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Challenges in treating coexisting scrotal apocrine carcinoma and gastric cancer: insights from an elderly patient: a case report and literature review

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Abstract

Background Apocrine carcinoma associated with Paget's disease is a rare malignancy that typically manifests in elderly individuals, predominantly affecting the geriatric population. It commonly arises in regions rich in apocrine glands and often exhibits an insidious onset, potentially requiring several years to be diagnosed.

Case presentation An 80-year-old male was simultaneously diagnosed with scrotal apocrine carcinoma (showing Paget changes) and early-stage gastric cancer. Whole-genome exome sequencing confirmed these as independent malignancies with minimal genetic overlap, indicating that they were two primary tumors. The patient initially underwent successful surgery but experienced recurrence and metastasis. Treatment with capecitabine and paclitaxel showed promising responses, highlighting similarities between breast and apocrine carcinomas. Challenges were noted in the use of genetic testing and drug susceptibility assessments for treatment guidance. Notably, HER-2 expression in metastatic lesions, a trait of apocrine carcinoma, has remained unexplored due to negative HER-2 FISH results and a lack of available targeted therapies in China.

Conclusion Elderly patients often exhibit a lesser degree of aggressiveness toward treatment following a diagnosis of malignant tumors. It is imperative to carefully consider how to strike a balance between effective treatment and maintaining a satisfactory quality of life for these patients. This case underscores the complexity of treating coexisting rare cancers in older adults and emphasizes the need for personalized treatments and continued innovation in cancer therapy. The insights gained offer significant value in understanding and managing such rare cancer cases.

Keywords Apocrine carcinoma, EMPD, HER-2, Chemotherapy, Gastric cancer

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Background

Apocrine carcinoma is a rare and aggressive malignancy, often presenting as asymptomatic, indolent, firm or cystic, erythematous nodules, sometimes with ulceration [1, 2]. This disease primarily affects Caucasians, with an incidence rate of 0.18 to 0.23 cases per 100,000 people annually, while other ethnic groups experience lower rates [3]. Extramammary Paget's Disease (EMPD) is even more rare, with an incidence of 0.11 cases per 100,000 person-years in the Netherlands [4]. This neoplasm is prone to hematogenous dissemination to the liver, lungs, osseous structures, and lymphatic system. Extramammary Paget's disease (EMPD), which is also infrequent, predominantly affects geriatric populations and typically arises in regions abundant in apocrine glands. The concurrence of scrotal apocrine carcinoma with EMPD is exceedingly uncommon, posing risks of misdiagnosis and consequent therapeutic delays [1, 2].

Apocrine carcinoma represents a scarce cutaneous neoplasm, predominantly emerging in zones with high concentrations of apocrine sweat glands. EMPD, particularly in the scrotal and inguinal locales, is even more exceptional [5]. This pathology primarily afflicts individuals aged 50 and above, exhibiting gradual clinical progression with lesions that lack pathognomonic characteristics [6]. Owing to its nonspecific clinical presentation, EMPD is frequently misinterpreted as scrotal dermatitis or other dermal pathologies, leading to protracted periods of inappropriate management [7].

Some researchers postulate a histopathological correlation between scrotal apocrine carcinoma and Paget's disease, suggesting that apocrine carcinoma may represent an initial metastatic phase in EMPD [8]. EMPD is often linked to the emergence of secondary tumors in nearby tissues or internal organs [9]. Nonetheless, reports of concurrent gastric cancer are rare. In this paper, we present a unique case involving scrotal apocrine carcinoma, extramammary Paget's disease, and gastric cancer in an elderly male patient.

Consent for the publication of this case report was obtained from the patient.

Case presentation

An 81-year-old male patient presented with a decade-long history of pruritus and ulcerative lesions on his right scrotum. In February 2017, he underwent excision of a right scrotal lesion at a tertiary general hospital following an exacerbation of the ulceration. Postoperative pathological findings of the primary scrotal lesion stained with Hematoxylin-Eosin (HE): Histological examination of the primary scrotal epidermis reveals the presence of characteristic large, round cells with prominent nuclei and pale cytoplasm, cancer cells infiltrate the dermis, demonstrating epidermal invasion and Paget's disease like alteration (Fig. 1A-D). Histopathological examination revealed a malignancy originating from sweat glands. The diagnosis of apocrine carcinoma was supported by immunohistochemical analysis: S-100(-)、P63(-)、AR(-)、GATA-3(local+)、ER(focal+)、GCDFP-15(+)、c-erbB-2(++)、CK(+)、CEA(+). After the surgery, no adjuvant radiotherapy or chemotherapy was administered. Postoperatively, the patient experienced recurrent scrotal skin ulceration with purulent discharge. Symptomatic relief for pruritus was achieved through intermittent medication, but no specific therapeutic interventions were pursued.

