Case Report

PIK3CA inhibitor treatment for metastatic scrotal extramammary Paget's disease: a case report and literature review

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Background: Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma that occurs in the genitals, axilla, and anus, where apocrine sweat glands are abundant. This disease is mainly characterized by localized lesions and rare distant metastasis. Scrotal Paget's disease is a rare type of EMPD, and there is no standard treatment for metastatic EMPD.

Case Description: Here, we reported the genetic results of a patient with a *PIK3CA* gene mutation in scrotal Paget's disease who developed multiple metastases to the lymph nodes, liver, and bones during adjuvant radiotherapy, as well as the results of treatment with a PIK3CA inhibitor. The latest advances in this field were also summarized. The treatment response was evaluated as stable disease (SD) after 6 courses of docetaxel plus tegafur (DS regimen) chemotherapy. Then, a second-line treatment, a PIK3CA inhibitor, WX390, was administered with tolerable toxicity. There was a treatment-induced increase in blood glucose level during treatment, and insulin was administrated with good control. The progression-free survival (PFS) was 3.9 months and the overall survival (OS) was 16 months.

Conclusions: *PIK3CA* is a commonly mutated gene in EMPD. To the best of our knowledge, this is the first case report of a PIK3CA inhibitor for the treatment of primary metastatic EMPD, and the treatment efficacy was good. PIK3CA inhibitors may be promising for the treatment of metastatic EMPD in the future.

Keywords: Extramammary Paget's disease (EMPD); treatment; PIK3CA; case report; literature review

Received: 03 August 2024; Accepted: 13 December 2024; Published online: 10 April 2025.
doi: 10.21037/acr-24-170
View this article at: https://dx.doi.org/10.21037/acr-24-170

Introduction

Paget's disease can be divided into mammary Paget's disease (MPD) and extramammary Paget's disease (EMPD) according to the site of disease onset. The first MPD case with eczematous lesion occurring on the nipple and areola was reported by Paget in 1874. In 1889, Crocker first discovered Paget's disease in the scrotum and penis. Since then, Paget's disease, which is distributed in the vulva, scrotum, axilla, inguinal area, anus, and other apocrine sweat glands, has been collectively referred to as EMPD (1). The incidence of EMPD is very low, which is about 0.04/100,000 to 0.06/100,000 per year. Scrotal Paget's

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disease is a rare type of EMPD. Vulvar Paget's disease accounts for approximately 65% of EMPD cases while scrotal Paget's disease accounts for only 0.4–14% (2-4). *PIK3CA* is a commonly mutated gene in EMPD (5). However, there are no any reports about PIK3CA inhibitors efficacy in the treatment of EMPD (6). Evidence-based treatment guidelines are not available for metastatic EMPD. In this case report, we provide a case of metastatic scrotal Paget's disease with *PIK3CA* gene mutation which soon developed distant metastases after surgery. We describe the efficacy and side effects of PIK3CA inhibitor after first-line chemotherapy. To our knowledge, this is the first case report of a PIK3CA inhibitor for the treatment of primary metastatic EMPD. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-170/rc).

Case presentation

A 66-year-old male was admitted to Jiangmen Central Hospital in June 2021 for the presentation of recurrent erythema on the right scrotum accompanied by persistent itching for one year. Physical examination showed the patient had an eczema-like rash in the right scrotum, about 3 cm × 4 cm in size, with a reddish surface. The patient was diagnosed with Paget's disease of the scrotum without distant metastasis and underwent "partial scrotal resection plus skin flap transplantation and scrotoplasty" in the Department of Urology in Jiangmen Central Hospital on June 21, 2021. Postoperative pathology revealed Paget's disease of the scrotum, nerve bundles (+), vascular thrombus (+), skin margins and basal margin involvement (+). The immunohistochemistry results were cytokeratin (CK, +), epithelial membrane antigen (EMA, +), carcinoembryonic antigen (CEA, +), GATA binding protein 3 (GATA3, +), P40 (–), Sangtec-100 (S-100, –), prostate specific antigen (PSA, –), P504S (+), androgen receptor (AR, approximately 100+), cytokeratin 7 (CK7, +), cytokeratin 20 (CK20, –), caudal-type homeobox protein 2 (CDX2, –), and proliferation cell nuclear antigen-67 (Ki-67, 70%+). Special staining showed alcian blue (AB, +). The patient was referred to the Department of Radiotherapy for further radiotherapy due to positive surgical margins, with mild postoperative edema of the right lower extremity. The patient had a previous history of primary hypertension for 2 years and no any tumor family history.

