMPD than in those with vulvar/labial EMPD, partly due to the sensitive location that makes it difficult to perform wide local excisions.[13,14] Assessing the entire margins with tissue preservation using Mohs micrographic surgery has been shown to be successful in decreasing the recurrence rate, especially when coupled with the use of cytokeratin 7 immunohistochemistry.[4] Other treatment modalities include radiation, topical imiquimod, and photodynamic therapy.[15,16] Regardless of treatment modality, EMPD requires long-term follow-up to monitor for disease recurrence, regional lymphadenopathy, distant metastasis, or development of an internal malignancy.

The pathogenesis of primary EMPD remains unclear. The tumor is thought to be derived from Toker cells, which are pluripotent adnexal stem cells located in the epidermis that normally give rise to apocrine glands.[17] There have been few studies investigating the genetic characteristics of EMPD lesions in an attempt to understand pathogenesis as well as to find druggable targets. Current data for targeted therapy have focused on HER2 (human epidermal growth factor receptor 2) hormone receptor expression,[18] ERBB (erythroblastic oncogene B) amplification,[19] CDK4 (cyclin-dependent kinase 4)–cyclin D1 signaling,[20] and most recently PD-1/PD-L1 pathway.[5-7]

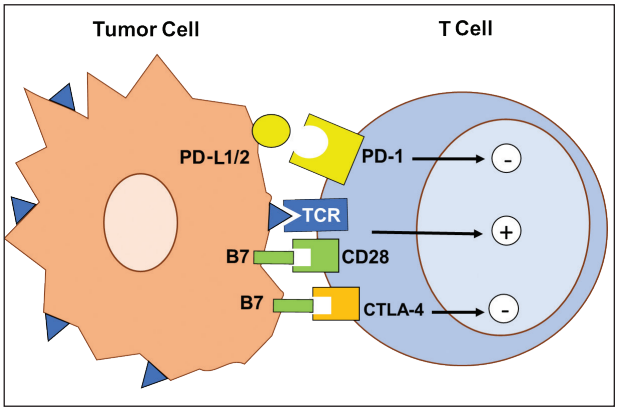
PD-1 Expression in EMPD: Implication for Immunotherapy

Most tumors display novel antigens that are recognized by the host immune system and thus stimulate cell-mediated and humoral pathways. The immune system naturally provides regulatory immune checkpoints to T cell–mediated immune responses. One of these checkpoints involves the interaction between PD-1 on T cells and its ligand PD-L1 on tumor cells.[21] When PD-1 binds to PD-L1 on tumor cells, there is inhibition of T-cell proliferation, a decrease in cytokine production, and induction of T-cell cytolysis.[22] The Figure summarizes the dynamics for T-cell regulation.

Naturally, tumor-infiltrating T cells trigger their own inhibition by binding to PD-L1. However, certain tumor cells constitutively upregulate the expression of PD-L1. With that, the tumor cells gain the ability to suppress T cells and avoid T cell–mediated cytotoxicity,[23] which is known as the adoptive immune resistance mechanism. There have been several studies in the literature investigating the PD-1 signaling pathway in EMPD as a way to determine if EMPD would be susceptible to immune checkpoint blockade. The success of checkpoint inhibitor immunotherapy generally correlates with increased PD-L1 expression by tumor cells.

One study evaluated the expression of PD-L1 in tumor cells and tumor-infiltrating T cells in 18 cases of EMPD.[6] The authors identified that even though tumor cell PD-L1 expression was detected in only 3 (17%) cases, tumor-infiltrating lymphocytes expressed PD-L1 in the majority of the cases analyzed and in all of the cases positive for tumor cell PD-L1.[6]

Another study evaluated PD-1 and PD-L1 expression in EMPD tumor cells and tumor-associated immune



Overview of T-cell co-stimulatory signals. A tumor-infiltrating T lymphocyte recognizes and binds to the tumor-specific antigen. Another step is required for activation, which involves B7 binding to CD28 on T cells. This co-stimulatory secondary signal can be counteracted by binding of either B7 to cytotoxic T lymphocyte–associated protein 4 (CTLA-4) on tumor cells or expression of programmed death ligand 1 and 2 (PD-L1/2) by the tumor cells to activate programmed cell death receptor 1 (PD-1) on T cells. TCR indicates T-cell receptor.

infiltrate.[5] They found that PD-1 was expressed heavily by the tumor-associated immune infiltrate in all EMPD cases analyzed. Similar to the previously mentioned study,[6] PD-L1 was expressed by tumor cells in a few cases only. Interestingly, they found that the density of CD3 in the tumor-associated immune infiltrate was significantly (P=.049) higher in patients who were alive than in those who died, suggesting the importance of an exuberant T-cell response for survival in EMPD.[5]

A third study investigated protein expression of the B7 family members as well as PD-1 and PD-L1/2 in 55 EMPD samples. In this study the authors also found that tumor cell PD-L1 was minimal. Interestingly, they also found that tumor cells expressed B7 proteins in the majority of the cases.[7]

Finally, another study examined activity levels of T cells in EMPD by measuring the number and expression levels of cytotoxic T-cell cytokines.[24] The authors first found that EMPD tumors had a significantly higher number of $CD8^+$ tumor-infiltrating lymphocytes compared to peripheral blood (P<.01). These $CD8^+$ tumor-infiltrating lymphocytes also had a significantly higher expression of PD-1 (P<.01). They also found that tumor cells produced an immunosuppressive molecule called indoleamine 2,3-dyoxygenae that functions by suppressing T-cell activity levels. They concluded that in EMPD, tumor-specific T lymphocytes have an exhausted phenotype due to PD-1 activation as well as indoleamine 2,3-dyoxygenase release to the tumor microenvironment.[24]

These studies highlight that restoring the effector functions of tumor-specific T lymphocytes could be an effective treatment strategy for EMPD. In fact, immunotherapy has been used with success for EMPD in the form of topical immunomodulators such as imiquimod.[16,25] More than 40 cases of EMPD treated with imiquimod 5% have been published; of these, only 6 were considered nonresponders,[5] which suggests that EMPD may respond to other immunotherapies such as checkpoint inhibitors. It is an exciting time for immunotherapy as more checkpoint inhibitors are being developed. Among the newer agents is cemiplimab, which is a PD-1 inhibitor now US Food and Drug Administration approved for the treatment of locally advanced or metastatic cutaneous squamous cell carcinoma in patients who are not candidates for curative surgery or curative radiation.[26] Programmed cell death receptor 1 signaling can serve as a potential target in EMPD, and further studies need to be performed to test the clinical efficacy, especially in unresectable or invasive/metastatic EMPD. As the PD-1 pathway is more studied in EMPD, and as more PD-1 inhibitors get developed, it would be a clinical need to establish clinical studies for PD-1 inhibitors in EMPD.

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