In February 2021, the patient self-reported a palpable mass in the right inguinal region measuring approximately 1.0×0.5 cm, characterized by firmness, immobility, and distinct margins. No accompanying systemic symptoms, such as weight loss, night sweats, fever, or anorexia, were reported. Routine examinations revealed a progressive increase in carcinoembryonic antigen (CEA) levels, which were initially disregarded by the patient. The inguinal mass expanded to 3.0×1.0 cm, retained its original characteristics and was accompanied by skin ulceration and erythema in the bilateral groin and perineal regions. Continual monitoring of CEA levels at a local hospital indicated a persistent increase.

On June 1, 2021, the patient was admitted to our institution. Elevated CEA levels of 184.19 ng/ml (normal range: 0–5 ng/ml) were detected. Investigations for liver, lung, or bone metastases (conducted through CT scans) were negative at this time. A biopsy of the enlarged right inguinal lymph node was conducted, revealing nests of tumor cells with clear cytoplasm and hyperchromatic nuclei, indicative of significant atypia. These findings led to the presumptive diagnosis of an epithelial-origin malignancy, likely adenocarcinoma. Integration of clinical data with immunohistochemical findings confirmed the diagnosis of apocrine carcinoma, with the following immunohistochemical markers: CK7 (+), GCDFP-15 (+), GATA3 (+), EMA (+), CEA (+), ER (-), and Ki67 (approximately 10%+) (2021-06-01).

Concurrently, the patient experienced unexplained CEA elevation (184.19 ng/ml, reference range: 0–5 ng/ml) and underwent gastroscopy on June 4, 2021 (Fig. 2C). Gastric biopsy identified moderately differentiated adenocarcinoma as a second primary tumor. On June 11, he was referred for radical gastrectomy at the Department of Gastrointestinal Oncology Surgery. The postoperative stage was determined to be pT1N0M0, and the pathology report confirmed moderately to poorly differentiated adenocarcinoma. The immunohistochemistry results were as follows: CEA (+), c-erbB-2 (1+, negative), and Ki-67 (40%+) (2021-06-11). The patient was advised to seek further treatment for apocrine carcinoma after a month of rest; however, he delayed his return for