From August 25, 2021 to September 24, 2021, the patient received 6-field intensity-modulated radiotherapy (IMRT) in the tumor bed and right inguinal region. The prescribed dose of the IMRT plan for high-risk tumor bed areas [i.e., tumor bed of primary gross tumor volume (pGTVtb)] was 6,020 and 5,040 cGy for the low-risk areas [i.e., clinical tumor volume (CTV)] in 28 fractions, 5 days per week for 5.6 weeks. The patient developed grade 3 radiation dermatitis and moderate pitting edema of the right lower limb after undergoing 21 fractions of radiotherapy (the last radiotherapy was delivered on September 24, 2021). Thus, subsequent radiotherapy was discontinued, and symptom-related supportive treatment was given to the patient. On November 1, 2021, radiation dermatitis was improved. However, there was a persistent increase in the CEA level and grade 1 toxicity of aminotransferase [Common Terminology Criteria for Adverse Events (CTCAE) 5.0] level, which did not significantly improve despite the administration of hepatoprotective therapy. Subsequent positron emission tomography-computed tomography (PET-CT) (*Figure 1*) revealed multiple enlarged lymph nodes with elevated glycemic metabolism in the mediastinum, hilus of lung, abdominal cavity, and pelvic cavity [maximum standardized uptake value (SUVmax) 4.1–7.2]; multiple nodules and swellings with elevated glycemic metabolism in the metastatic lesions of the liver (SUVmax 10.6), cervical vertebras, thoracic vertebras, lumbar vertebras, and pelvic bones (SUVmax 8.7). On

Highlight box

Key findings

- The efficacy of the PIK3CA inhibitor for metastatic scrotal Paget's disease with *PIK3CA* gene mutation after chemotherapy is promising.

What is known and what is new?

- Metastatic scrotal extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma which has no standard treatment option for it. There are no any reports of PIK3CA inhibitor therapy in this field.
- *PIK3CA* is a commonly mutated gene in EMPD. The efficacy and side effects of PIK3CA inhibitor in the treatment of metastatic scrotal EMPD are reported.

What is the implication, and what should change now?

- To the best of our knowledge, this is the first case report of a PIK3CA inhibitor for the treatment of primary metastatic EMPD, and the treatment efficacy was good. PIK3CA inhibitor may be promising for the treatment of metastatic EMPD in the future.
- Multidisciplinary collaboration is necessary in the management of rare tumors.

