Invasive papillary carcinoma of the breast: A case report

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Abstract. Invasive papillary carcinoma (IPC) of the breast is a rare form of cancer. The current report documents a case of IPC characterized by a large tumor size and skin involvement. Surgical exploration revealed no evidence of axillary lymph node metastasis in breast cancer. Due to financial constraints, the patient opted solely for anastrozole endocrine therapy at a dosage of 1 mg/day for a period of 5 years post-surgery, foregoing other treatments such as radiotherapy and chemotherapy. Since discharge, 2.5 years have passed, during which the patient has been followed up via phone every 3 months, showing a good prognosis. A literature review indicated that IPC is prevalent amongst the elderly population and can be misdiagnosed due to its morphological, cytomorphological and immunophenotypic overlap with other types of papillary neoplasms. This tumor exhibits a more favorable prognosis compared with IDC, primarily attributed to its advantageous gene and molecular expression patterns, coupled with its decreased invasiveness. Despite limited evidence-based research on the treatment of IPC, the present case report, albeit with limitations, underscores the importance of avoiding over-treatment and suggests the feasibility of combining surgery with endocrine therapy for IPC.

Introduction

Based on the latest data from the World Health Organization (WHO), breast cancer continues to be the most frequently diagnosed cancer among women, accounting for 11.6% of all cancer cases, and remains the leading cause of cancer-related deaths in women, responsible for 6.9% of all cancer-associated deaths (1). With the rise in breast cancer incidence, there is also a proportional increase in the incidence of rare histologic subtypes (2). Invasive papillary carcinoma (IPC) is a rare type of breast cancer, accounting for <1% of breast cancer cases in most case series, and is commonly seen in postmenopausal women (3-5). In 2003, the WHO classified IPC as a type of invasive mammary carcinoma in Classification of Tumors of the Breast and Female Genital Organs (6). Certain studies on IPC actually targeted variants of solid papillary carcinoma (SPC) or encapsulated papillary carcinoma (EPC) due to the lack of specificity in the description (3,7). In 2012, the WHO defined IPC as aggressive adenocarcinoma in the fourth edition of Classification of Breast Tumors, with papillary structures accounting for >90% of the invasive part (8). This definition was maintained without modification in the subsequent fifth edition of the classification (2019) (9). Currently, research on IPC is limited to case reports and small retrospective studies (2,10-12), which has resulted in a lack of understanding of this rare tumor. Diagnosing IPC can be difficult due to a lack of in-depth knowledge and understanding, and there is currently no established standard treatment in the medical community. The present article reports an exceptional case of IPC. The disease course lasted for 2 years, and the lesion involved the skin; however, no breast cancer lymph node metastasis was found. The patient received only endocrine therapy after surgery, and the prognosis is good. The present case not only highlights the favorable pathological characteristics and indolent biological behaviors inherent to this tumor type, but also offers invaluable insights for formulating effective therapeutic strategies against it.

Case report

In 2019, a 51-year-old female patient discovered a palpable lump, with a diameter of ~2 centimeters, in the right breast. The tumor progressively increased in size, and by June 2021, ulceration of the skin on the right breast became apparent, accompanied by a considerable exudation of straw-colored fluid. In September 2021, the patient was admitted to the First Affiliated Hospital of China Medical University (Shenyang, China). Throughout the period from symptom onset until hospital admission, the patient remained untreated. The patient experienced local pain; however, sleep, diet, bowel movements and body weight remained normal. The patient denied any history of chronic diseases, including diabetes mellitus, hypertension and coronary artery disease.

The physical examination of the patient revealed asymmetrical breasts, with the nipples at the different levels (Fig. 1A). The tumor involved the entire right breast, measuring ~15x

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15 cm with a firm consistency, indistinct boundary and restricted movement (Fig. 1B). The skin of the breast was red and swollen with visible dehiscence (Fig. 1C). No lymph node was palpable in the bilateral axilla or in the upper and lower clavicular areas, and the skin did not show dimpling.

Laboratory tests revealed that the hepatitis B-related indicators of the patient were as follows: Hepatitis B surface antigen-positive, hepatitis B e-antibody-positive, hepatitis B core antibody-positive, hepatitis B surface antibody-negative and hepatitis B e-antigen-negative. The liver function of the patient was also assessed, with results showing alkaline phosphatase at 41 U/l, total protein at 57 g/l, and albumin at 36.6 g/l, all slightly below the reference range (13). Blood cell analyses revealed a red blood cell count of $3.38x10^{12}$/l, hemoglobin level of 83 g/l, mean corpuscular volume of 78.5 fl and mean corpuscular hemoglobin of 24.6 pg. The white blood cell count was $4.54x10^{9}$/l and platelet count was $371x10^{9}$/l. The urinary routine and coagulation function showed no obvious abnormalities (Table I).

Imaging revealed a space-occupying lesion with bleeding in the right breast parenchyma, leveled Breast Imaging-Reporting and Data System 5 (14). High-resolution (HR) computed tomography (CT) revealed a large irregular low-density mass in the right breast (Fig. 2A). A Doppler ultrasound indicated the loss of the normal glandular architecture of the right breast, with mixed cystic (>90%) and solid echoes (Fig. 2B). Additionally, a lymph node echo was detected in the right axilla, measuring 1.09x0.61 cm with slight cortical thickening (Fig. 2C). Magnetic resonance imaging (MRI) indicated tortuous vessels within the solid portion and a fluid-fluid plane within the lesion capsule (Fig. 2D). Mammography with splint compression was not performed due to the size, cystic nature and lesions over the skin surface of the mass.