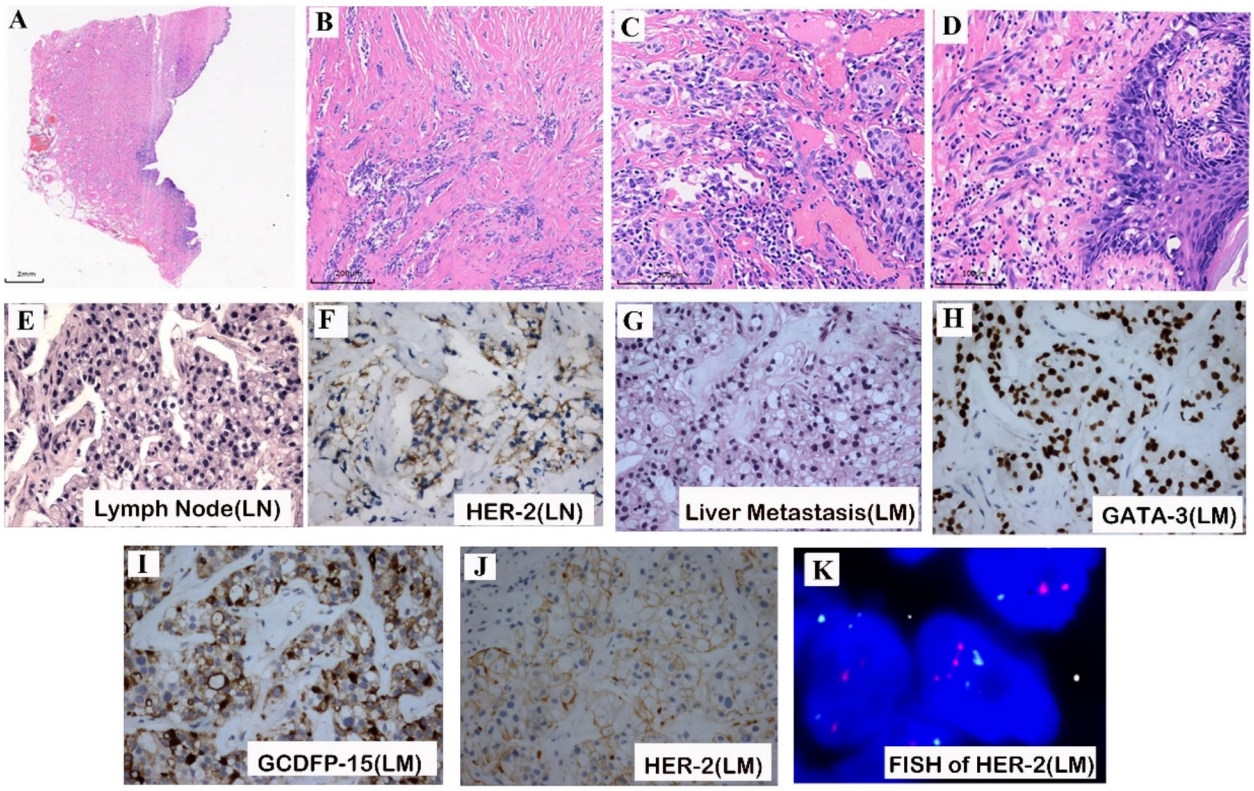

Fig. 1 (**A**-**D**) Hematoxylin-Eosin (HE) stained pathological results of primary scrotal lesion: (**A**-**C**) Histologic section of the primary scrotal epidermis showing characteristic large, round cells with large nuclei and light cytoplasm, which were consistent with apocrine carcinoma. Cancer cells are visible in the dermis. (**D**) The squamous epithelium covering the skin shows Paget's disease-like changes(20x). (**E**, **F**) Pathological biopsy results of right inguinal node (40x): (**E**) The histological morphology of the tumor cells in the right inguinal lymph node are consistent with that in the liver metastatic lesions: The tumor cells are arranged in a nest-like manner, with clumps of empty cytoplasm, large and deeply stained nuclei, and obvious atypia. (**F**) The cell membrane exhibits HER-2 expression at a moderate level: HER-2 (2+). (**G**-**H**) Pathological biopsy results of liver metastases(40x): (**G**) Liver biopsy: A small biopsy specimen showed metastatic sweat gland carcinoma based on the histologic morphology and immunohistochemical results. Tumor cells are arranged in nests and clumps, with enlarged and deeply stained nuclei and atypia, and clear cytoplasm. (**H**, **I**) Immunohistochemistry: The cell nucleus exhibits positive expression of GATA-3, while the cell membrane and cytoplasm are positive for GCDFP-15, which are both signature molecular markers of apocrine carcinoma. (**J**)The cell membrane exhibits HER-2 expression at a moderate level: HER-2 (2+). (**K**) FISH of HER-2 detection: no amplification

follow-up by three months. Notably, human epidermal growth factor receptor 2 (HER2) was expressed in all three pathological biopsies.

In September 2021, a follow-up computed tomography (CT) scan indicated multiple hepatic metastases, enlarged inguinal lymph nodes, and metastasis in the right iliac vessel lymph node. To identify the source of hepatic metastasis, a liver biopsy, which was declined by the patient, was suggested. Then, chemotherapy was initiated with oral capecitabine (2 tablets twice daily on days 1–14, q3w) and apatinib (250 mg/day continuously). A review CT in September 2021 revealed a reduction in the size of the right inguinal lymph nodes, a significant decrease in the liver mass, and a substantial decrease in CEA levels, and the treatment efficacy was classified as a partial response (PR). The combination of capecitabine and apatinib was continued.

On February 20, 2022, the patient experienced an increase in the size of the groin mass. Subsequent abdominal CT confirmed progression with enlarged liver lesions and inguinal lymph nodes. Vinorelbine metronomic chemotherapy was initiated on February 28th at a dose of 40 mg three times a week, in addition to ongoing apatinib therapy. During this treatment phase, a rise in CEA levels and increasing fatigue were observed. Notably, the inguinal lymph nodes became progressively larger, accompanied by bilateral lower limb edema, predominantly affecting the right leg.

On April 26, 2022, a comprehensive evaluation highlighted significant enlargement of lymph nodes in the inguinal and iliac regions, as well as an increase in both the number and size of liver lesions. Consequently, the antitumor treatment was discontinued. Subsequent next-generation sequencing (NGS) analysis of blood samples performed on May 6, 2022, by the Huayin Medical Laboratory Center revealed no mutations of strong or potential clinical significance, four mutations of unknown clinical significance, a tumor mutation burden (TMB)