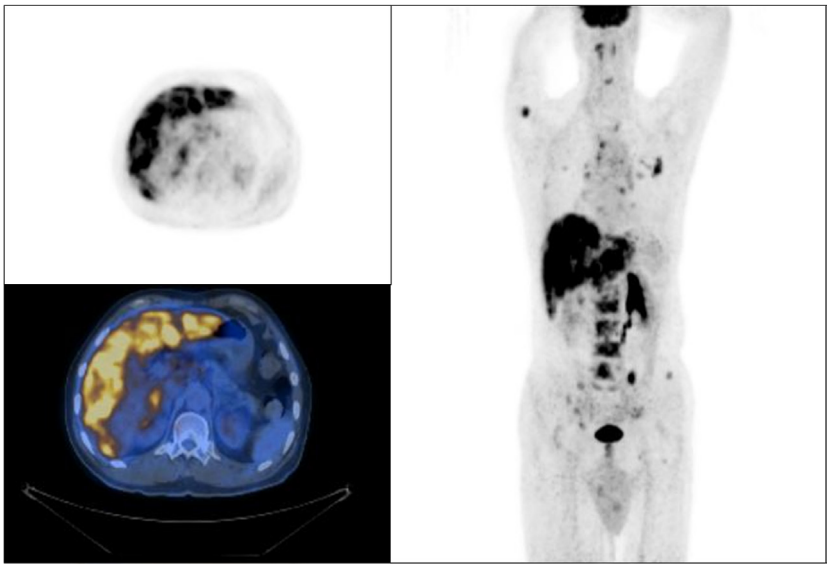

Figure 1 Metastatic lymph nodes in the mediastinum, hilar, abdominal and pelvic cavities, and multiple diffused metastases in the liver. Multiple metastases to the cervical, thoracic, lumbar vertebras and pelvic bones.

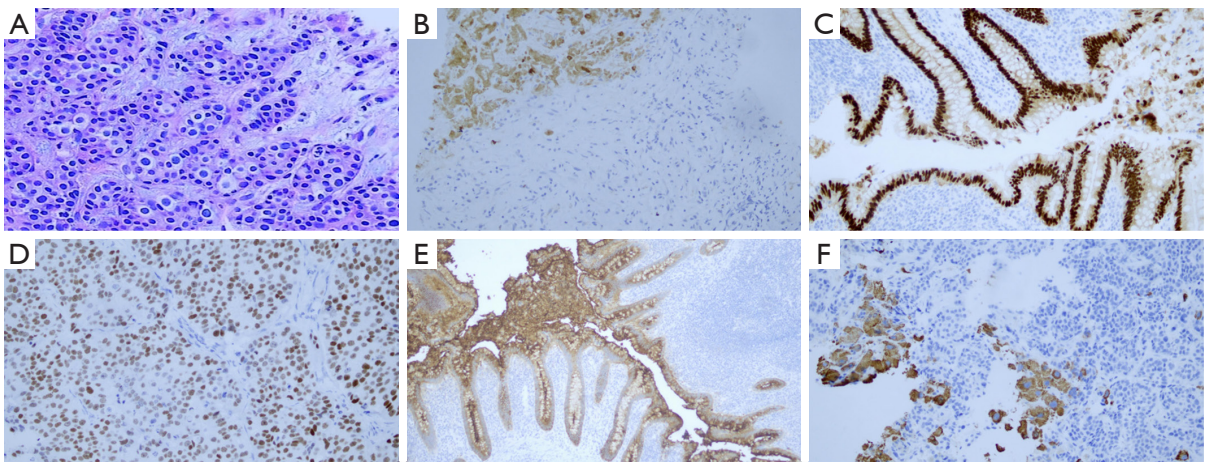

Figure 2 The pathological and immunohistochemical results from liver needle biopsy specimen. Pathological result: (A) HE stain, ×100 magnification. Plate-like arrangement of liver tissue is seen. Nests of heterogeneous cells arranged in clusters, which have large cell bodies, abundant and light-stained cytoplasm, large and dark-stained nuclei. Immunohistochemical staining results (×200 magnification): (B) positive staining for CK7. (C) Negative staining for CDX2. (D) Positive staining for GATA3. (E) Weakly positive staining for CEA. (F) Negative staining for hepatocyte. CEA, carcinoembryonic antigen; CK7, cytokeratin 7; CDX2, caudal-type homeobox protein 2; HE, hematoxylin-eosin; GATA3, GATA binding protein 3.

April 7, 2022, the pathological and immunohistochemical results from the liver needle biopsy specimen clearly showed the presence of metastatic Paget's disease (*Figure 2*). Programmed death ligand-1 (PD-L1) was negative expression, with a tumor proportion score (TPS) and combined positive score (CPS) of less than 1% based on immunohistochemical staining using hematoxylin and eosin (testing company: Geneseeq, Nanjing, China). The detailed results from next-generation sequencing (NGS) were as follows (*Table 1*): *PIK3CA*, erb-b2 receptor tyrosine kinase 2 (*ERBB2*), and adenosine triphosphate-binding cassette subfamily B member 1 (*ABCB1*) gene mutations,