Tissue from the lesion was obtained using core needle biopsy (CNB), which was followed by hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC). Microscopically, the dilated ducts exhibited broad papillary structures with a monolayer-multilayer epithelial covering on their surface, revealing densely packed tumor cells with weak eosinophilic cytoplasm and moderately atypical nuclei, thus pointing towards a preliminary diagnosis of papillary neoplasms (Fig. 3). Papillary neoplasms include several subtypes such as benign papilloma, intraductal papillary carcinoma, EPC, SPC and IPC (15). IHC revealed a luminal-type breast cancer, which was characterized by estrogen receptor (ER) positivity (90%), progesterone receptor (PR) positivity (90%), human epidermal growth factor receptor-2 (HER-2) negativity (-), a Ki-67 index of 20%, cytokeratin 5/6 (CK5/6) (-) and E-cadherin positivity (+) (Fig. 4A-F). The assessment of myoepithelial cells was performed through the utilization of specific immune markers, namely p63 and calponin (Fig. 4G,H); however, both markers returned negative outcomes, a characteristic that rules out benign papilloma and intraductal papillary carcinoma (16). Encapsulated papillary carcinoma is typically characterized by a distinct fibrous cystic capsule, whilst solid papillary carcinoma demonstrates expansive growth with minimal fibrous-vascular cores (17,18). In the present case, the absence of a fibrous cystic capsule, along with fused papillary networks and abundant fibrous-vascular cores, allowed the exclusion of both encapsulated and solid papillary carcinomas. Consequently, the diagnosis was narrowed down to IPC (8,9). Furthermore, the positivity of ER, PR and GATA binding protein 3 (GATA3; Fig. 4I), combined with the medical history of the patient, strongly suggested that the lesion originated from the breast. Therefore, a preoperative diagnosis of primary IPC of the breast was made via CNB.

Table I. Blood and biochemical test results of the patient.

Parameter	Result	Reference range
Hepatitis B surface antigen (index)	>1,000.00	<1.00
Hepatitis B surface antibody, mIU/ml	<3.10	<10.00
Hepatitis B e antigen (index)	0.00	<1.00
Hepatitis B e antibody (index)	3.14	<0.80
Hepatitis B core antibody (index)	>8.00	<0.50
ALP, U/l	41	50-135
TP, g/l	57.0	65.0-85.0
ALB, g/l	36.6	40.0-55.0
RBC, 10^{12}/l	3.38	3.80-5.10
HGB, g/l	83	115-150
MCV, fl	78.5	82-100
MCH, pg	24.6	27.0-34.0
WBC, 10^{9}/l	4.54	3.50-9.50
PLT, 10^{9}/l	371	125-350
Prothrombin time, sec	11.0	9.0-13.0
Activated partial thromboplastin time, sec	25.0	24.2-32.8
Prothrombin time activity, %	95.2	70.0-130.0
Fibrinogen, g/l	3.59	2.00-4.00
Urea, mmol/l	6.70	2.60-7.50
Creatinine, μmol/l	71	41-73

ALP, alkaline phosphatase; TP, total protein; ALB, albumin; RBC, red blood cell count; HGB, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; WBC, white blood cell count; PLT, platelet.

The patient had locally advanced breast cancer but declined preoperative adjuvant therapy, including neoadjuvant chemotherapy and endocrine therapy, due to economic reasons. Therefore, surgical treatment was considered, accounting for the request of the patient and the lack of standardized treatment guidelines and evidence-based medical evidence for neoadjuvant treatment of IPC. In September 2021, the patient underwent a modified radical mastectomy to remove the lesion and drain lymph nodes in the axillary region, reducing the risk of metastasis and recurrence. In addition, as the tumor occupied the entire breast, the surgery resulted in significant loss of local skin and tissue. To address this, a pedicled transverse rectus abdominis myocutaneous flap was used for immediate reconstruction upon completion of the modified radical mastectomy (Fig. 5) (19,20). Notably, there is presently no standardized surgical protocol for IPC, and the aforementioned surgical procedures were primarily based on

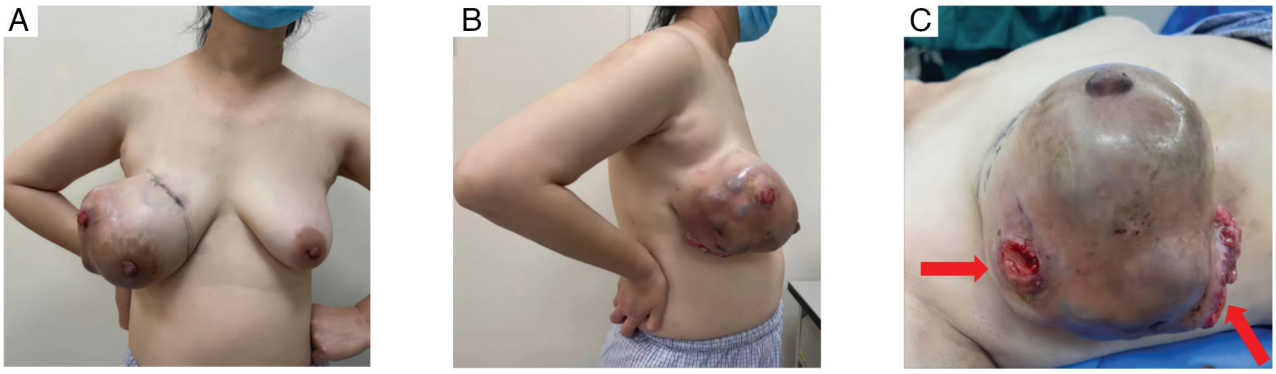

Figure 1. Images of the patient captured on admission. (A) Patient presented with asymmetrical breasts and uneven nipples. (B) Mass measuring ~15x15 cm was observed in the right breast, occupying the entire breast. (C) Skin of the right breast appeared red and swollen, and had an altered temperature, with two visible breaches (red arrows).