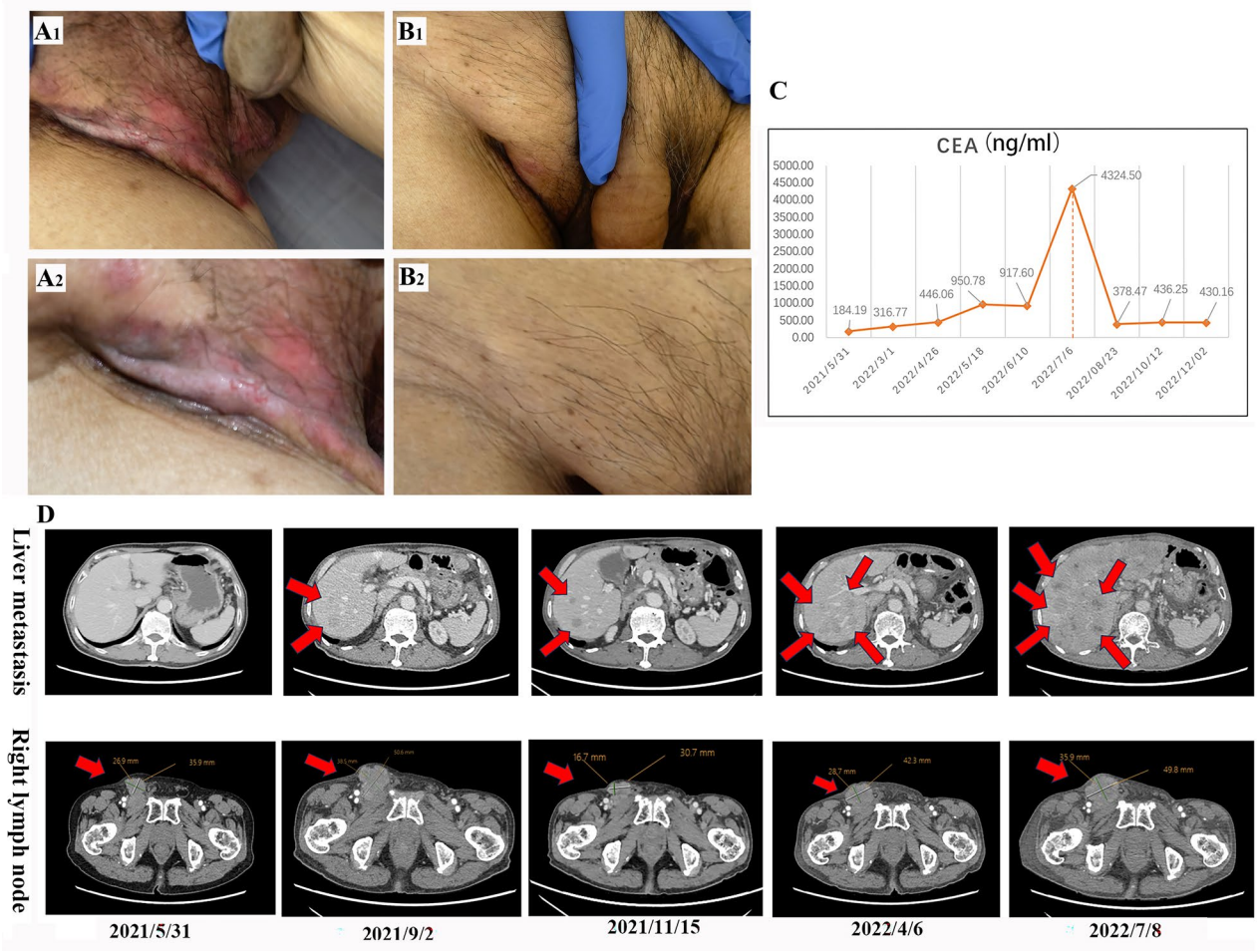

Fig. 2 Changes in the right inguinal lymph nodes and liver metastases and CEA expression during treatment. (**A**, **B**) The patient's right inguinal lymph nodes shrank significantly, and the ulcer healed (A1, A2. Before treatment: May 2021; B1, B2. After treatment: November 2021). (**C**) Changes in carcinoembryonic antigen (CEA) levels during treatment. (**D**) Changes in the right inguinal lymph nodes and liver metastases on abdominal CT during treatment. The patient refused all CT scans and only underwent ultrasound examinations after July 2022

of 0.66 Muts/Mb, microsatellite stability (MSS), and no germline variations. Drug sensitivity predictions indicated potential responsiveness to fluorouracil, cyclophosphamide, and methotrexate. Genetic testing of the lymph node tissue was not performed due to patient refusal. Considering the patient's previous response to capecitabine, the drug sensitivity predictions and the histological similarities between apocrine carcinoma and breast adenocarcinoma, we selected the classical CMF chemotherapy regimen commonly used in breast cancer, which involves the administration of 80% of the standard dosage. The regimen included two cycles, starting on May 20th and second on June 10th, 2022, consisting of cyclophosphamide (350 mg, intravenously on days 1 and 8), methotrexate (25 mg/20 mg, intravenously on days 1 and 8), and 5-fluorouracil (700 mg, intravenously on day 1), with a 21-day cycle. A follow-up CT scan on July 8, 2022, revealed disease progression, with increases in the size of the inguinal lymph nodes and liver metastases. Hepatic biopsy reconfirmed the presence of apocrine carcinoma. The immunohistochemistry results revealed no loss of mismatch repair (MMR) protein and Her-2(2+) expression (2022-06-13) (Fig. 1J).