Table 1 The details for the patients with positive NGS results

Gene	Variation type	Mutation	Tissue abundance (%)
PIK3CA	Missense mutation in exon 4 of p.V344G	c.1031T>G (p.V344G)	14.5
ERBB2	Missense mutation in exon 8 of p.S310F	c.929C>T (p.S310F)	22
ABCB1	A missense mutation in exon 15 of p.F520L	c.1560T>A (p.F520L)	32.6

ABCB1, adenosine triphosphate-binding cassette subfamily B member 1; *ERBB2*, erb-b2 receptor tyrosine kinase 2 gene; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene.

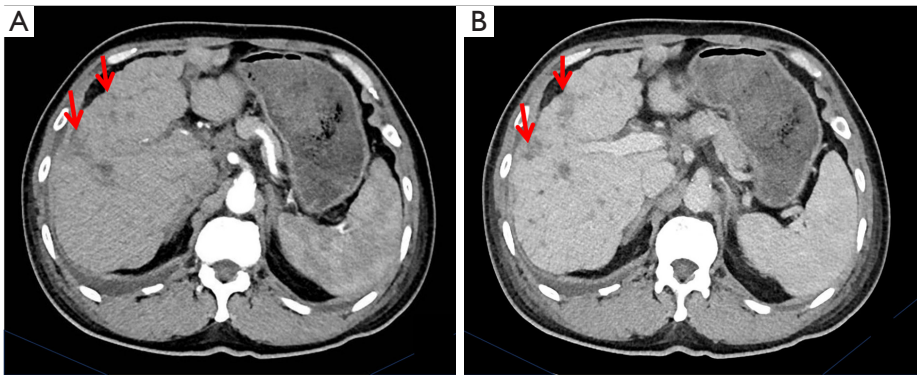

Figure 3 Computed tomography of the liver before treatment with PIK3CA inhibitor. (A) Arterial phase, (B) venous phase: reduced liver volume, with uneven surface and widened hepatic fissure, and scattered distribution of nodular lesions in the liver; considering metastatic tumors, red arrows.

microsatellite instability low (MSI-L); and tumor mutation burden low (TMB-L, 6.2 mutation/Mb).

The patient underwent 6 cycles of chemotherapy using the DS regimen (docetaxel 140 mg intravenous infusion on day 1, tegafur 60 mg orally twice daily from day 1 to day 14 every 3 weeks) from December 9, 2021 to March 30, 2022. The chemotherapy efficacy was evaluated as stable disease (SD) after 2, 4, and 6 courses of chemotherapy.

Subsequently, the patient was treated with a PIK3CA inhibitor (WX390) (1 mg orally once a day) on May 13, 2022 (pretreatment liver images are shown in *Figure 3*). On July 21, 2022, the numbers and volume of metastatic lesions in the liver decreased significantly, and efficacy was evaluated as a partial response (PR) (*Figure 4*). On September 8, 2022, there was significant progression of metastatic lesions in the liver, as shown in *Figure 5*. Then, the treatment of the patient was terminated. The progression-free survival (PFS) was 3.9 months for this patient. Additionally, there was a treatment-induced increase in blood glucose level during PIK3CA inhibitor treatment, and insulin was administrated with good control.

The drug used for treatment, WX390, is a dual inhibitor of the PI3K/mTOR pathway that was produced and provided by Hequan Pharmaceutical Co., Ltd. (Shanghai, China). It was used in a multicenter, open phase Ib/IIa prospective clinical trial to evaluate its safety and preliminary efficacy in the treatment of patients with *PIK3CA* gene-mutated advanced solid tumors. This trial was approved by Jiangmen Central Hospital's Ethics Committee.

The patient died of tumor progression and multiple organs failure on October 19, 2022.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). This case participated in a multicenter clinical trial that had received ethical approval from Jiangmen Central Hospital Clinical Trial Ethics Committee (ethical approval number is 202201A). Informed consent for publication of this case report and accompanying images was not obtained from the patient's relatives after all possible attempts were made.