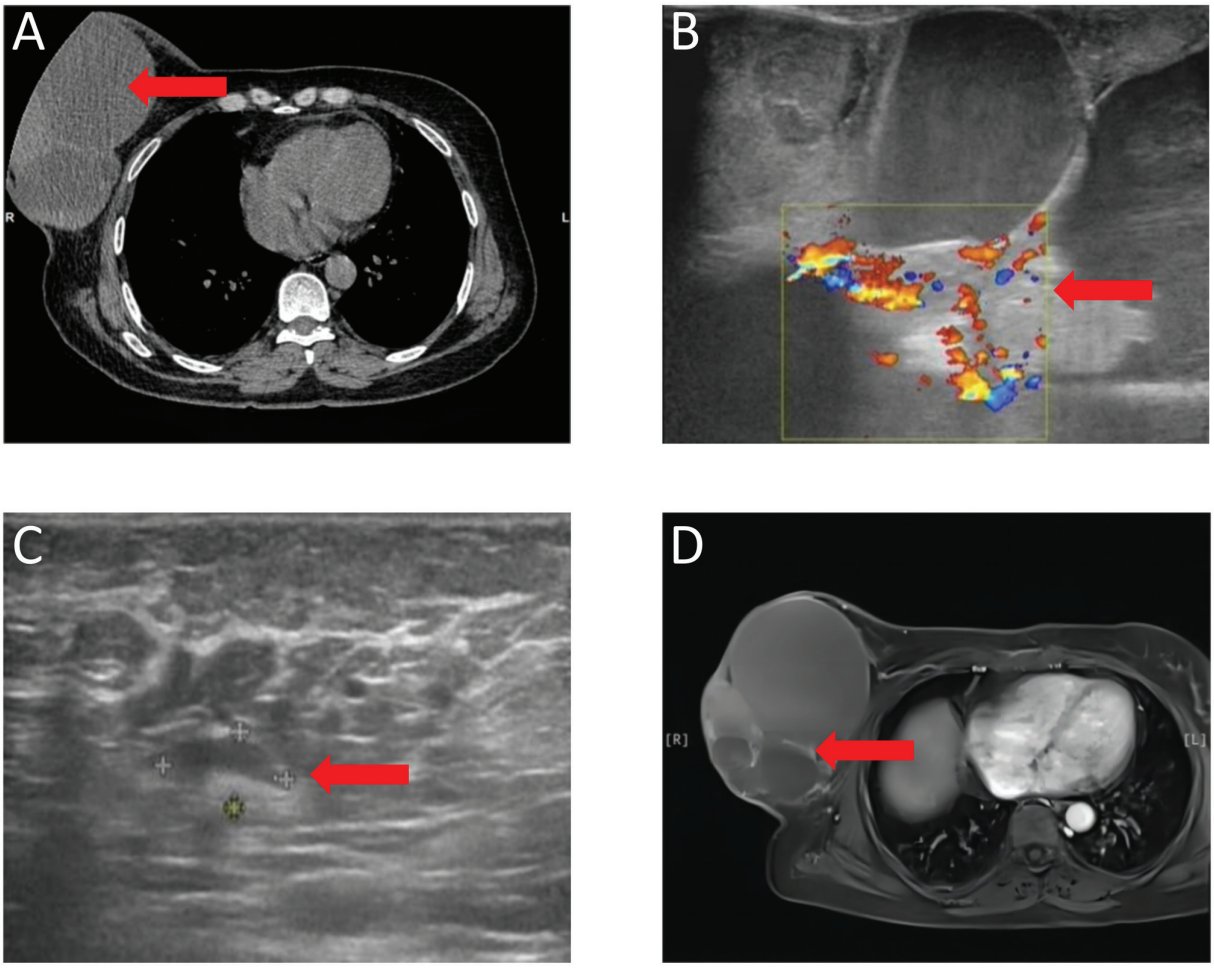

Figure 2. Results of the patient's preoperative imaging examination. (A) High resolution computed tomography of the thorax presented a large irregular low-density mass in the right breast (red arrow). Doppler ultrasound of the breast and axilla revealed (B) significant blood flow in the solid part of the lesion (red arrow) and (C) a lymph node measuring 1.09x0.61 cm (red arrow). (D) Magnetic resonance imaging indicated the presence of multiple cystic-solid lesions, some of which appeared to be fused (red arrow). The solid component showed inhomogeneous enhancement, and there was thickening of the skin.

the prevalent surgical techniques used for non-specific types of breast cancer (2).

The specimen appeared wrinkled on the surface and had two fissures, measuring ~6x6 and 3x3 cm, respectively (Fig. 6A). Multiple fine papillary masses were observed immediately adjacent to the skin. The cut surface exhibited a grayish-white texture and was brittle, more delicate and felt tough in certain areas. Dark-brown blood clots were observed within the capsule and the luminal wall, with a substantial amount of necrosis in certain areas (Fig. 6B). To definitively ascertain the type and nature of the tumor, tissue samples were collected from several regions and H&E staining and IHC were

performed. The cancerous tissue primarily exhibited papillary structures, with papillae fusing to form complex papillae and a reticulated papillary structure. The papillae surface was covered by atypical epithelium (Nottingham score of 7) (21), with a central fibrovascular core (Fig. 7A). The lesion had extended to involve the skin, where histological examination revealed an incomplete basal cell layer with visible tumor cells infiltrating the epidermis, whilst the dermis had completely vanished (Fig. 7B). However, lymph node examination did not detect the presence of any tumor cells (Fig. 7C). The IHC results aligned with the preoperative CNB results, affirming the diagnosis of IPC (Fig. 8A-I).