On July 8, 2022, we evaluated the patient's liver and right inguinal lymph node lesions through CT for the last time and confirmed the overall progress (Fig. 2D). The patient subsequently refused any further CT examinations. A retrospective analysis of the patient's 2017 postoperative pathology revealed Her-2(2+) expression in both the perineal and inguinal lymph node biopsy specimens, which was also confirmed via liver biopsy. When anti-Her-2 pathway therapy was considered, further immunohistochemistry and negative fluorescence in situ hybridization (FISH) results at an external hospital precluded traditional anti-HER-2 treatments (Fig. 1K). Additionally, anti-Her-2 ADC drugs were not available in China in 2022, limiting treatment options for patients with low to moderate Her-2 expression.

On July 13th, 2022, the patient commenced chemotherapy with Albumin-Bound Paclitaxel (300 mg). This treatment led to Grade IV bone marrow suppression, increased white blood cells, and necessitated empirical anti-infection measures. The second chemotherapy cycle, on August 24, 2022, involved the administration of a reduced dose of Albumin-Bound Paclitaxel (300 mg, 80% of the standard dose), which was scheduled every three weeks (Q3W). This regimen led to a decrease in carcinoembryonic antigen (CEA) levels from 4324.5 ng/ml to 378.47 ng/ml, indicating a positive response. Despite the recommendation for continued scheduled chemotherapy, the patient, considering his advanced age and slow physical recovery, chose to extend treatment intervals. The third chemotherapy cycle was administered on October 14th, 2022, at a reduced dose and schedule.

Considering that the patient's recovery from chemotherapy was slow, the patient refused chemotherapy. At this time, we suggest that the patient re-biopsy the inguinal lymph nodes and liver metastatic lesions and perform a WES test free of charge in the hope of finding a new therapeutic breakthrough. Re-biopsy of the inguinal lymph nodes was completed, but liver biopsy was refused by the patient's family. WES was performed on newly obtained inguinal lymph nodes, previous liver biopsy specimens, and postoperative gastric cancer specimens. Quality control standards were met for both samples, except for the liver sample, which did not meet quality control standards for testing. The results showed limited mutations in metastatic lesions, with a TMB higher than that in TCGA samples, suggesting potential responsiveness to immunotherapy (Fig. 3C). Compared with previous genetic testing, these results suggest heterogeneity in the TMB between blood samples and lymph node metastases. However, the patient's physical condition precluded the use of immunotherapy.

Eventually, the patient and his family decided against further antitumor treatment. On November 23, 2022, the patient was hospitalized for deep vein thrombosis in his left lower limb. Amid the changing epidemic prevention policies in China, he contracted COVID-19, leading to viral pneumonia, and passed away on December 1, 2022. The entire course and treatment of the patient's disease are shown in Fig. 4.