Discussion

EMPD is predominantly a localized lesion, and the lymph

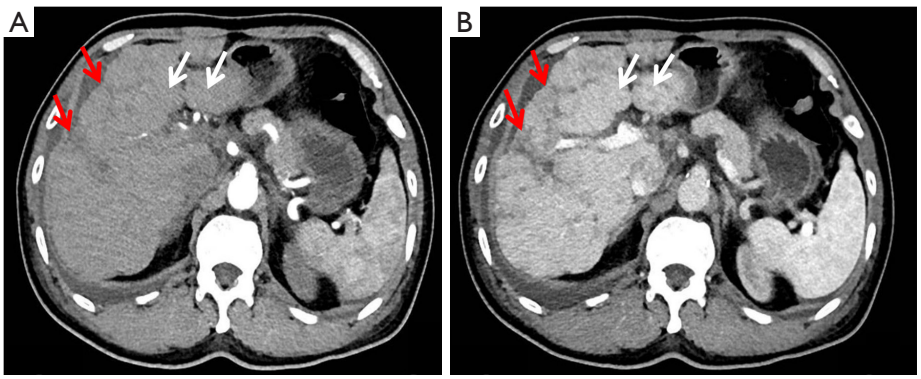

Figure 4 Computed tomography show a reduction in the size and number of metastases of Paget's disease in the liver. (A) Arterial phase, (B) venous phase: metastatic lesions (red arrows) and cirrhotic regenerative nodules (white arrows) in the liver were mixed and diffusely distributed throughout the liver shrank with treatment.

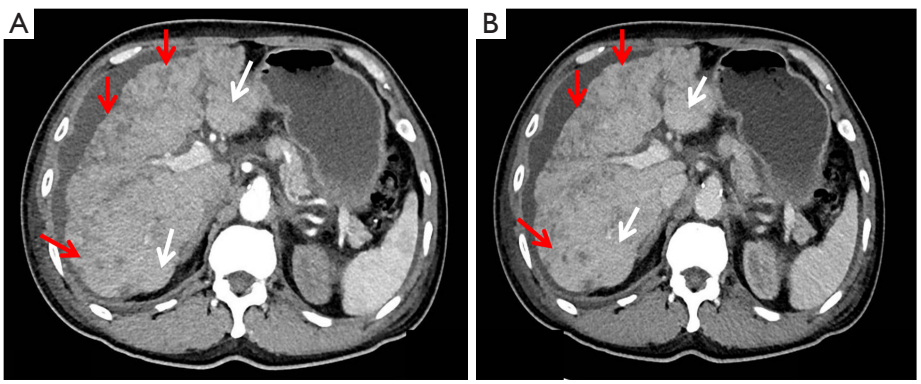

Figure 5 Computed tomography of the abdomen demonstrating the liver volume decreased and metastatic lesions enlarged in the liver. (A) Arterial phase, (B) venous phase: the liver volume decreased with treatment, and the metastatic lesions in the liver progressed (metastatic tumors, red arrows; cirrhotic regenerative nodules, white arrows); the nodule types were mixed and diffusely distributed throughout the liver.

node metastasis rate is 16.9%. If the tumor cells invade the dermis, the lymph node metastasis rate can reach to 42.8%, and the incidence of distant metastasis is 16% (7,8). Scrotal Paget's disease is a rare type of EMPD, and most of the patients have a long history of the disease before final diagnosis. The patient in this study presented with a one-year history of scrotal erythema accompanied by pruritus.

EMPD can be divided into primary EMPD (cutaneous origin) and secondary EMPD (extracutaneous origin) based on its histologic origin. Primary Paget's disease originates from epidermal cells and is microscopically characterized by typical Paget cells, which is mainly distributed in the basal or subspinal layers (9). Secondary Paget's disease originates from adenocarcinomas of the rectum, anus, or urinary system. Morphology under microscopy resembles gastrointestinal glandular cells (e.g., complex columnar epithelial cells, cup cells, etc.) and high-grade uroepithelial carcinoma cells (10).