Postoperatively, the patient reported slight incision pain but denied upper extremity numbness, swelling, chills, fever or shivering. Pressure dressing and daily dressing changes were administered. On postoperative day 21, during the dressing change, the incision appeared well healed without signs of redness, swelling or infection. The patient requested discharge, and upon a comprehensive assessment of the physical condition and recovery progress of the patient, they were discharged in October 2021. Due to financial constraints, the patient received only anastrozole endocrine therapy at a dosage of 1 mg/day for 5 years (22). Additionally, the patient did not return for hospital follow-ups or undergo any imaging examinations such as CT, MRI or ultrasound. Postoperative telephone follow-ups were performed every 3 months. From October 2021 to April 2024, the patient reported no discomfort, and self-examination revealed no lumps in the surgical area, axilla or contralateral breast. However, it should be noted that the postoperative follow-up has limitations, necessitating a longer and more comprehensive evaluation.

Imaging instrumentation and parameters

HRCT. CT scanning was performed using a Siemens 64-Row 128-Slice Spiral CT Machine and a tube voltage of 100 keV and automatic milliampere-second tube current modulation. The scanning process was performed in a spiral fashion, progressing from the apex to the base of the lungs, with a pitch of 0.8 and a slice thickness of 1 mm. A matrix of 512x512 was implemented. For image interpretation, the lung window was adjusted to a window width ranging from 1,200-1,500 HU, with a window level between -600 and -700 HU. Similarly, the mediastinal window was set to a width of 400 to 500 HU, and a level of 40-50 HU.

Ultrasonography. Ultrasonography was performed using a Philips ATL HDI 5000 Ultrasound Machine. The patient was positioned supine, with their upper limbs extended laterally and elevated. The breasts and axillae were exposed to facilitate bilateral scanning using a probe operating within a frequency range of 8-12 MHz. Lesion scope, characteristics and the distribution of blood flow were observed using color Doppler flow imaging.

MRI. MRI was performed using a GE HealthCare Signa HDxt 3.0T MRI Scanner. The patient entered the examination room, lay flat on the examination bed in a prone position, and allowed both breasts to naturally hang due to gravity and fit into the concave cavity of the coil. The anterior chest wall was positioned tightly against the coil. During the examination, the team endeavored to scan the axilla and anterior chest wall regions of the patient. The routinely performed MRI scans included horizontal T1 weighted image (WI) plain scans, T2WI fat-suppressed scans and diffusion-weighted imaging (DWI) scans. Dynamic contrast-enhanced scanning was performed using dynamic-enhanced T1 high-resolution isotropic volume excitation (dyn-eTHRIVE) technology. The scanning parameters were set as follows: i) T1WI/turbo spin echo: repetition time (TR), 639 msec; echo time (TE), 6.8 msec; slice thickness, 5 mm; slice gap, 1 mm; field-of-view (FOV), 340x340 mm; ii) T2WI/Spectral Attenuated Inversion Recovery: TR, 5,620 msec; TE, 110 msec; slice thickness, 4.5 mm; slice gap, 1 mm; FOV, 340x340 mm; iii) DWI (b=1,000): TR, 3,894 msec; TE, 69 msec; slice thickness, 4.5 mm; slice gap, 1 mm; FOV, 350x350 mm; iv) dyn-eTHRIVE dynamic contrast-enhanced scanning: TR, 4.2 msec; TE, 2.0 msec; slice thickness, 2.0 mm; FOV, 200x200 mm. Following the plain scans, Gadolinium-diethylenetriaminepentaacetic acid, a paramagnetic contrast agent, was intravenously injected through the median cubital vein for contrast-enhanced scanning. The standard dosage administered was ~0.1 mmol/kg at a flow rate of ~2 m/sec. Immediately after the contrast agent injection, 20 ml normal saline was flushed through at the same rate of 2 ml/sec. A mask acquisition was taken prior to the intravenous bolus injection of the contrast agent, and subsequently, eight consecutive image acquisitions were performed over a total duration of 7-9 min.

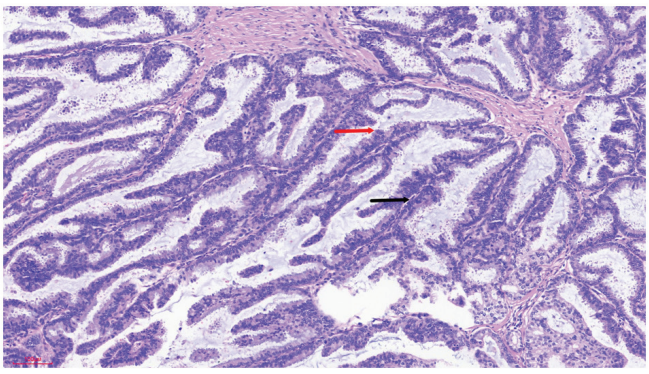

Figure 3. Preoperative hematoxylin and eosin staining results of the core needle biopsy. The lesion consisted of papillary structures, with papillae containing a fibrovascular core (black arrow), and their surfaces were covered by epithelial cells (red arrow). Magnification, x200.

H&E staining. The tissue samples were preserved in a 10% neutral formalin solution at room temperature for 22-24 h, subsequently placed in molds filled with liquid paraffin, and allowed to cool and solidify. After fixation, the samples were sliced into 4-μm sections using a microtome. Following the slicing process, the tissue sections were dewaxed procedure at 45˚C for ~6 min to remove any residual paraffin from the tissue, preparing it for subsequent staining. The Roche Ventana HE 600 automated staining system (Roche Diagnostics) was used for staining, in which the tissue sections were stained with H&E, two commonly used histological dyes, for 3 min at room temperature. After staining, the tissue sections were dehydrated and clarified by sequential immersion in 95% alcohol I for 5 min, 95% alcohol II for another 5 min, absolute ethanol I for 5 min, absolute ethanol II for 5 min, xylene I for 5 min and xylene II for 5 min. The sections were then removed from the xylene, allowed to air dry briefly and sealed with