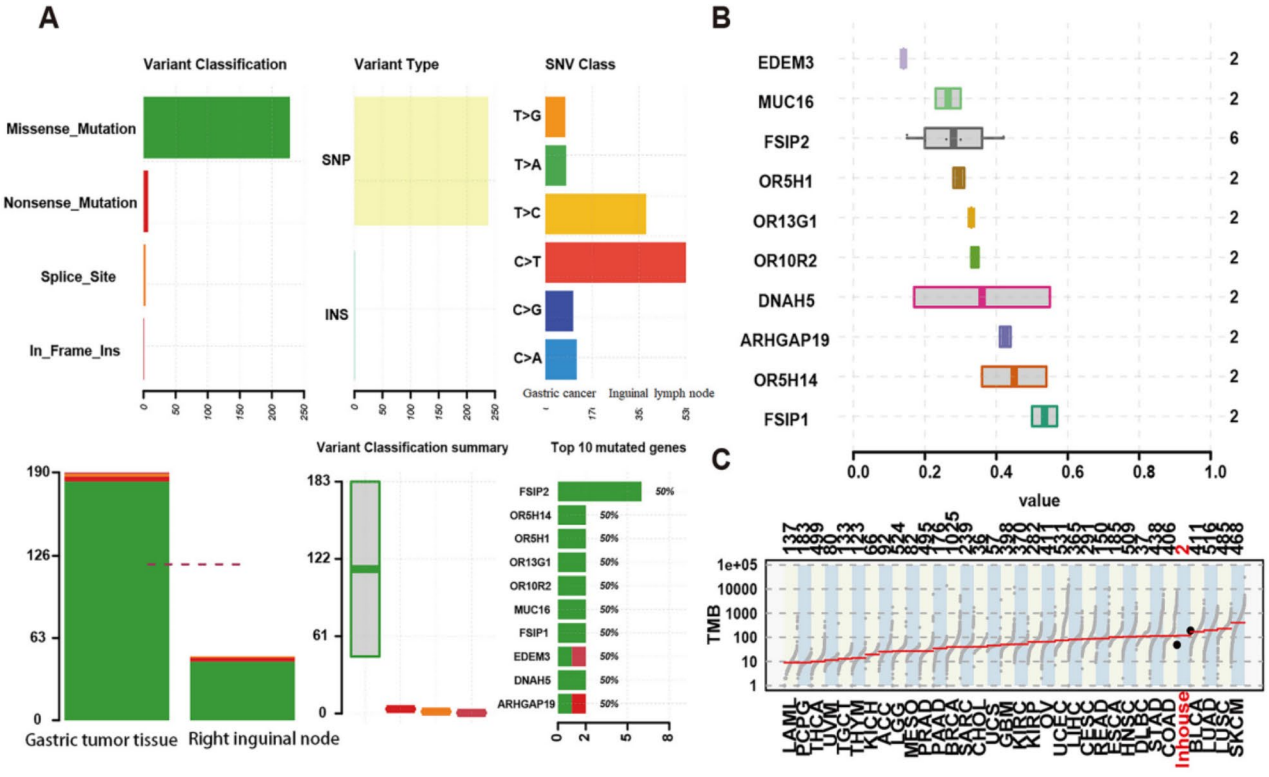

Fig. 3 WES sequencing results of gastric cancer and inguinal lymph nodes in the patient. (**A**) Missense mutations are the main type of mutations. Single nucleotide mutations are the main type of gene mutation. Nucleotide mutations are mainly reflected in the conversion of C > T and T > C. (**B**) Patients with gastric cancer have a greater number of mutations than patients with lymphadenectomy. Combining the two samples revealed that the patients had a greater number of missense mutations, with an average of 120 gene mutations, and fewer other types of mutations. Based on gene mutation changes, the 10 genes with the highest proportion of mutations were identified. (**C**) Compared with TCGA samples, this patient had a greater tumor mutation burden (TMB), which is between that of colorectal cancer and bladder cancer, suggesting that the effect of immunotherapy may be better

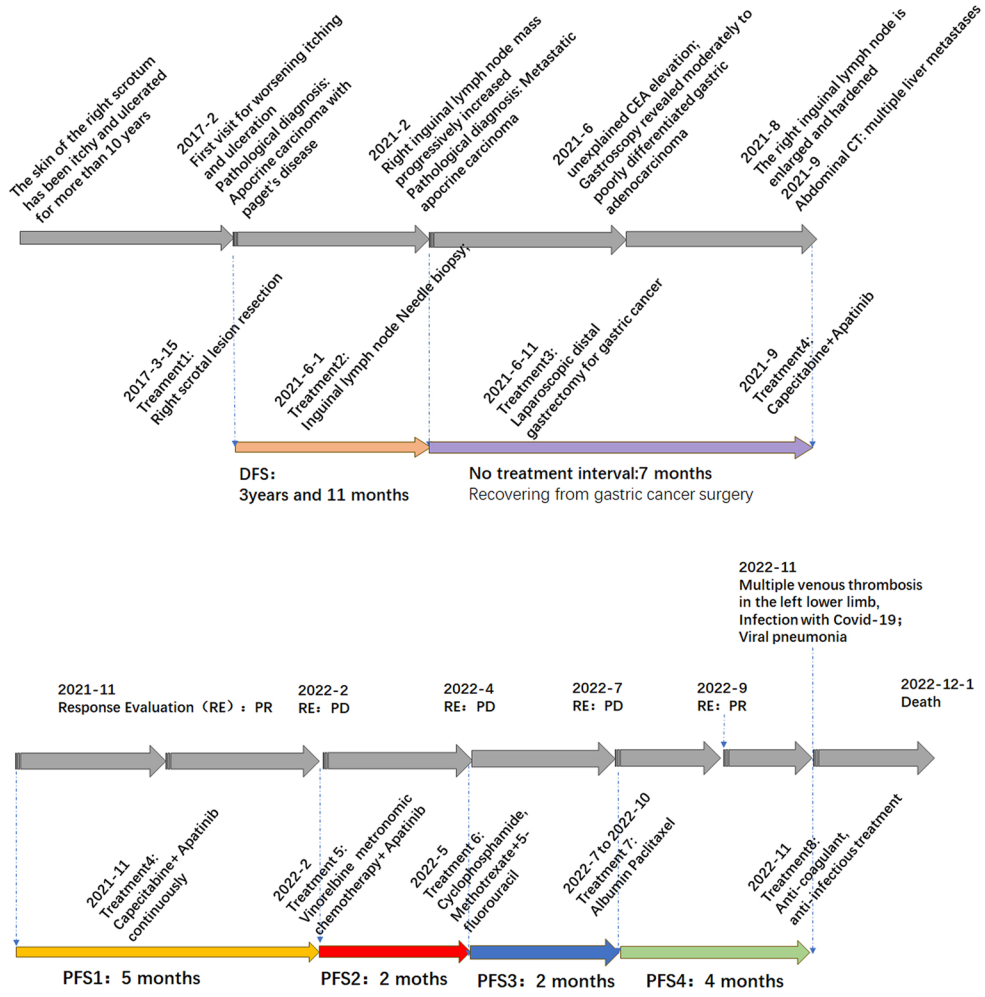

Fig. 4 Clinical timeline of the patient's disease course (OS: 5 years and 8 months)