EMPD is mainly diagnosed by immunohistochemical staining. CK7 and CK20 are sensitive and highly specific (nearly 100%) for diagnosing EMPD. Primary EMPD typically exhibits positive CK7 expression rather than CK20 and is characterized by HER2/neu overexpression and negative CDX2 expression. Conversely, secondary EMPD demonstrates the opposite pattern (11). Gross cystic disease fluid protein 15 (GCDFP-15), CEA, and GATA-3 were stained positively in primary EMPD (9,12). In contrast, Paget cells stained negatively for the antimelanoma-specific antibody 45 [human melanoma black 45 (HMB 45)] and S-100, which

can be differentiated from melanoma and Bowen's disease (13). The combination of immunohistochemical phenotypes (CK7+, CK20–, CDX2–) in our patient is consistent with the diagnosis of primary EMPD.

The pathogenesis of Paget's disease remains unclear. The epidermotropic theory suggests that this may be attributed to the migration of breast ductal cells (14). Wachter *et al.* (15) analyzed the immunohistochemistry results and hormone receptor phenotypes of 48 patients with MPD and found that 28.9% and 5.3% of patients had luminal B and triple-negative phenotype, respectively, but no patients had the luminal A phenotype. No any correlation between different molecular subtypes and tumor infiltrative property was observed.

The coexpression of PD-L1 on tumor cells and programmed death receptor-1 (PD-1) on immune T cells hampers the host immune response, thereby facilitating tumor progression and metastasis. Karpathiou *et al.* (16) tested specimens from 41 patients with Paget's disease (19 with MPD, 22 with EMPD) and found that all of these patients were negative expression for PD-L1. However, Garganese *et al.* (17) tested 41 specimens of vulvar Paget's disease and found that PD-L1 expression was positive in 10% of noninfiltrative vulvar Paget's disease and 27% infiltrative disease, respectively. Mauzo *et al.* (18) reported 14% PD-L1-positive rate in tumor cells and 71% PD-L1-positive rate in tumor cells and tumor-associated lymphocytes by analyzing the pathological specimens of 21 patients with EMPD, and there was no correlation between the level of PD-LI expression and clinical parameters.

The molecular mechanism of EMPD has not been fully investigated, and common gene mutations reported in the literature on EMPD include mutations in *PIK3CA*, *ERBB2*, *KRAS*, *NRAS*, *BRAF*, and *TP53* (6,19).

Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) is a pivotal kinase within the PI3K-AKT-mTOR pathway that plays a critical role in the proliferation and growth of diverse solid tumor cells (20). PIK3CA is a type of somatic oncogene, and its gene mutation causes continuous activation of PI3K enzymes, which disrupts cellular PI3K-AKT-mTOR pathway signaling and plays an important role in the development of malignant tumors (21). The mutation rate of PIK3CA in breast cancer patients was 35.7% (22). The addition of a PIK3CA inhibitor significantly improved the median overall survival (OS) of advanced breast cancer patients with *PIK3CA* gene mutation, HR^+, $HER2^-$ (23). Similarly, PIK3CA inhibitors have demonstrated promising efficacy in *PIK3CA* gene-mutated gastrointestinal and gynecological malignant solid tumors (24); 30.8–35% EMPD patients have *PIK3CA* gene mutation which indicates enhanced aggressiveness (5,25). However, there are no any reports about PIK3CA inhibitors efficacy in the treatment of EMPD (6).

The patient in our study also exhibited mutation in the *HER2* gene. Liu *et al.* (26) reported that the HER2-positive rate in patients with MPD and EMPD was 87.5% and 35.7%, respectively. Compared with HER2-negative patients, HER2-positive EMPD patients had worse tumor differentiation and significantly higher risk of lymph node metastasis and recurrence (27). The HER2-positive rate in scrotal Paget's disease is 38% (12). *HER2* gene mutation also provides a targeted therapeutic option for this disease.