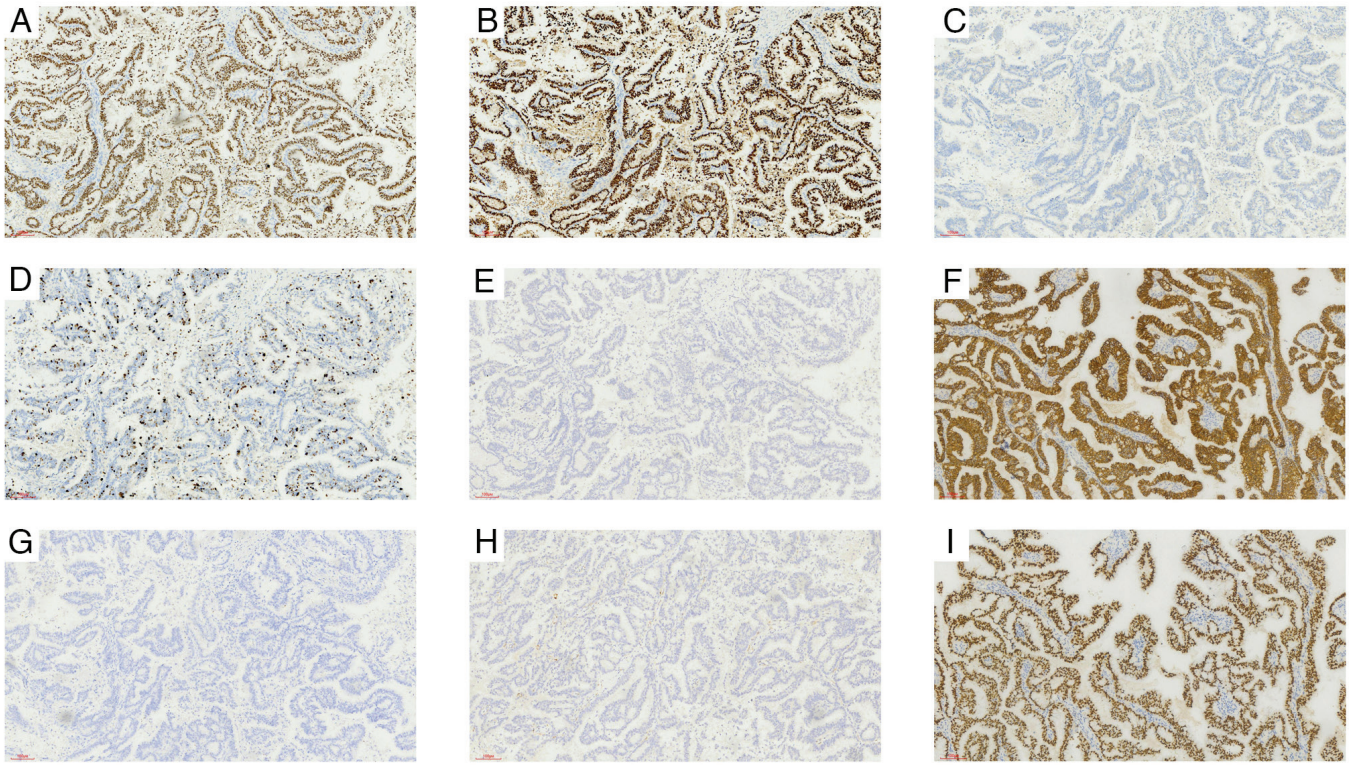

Figure 4. Preoperative immunohistochemical staining results of the core needle biopsy. (A) Estrogen receptor (90%). (B) Progesterone receptor (90%). (C) Human epidermal growth factor receptor-2 (0%). (D) Ki-67 (20%). (E) Cytokeratin 5/6(-). (F) E-cadherin(+). (G) p63(-). (H) Calponin(-). (I) GATA binding protein 3(+). Magnification, x200.

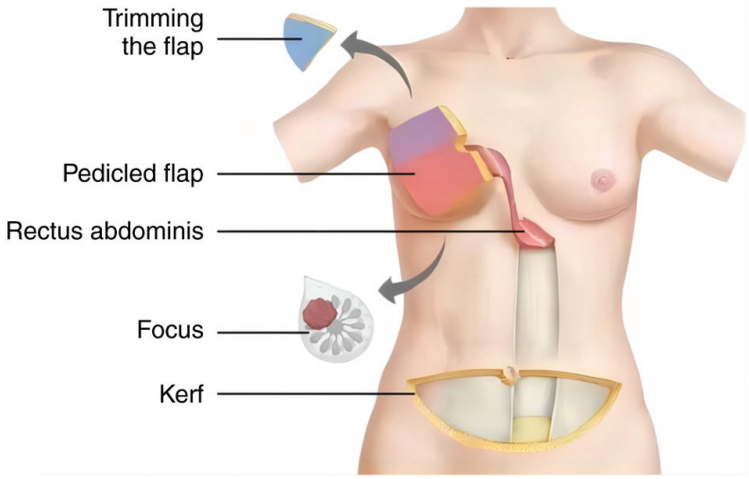

Figure 5. Schematic diagram of a modified radical mastectomy combined with immediate breast reconstruction surgery for breast cancer. The procedure starts with a modified radical mastectomy for complete tumor resection and lymph node dissection, immediately followed by breast reconstruction using the pedicled transverse rectus abdominis myocutaneous flap, which involves using the abdominal skin and tissue of the patient to recreate the breast, aiming to restore the bodily appearance of the patient.

neutral gum. The staining quality and tissue morphology were then evaluated under a light microscope at a magnification of x200.