Discussion and literature review

This case involved an 80-year-old male who was diagnosed with scrotal apocrine carcinoma exhibiting Paget changes, which is rare in clinical practice. Additionally, early-stage gastric cancer was identified following recurrence and metastasis of the primary tumor. Whole-genome exome sequencing (WES) of metastatic and postoperative gastric cancer samples revealed minimal genetic overlap (Fig. 3), suggesting the coexistence of two primary tumors: apocrine carcinoma and gastric cancer. Compared to patients in The Cancer Genome Atlas (TCGA) database, patients with gastric cancer and inguinal metastases exhibited a greater tumor mutation burden (TMB), which is indicative of a potentially favorable response to immunotherapy.

Tumor Mutation Burden (TMB) can vary based on tissue source, detection methods, and sample collection timing. In this study, an earlier blood sample was analyzed using Next-Generation Sequencing (NGS), while a later lymph node sample with a higher tumor burden was assessed with Whole Exome Sequencing (WES). These differences may lead to variations in TMB measurements. To comprehensively evaluate treatment options, it may be beneficial to use multiple testing methods and assess TMB at different time points.

While using both NGS and WES early in treatment could provide more management options, specific considerations apply: the patient is elderly with slow disease progression, and both the patient and their family were not proactive in seeking treatment. Additionally, conducting both tests simultaneously would impose a significant financial burden. Consequently, after obtaining the NGS results, WES was not pursued initially. Later, with informed consent from the patient and family, we provided free WES testing funded by research grants.

Studies have demonstrated significant PD-L1 expression in tumor cells and tumor-infiltrating T cells in extramammary Paget's disease (EMPD), indicating that the PD-1 signaling pathway is a viable target in EMPD [10]. This finding suggested that immunotherapy might benefit patients with apocrine carcinoma, including this

patient. However, the patient opted for treatment in the later stages.

Early-stage apocrine carcinoma, characterized by a high risk of relapse and metastasis, typically requires surgical resection [11, 12]. Surgical margins should be examined pathologically to ensure complete resection. In cases of lymph node metastasis, regional lymph node dissection may be warranted. Postoperative radiotherapy serves as an adjunctive treatment, particularly for patients at high risk of recurrence, such as those with pathological malignancy, lymph node metastasis, or positive tumor margins. Palliative chemotherapy, a mirroring regimen used for treating breast cancer, may be beneficial for patients with recurrence or metastasis, as it can improve quality of life and potentially prolong survival.

When perineal ulceration occurs again in our patient after surgery, local radiotherapy can be considered to control the condition, thus delaying the course of the disease. The patient's treatment paralleled that of breast cancer patients, who responded well to capecitabine and paclitaxel. Genetic testing indicated sensitivity to capecitabine, cyclophosphamide, and methotrexate, but the CMF regimen did not elicit a tumor response. This highlights the limitations of blood genetic testing and drug susceptibility predictions as definitive guides for treatment. Considering the patient's advanced age and comorbidities such as hypertension and arrhythmia, cardiotoxic agents such as anthracyclines were avoided. Despite positive responses to certain regimens, the patient did not respond favorably to CMF or vinorelbine.

Because the patient had numerous metastatic lesions, a large tumor burden and low single-drug efficacy, apatinib was used in combination with capecitabine. Apatinib is a domestic small-molecule antiangiogenic tyrosine kinase inhibitor. Apatinib in combination with other treatments has been used to treat breast cancer [13, 14]. A systematic evaluation and meta-analysis revealed that compared with the control group, the apatinib group exhibited significant improvements in the disease control rate (DCR) and objective response rate (ORR) [14]. The initial efficacy of the "capecitabine+apatinib" regimen was evaluated as a partial response (PR), with a progression-free survival (PFS) of 5 months. However, subsequent regimens can result in progressive disease (PD). Fourth-line treatment with albumin-bound paclitaxel showed therapeutic efficacy, as evidenced by reduced carcinoembryonic antigen levels and diminished lymph node size (Fig. 2C, D). Nonetheless, the patient discontinued treatment due to severe myelosuppression.

Approximately 30–40% of patients overexpress HER-2, making anti-HER-2 therapies viable [15]. In this patient, moderate HER-2 expression was observed in the scrotal primary tumor, metastatic liver tumor and groin lymph node lesions (Fig. 1F, J). We consulted with the pathology department at the hospital where the first surgery was performed and confirmed that the primary lesion, liver, and groin metastasis lesions all moderately expressed HER-2. We hoped to identify anti-HER-2 treatment options, but unfortunately, the HER-2 FISH test was negative. However, negative HER-2 FISH results precluded traditional anti-HER-2 treatments. ADC drugs such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (DS8201) have shown promise in treating tumors with low HER2 expression in various cancers [16, 17] and have also displayed potent antitumor activities in preclinical extramammary Paget's disease models [18]. However, they were unavailable in China at that time. A literature review indicated that nearly half of scrotal sweat gland cancer patients exhibit HER-2 expression, yet not all respond to anti-HER-2 therapy [19]. This case highlights the potential of anti-HER-2 treatment in apocrine carcinoma patients expressing HER-2.