ABCB1 is an adenosine triphosphate (ATP)-binding cassette (ABC) gene and widely presents in all areas of life. Mutations in this gene can lead to a significant increase in tumor drug resistance (28). Our patient was positive expression for *ABCB1* gene mutation. The DNA mismatch repair (MMR) system helps to ensure genome stability by correcting replication errors. The gene type of our patient was MSI-L. Whether microsatellite status is associated with prognosis and treatment response in patients with EMPD is still unclear.

The treatment of EMPD includes local surgery and radiotherapy, as well as systemic therapies. Surgery includes local enlarged resection and Mohs micrographic surgery (MMS). Compared with extended resection, MMS can maximize the resected lesion area and preserve normal skin tissue (29). The local administration of radiotherapy is a crucial therapeutic approach for EMPD. A median radiation dose of 50 Gy (ranging from 40 to 60 Gy) delivered in 22–33 fractions (with 1.8–2.5 Gy per fraction) results in an impressive 5-year local PFS rate of 91.7% and 5-year survival rate of 84.3% with good tolerance (30). Positive lymph node is a major risk factor for distant metastasis in EMPD patients, and adjuvant radiotherapy in patients with greater than or equal to three positive lymph nodes significantly improved OS (31). In this case, the patient had positive postoperative margins and was given postoperative radiotherapy (actual irradiation dose of 45 Gy for pGTVtb) with good local control.

There is no standardized chemotherapy regimen available for metastatic EMPD. Single-agent docetaxel has demonstrated potential effectiveness in cases of locally advanced or metastatic EMPD (32). Other regimens for the treatment of metastatic EMPD mainly include PET (cisplatin, epirubicin, paclitaxel), PF (cisplatin, 5-fluorouracil), DS, and

single agent 5-fluorouracil (33).

HER2-targeted therapy and immunotherapy for metastatic EMPD are currently only confined to some case reports, and the efficacy of anti-HER2-targeted agents (trastuzumab) in combination with paclitaxel in the treatment of HER2-positive metastatic EMPD is promising (34). There is one case report on the utilization of immunotherapy for metastatic EMPD, the efficacy of 3 cycles of ipilimumab and nivolumab was evaluated PR, and subsequent treatment was discontinued due to immune-related hepatitis (35).

PIK3CA gene mutations are closely related to the pathogenesis of EMPD, and the prognosis of EMPD patients with *PIK3CA* gene mutations are worse than those without mutations (6). The patient in this study has a mutation in exon 4 of *PIK3CA* gene, developed distant metastases 5 months after surgery. The efficacy of chemotherapy was evaluated as SD after 6 courses of chemotherapy, and targeted therapy with a PIK3CA inhibitor, WX390, was found to be effective, and obtained a PFS of 3.9 months. To the best of our knowledge, this case report represents the first example of metastatic primary EMPD treated with PIK3CA inhibitor.

Conclusions

This EMPD patient was treated with local radiotherapy without recurrence after R1 resection, and genetic testing revealed mutations in the *PIK3CA*, *ERBB2*, and *ABCB1* genes. Multiple systemic metastases occurred 5 months after surgery. PFS was 3.9 months after treatment with the PIK3CA inhibitor. To the best of our knowledge, this is the first case report of metastatic EMPD treated with PIK3CA inhibitor. The patient developed drug-induced diabetes during treatment, which was controlled well with insulin therapy. The OS of this EMPD patient was 16 months.

Acknowledgments

We thank the patient and his families for their support and cooperation throughout the treatment.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-170/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-24-170/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-170/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). This case participated in a multicenter clinical trial that had received ethical approval from Jiangmen Central Hospital Clinical Trial Ethics Committee (ethical approval number is 202201A). Informed consent for publication of this case report and accompanying images was not obtained from the patient's relatives after all possible attempts were made.

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doi: 10.21037/acr-24-170
Cite this article as: Huang Y, Dong S, Ren J, Li J, Wu C, Chen H, Liu Y, Yuan J, Huang J, Xiao L. PIK3CA inhibitor treatment for metastatic scrotal extramammary Paget's disease: a case report and literature review. AME Case Rep 2025;9:47.