IHC. The reagents and steps used for paraffin sectioning are consistent with those described for the aforementioned H&E staining. Tissue sections were placed in a 60˚C incubator for 30 min to melt the paraffin, followed by thorough dewaxing using xylene (xylene I, 30 min and xylene II, 30 min) and gradual rehydration in a graded ethanol series (100% ethanol, 10 min; 95% ethanol, 10 min; 80% ethanol, 10 min; and 70% ethanol, 10 min). The sections were then rinsed with tap water for 10 min. Subsequently, they were immersed in 0.01 M citrate buffer (pH 6.0), microwaved to boiling for 5 min, and allowed to cool naturally to room temperature. To block endogenous peroxidase/phosphatase activity, the tissue sections were incubated in a 3% hydrogen peroxide solution for 10 min. Subsequently, at room temperature, antibody treatment commenced with the blocking of non-specific binding

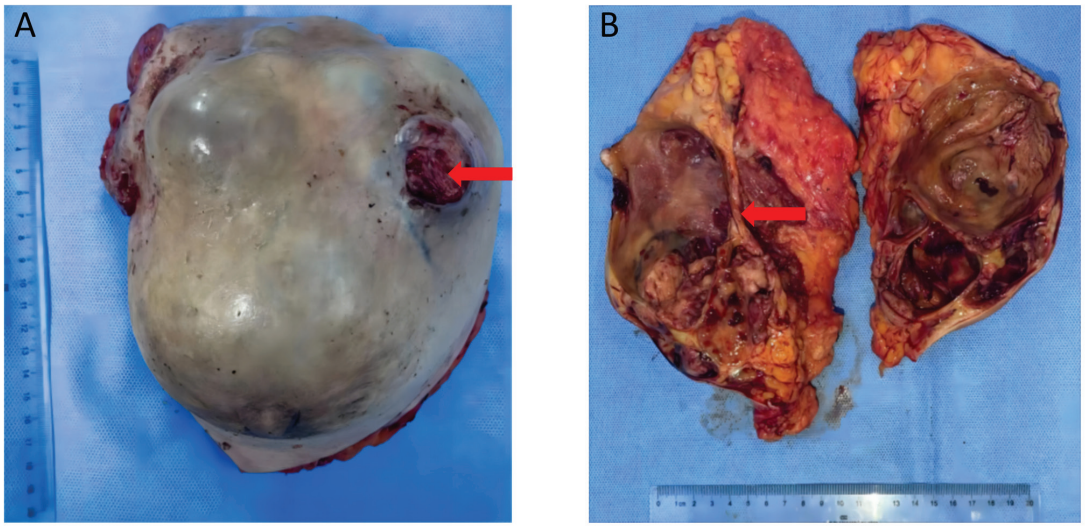

Figure 6. Images of the breast specimen. The lesion (A) occupied the entire breast and (B) appeared to be both cystic and solid (red arrow).

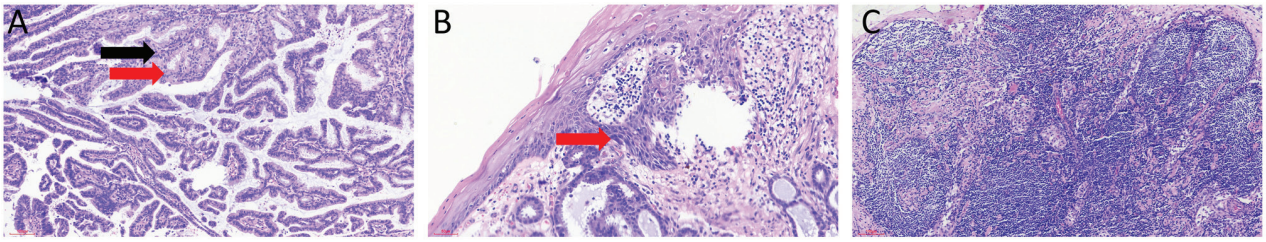

Figure 7. Postoperative hematoxylin and eosin staining of the lesion and lymph node. (A) Fibrovascular core (black arrow) was covered by a monolayer-to-multilayer epithelium, with crowded cells, lightly stained cytoplasm, eosinophilic and moderately atypical nuclei (red arrow). Magnification, x200. (B) Invasion of tumor cells (red arrow) in to the skin. Magnification, x400. (C) No tumor cells were observed in the lymph nodes. Magnification, x200.

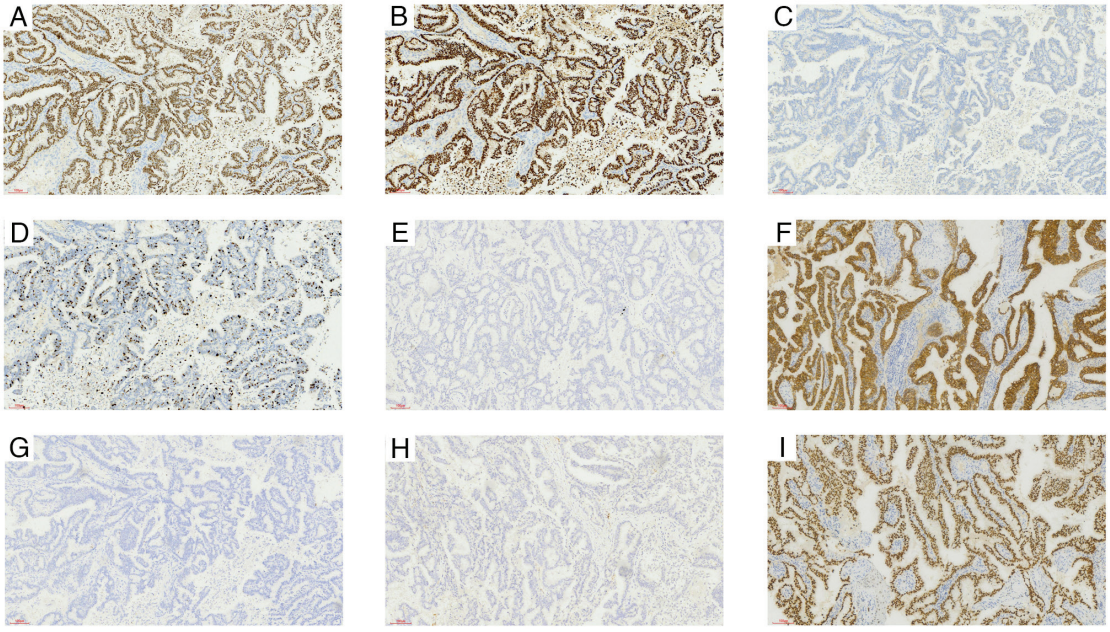

Figure 8. Postoperative immunohistochemical results. (A) Estrogen receptor (90%). (B) Progesterone receptor (90%). (C) Human epidermal growth factor receptor-2 (0%). (D) Ki-67 (20%). (E) Cytokeratin 5/6(-). (F) E-cadherin(+). (G) p63(-). (H) Calponin(-). (I) GATA binding protein 3(+). Magnification, x200.