After reviewing the literature, we found that trastuzumab monotherapy was effective in the treatment of 3 EMPD patients with HER-2 overexpression [20–22]. Trastuzumab combined with chemotherapy (taxane-based regimens) further demonstrated significant efficacy and long-term survival in recurrent advanced EMPD patients with HER-2 overexpression [23–25]. In one case report, a patient progressed after maintaining dual-target therapy for 14 months and was later changed to the second-line treatment regimen TDM-1. However, the treatment was terminated after 42 days due to significant worsening of nervous system symptoms and general conditions [1]. Previously reported cases that received anti-HER-2 therapy were all HER-2-overexpressing (HER-2 3+or HER-2 2+and FISH positive). One patient received the small molecule anti-HER-2 tyrosine kinase inhibitor (TKI) lapatinib as a first-line treatment for PD [26]. There is currently no clinical application of ADC drugs in patients with low to moderate HER-2 expression.

Apocrine carcinoma is often accompanied by other malignant tumors, especially gastrointestinal malignancies [9]. The patient responded well to capecitabine but poorly to vinorelbine and the CMF (cyclophosphamide, methotrexate, fluorouracil) regimen. With two primary tumors and an early clinical stage following gastric cancer surgery, we clinically assessed that the metastatic lesions were due to apocrine carcinoma. A liver biopsy confirmed that the liver lesions originated from apocrine carcinoma. Additionally, we aimed to explore potential therapeutic breakthroughs through the analysis of the biopsy results.

A retrospective case analysis of 1,268 patients with invasive EMPD based on the Surveillance, Epidemiology, and End Results (SEER) database revealed that 35 patients (2.8%) were diagnosed with synchronous cancer (diagnosed within one calendar year of the year of EMPD

diagnosis), and 195 patients (15.4%) developed a secondary malignancy (diagnosed > one year from the year of the year of EMPD diagnosis). The most common synchronous breast, gastrointestinal tract, and melanoma and the most common secondary cancers were breast, gastrointestinal tract and genitourinary tract cancers. The most frequently observed synchronous cancers were breast cancer, gastrointestinal cancer, and melanoma. Among secondary cancers, breast cancer, gastrointestinal cancer, and genitourinary tract cancer are the most prevalent [27]. Another article also reported 2 cases of nonsynchronous urinary and digestive malignancies in scrotal EMPD patients [28]. A recent study revealed a significant correlation between the anatomical location of EMPD and the type of secondary malignant tumor that developed. Notably, patients with perianal EMPD frequently present with concurrent gastrointestinal tumors, often leading to a poorer prognosis [29]. These patients often do not succumb to the direct effects of EMPD but rather to complications arising from other coexisting malignant tumors or comorbid diseases. However, the precise causal relationship between the onset and progression of invasive EMPD and gastrointestinal malignancies has not yet been established.

Conclusion

In conclusion, this case exemplifies the complexities involved in diagnosing and treating rare coexistent cancers, especially in the elderly population. For these patients, we should also be alert to the presence of other visceral malignancies. Individualized treatment with reference to breast cancer treatment protocols may be effective. This highlights the need for personalized treatment strategies, considering both the genetic makeup of tumors and patient-specific factors.

Abbreviations

EMPD	extramammary Paget's disease
CEA	carcinoembryonic antigen
CT	computed tomography
NGS	next-generation sequencing
TMB	tumor mutation burden
MSS	microsatellite stability
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor 2
WES	Whole-genome exome sequencing
TCGA	Cancer Genome Atlas
DCR	disease control rate
ORR	objective response rate
PR	partial response
PD	progressive disease
PFS	progression-free survival
TKI	tyrosine kinase inhibitor
SEER	Surveillance, Epidemiology, and End Results

Author contributions

B.H. composed the manuscript and literature review. G.H. and J.L. completed the bioinformatics analysis. X.Z. and M.D. collected the case history and radiological images. W.Y., D.R. and J.C. collected the pathological images. L.W. provided guidance, conducted reviews, revised, and refined the manuscript. X.H. specifically guided and reviewed the bioinformatics section. All authors contributed to the article and approved the submitted version.

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Data availability

Sequence data that support the findings of this study have been deposited in the GEO database with the accession code HRA006838.

Declarations

Ethical approval

The studies involving human participants were reviewed and approved by the Ethical Review Committee of Southern University of Science and Technology Hospital. The patient provided his written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

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