sites on the sections using 5% bovine serum albumin (Fuzhou Maixin Biotechnology Development Co., Ltd.) for 30 min to reduce background staining. Diluted primary monoclonal antibodies, purchased from Fuzhou Maixin Biotechnology

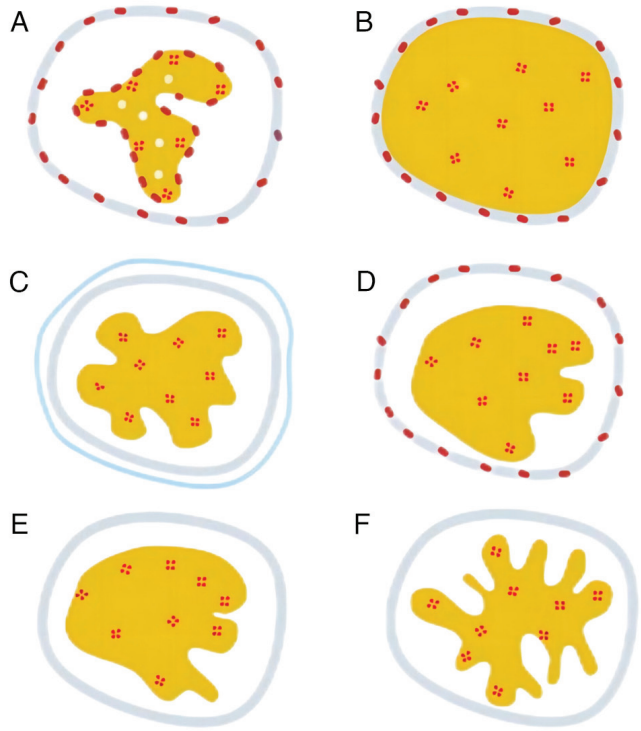

Figure 9. Schematic structure of different types of papillary neoplasms. (A) Benign papilloma. (B) Intraductal papillary carcinoma. (C) Encapsulated papillary carcinoma. (D) Solid papillary carcinoma *in situ*. (E) Solid papillary carcinoma with invasion. (F) Invasive papillary carcinoma. Yellow, epithelial cells; red, fibrovascular core; brown, myoepithelial cells; grey, affected duct; and blue, fibrous capsule-like structure.

Development Co., Ltd., were applied and incubated overnight at 4˚C to ensure sufficient antigen-antibody binding. These antibodies, along with their respective dilution ratios, were as follows: Rabbit anti-human ER (clone SP1; cat. no. Kit-0012) at 1:800, rabbit anti-human PR (clone SP2; cat. no. Kit-0013) at 1:800, rabbit anti-human HER-2 (clone MXR001; cat. no. Kit-0043) at 1:400, rabbit anti-human Ki-67 (clone SP6; cat. no. RMA-0542) at 1:400, mouse anti-human CK5/6 (clone MX040; cat. no. MAB-0744) at 1:800, mouse anti-human E-cadherin (clone MX020; cat. no. MAB-0738) at 1:400, mouse anti-human P63 (clone MX013; cat. no. MAB-0694) at 1:400, mouse anti-human Calponin (clone MX023; cat. no. MAB-0712) at 1:400 and mouse anti-human GATA3 (clone L50-823; cat. no. MAB-0695) at 1:400. The following day, the sections were thoroughly washed with PBS (cat. no. PBS-0060; Fuzhou Maixin Biotechnology Development Co., Ltd.) to remove unbound primary antibodies. Biotinylated secondary antibodies, specifically Goat anti-Mouse IgG (H+L) Secondary Antibody, Biotin (cat. no. A-11008) and Goat anti-Rabbit IgG (H+L) Secondary Antibody, Biotin (cat. no. A-11021), both purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., were then applied at a dilution ratio of 1:400 and incubated for 30 min at room temperature, followed by washing with PBS. Streptavidin-peroxidase conjugate was added and incubated for another 30 min at room temperature before another PBS wash. Finally, DAB chromogen (cat. no. DAB-1031; Fuzhou Maixin Biotechnology Development Co., Ltd.) was used for color development. Positive control slides (cat. no. P-0023) from Fuzhou Maixin Biotechnology Development Co., Ltd. were used, and a blocking serum (cat. no. BS-012-015) served as the negative control. The color development process was closely monitored under a light microscope (Leica DM2000), and once the desired staining intensity was achieved, the reaction was stopped by rinsing with tap water. The sections were then counterstained with hematoxylin (cat. no. CTS-1090; Fuzhou Maixin Biotechnology Development Co., Ltd.) at room temperature for 30 sec to enhance tissue structure visualization. Following this, the sections were dehydrated through a graded ethanol series, washed with xylene and mounted with neutral balsam. Evaluation was performed under an optical microscope at x200 magnification. All immunohistochemical sections were interpreted according to standard criteria (23).

Discussion

Based on the 5th edition of the WHO Classification of Breast Tumors, papillary neoplasms of the breast comprise a diverse group of diseases, encompassing benign papilloma, intraductal papillary carcinoma, as well as EPC, SPC and IPC (15). The rarest subtype of papillary neoplasms is IPC, characterized by a predominantly (>90%) papillary infiltrating component (24-26). Compared with other papillary neoplasms, IPC possesses distinct clinical and histological characteristics. However, the lack of large-scale epidemiological investigations poses significant challenges for clinical management. This challenge is reflected not only in the difficulty of histological diagnosis but also in the clinical treatment process (27). To the best of our knowledge, the present study is the first instance of three characteristics being included together: Firstly, the present study is the largest IPC case reported so far, with a diameter >15 cm; secondly, despite the patient having a long history of disease, a large tumor burden and skin lesions, there was no occurrence of axillary lymph node metastasis. This reflects, to a certain extent, the favorable pathological characteristics and biological behaviors of IPC; and finally, the patient only received endocrine therapy after surgery, and no recurrence or metastasis was found during the 2.5-year follow-up. The present case has never been reported before, to the best of our knowledge, and provides an important reference for the treatment of IPC. It is crucial to increase awareness of this rare tumor in the medical community and aid doctors to recognize and properly handle similar cases in the future.

IPC typically occurs in postmenopausal women of non-Caucasian descent, usually between the ages of 60-80 (3,28). In 2013, Liu *et al* (29) reviewed 284 IPC cases and 300 invasive ductal carcinoma (IDC) cases, and reported that most patients with IPC (79.23%) were >50 years at diagnosis, which was more than patients with IDC (39.00%). Additionally, most patients with IPC (74.30%) were postmenopausal, which was higher than patients with IDC (35.00%) (29). A large retrospective study recently demonstrated that IPC was more prevalent in older postmenopausal women, African-Americans and individuals with government insurance (30). Similarly, Chen *et al* (31) reported that 85.9% of patients with IPC were >50 years old at diagnosis, compared with 73.4% of patients with IDC.

IPC can occur at any location within the ductal system, spanning from the nipple to the terminal duct lobular unit (32). According to Zheng *et al* (2), among 524 reported cases of IPC, 50% occurred beneath the areola, whilst the remaining cases were found outside the areola. In addition, the presentation of IPC is typically characterized by bloody nipple discharge, an abnormal mass or radiographic abnormalities (5,29). In medical imaging, there are no distinct radiological features that differentiate between IPC and IDC. Both malignancies commonly manifest as irregular masses, occasionally accompanied by calcifications. Ultrasonography may reveal hypoechoic or mixed echogenic masses, whilst MRI may demonstrate heterogeneous enhancement in both tumor types. In the series of 18 IPC cases presented by Mitnick *et al* (33), the majority showcased a distinct multinodular pattern, featuring a notable increase in density within a segmental distribution. Additionally, IPC typically presents as a solid or cystic-solid mass, with the solid component being smaller than that of solid papillary carcinoma, and larger than that of encapsulated papillary carcinoma of the same size (18). In the present case, the patient was a 53-year-old premenopausal female patient with a mass located in the upper outer quadrant of the right breast that occasionally caused pain. Preoperative imaging and postoperative analysis of the gross specimen revealed multiple cystic-solid lesions in the breast that had fused together. Evaluating a tumor with a cystic component can be challenging due to its large volume, which may lead to overdetermination. Therefore, it is important to consider any solid components present. In breast pathology, the presence and distribution of myoepithelium are crucial for the identification and classification of papillary neoplasms: i) Benign papilloma: the lesion is characterized by uneven proliferation of epithelial cells around the fibrovascular core. There are myoepithelial cells present around the affected ducts and within the lesion (Fig. 9A); ii) Intraductal papillary carcinoma: the lesion is typically characterized by papillary hyperplasia of homogeneous tumor cells. There are no myoepithelial cells present within the lesion, however, there are clearly visible myoepithelial cells surrounding the affected ducts (Fig. 9B) (4,34); iii) EPC: the lesion is surrounded by a thick fibrous capsule-like structure. The tumor cells are homogeneous and exhibit papillary hyperplasia in the capsule. Myoepithelial cells do not surround the lesion and the vast majority of affected ducts (Fig. 9C) (35,36); iv) SPC: the lesion is characterized by expansive nodules and solid growth patterns, with an indistinct fibrovascular core. It is often accompanied by neuroendocrine and mucus secretion characteristics. Neuroendocrine markers, neuron-specific enolase, synaptophysin and chromogranin A, are positively expressed (17,37,38). The lesion lacks myoepithelial cells and, in most cases, the involved ducts are also devoid of myoepithelial cells (Fig. 9D) (39); however, in a few cases, it can be observed around the affected ducts (Fig. 9E) (40); and v) IPC: the lesion primarily forms delicate papillary structures, and the papillae fuse with each other to form larger, complex papillae and reticulated papillary structures (4). The papillary structures and the affected ducts lack myoepithelial cells (41) (Fig. 9F). Furthermore, in a study by Fisher *et al* (42). mucin secretion was noted in 2/3 of IPC cases. Notably, metastatic papillary carcinoma from other organs, such as the thyroid, ovary and lung, should not be misdiagnosed as IPC (43-45). Immunohistochemical markers such as paired-box gene 8, Wilms' tumor 1, thyroid transcription factor 1, napsin-A and thyroglobulin, combined with relevant clinical history, can help identify the origin of the tumor outside the breast. Moreover, it is important to distinguish between invasive micropapillary carcinoma and papillary neoplasms. The former is a distinct tumor type featuring clusters or nests of neoplastic cells without a true fibrovascular core and surrounded by empty spaces (46,47).

In the present case, the patient had a disease duration of >2 years with skin involvement but no axillary lymph node metastases. No recurrent metastases were detected in the 2.5 years of postoperative follow-up. This may reflect the relatively indolent biological behaviors of this type of tumor to a certain extent. The biological behaviors of tumors refers to the characteristics and abilities exhibited by tumor cells during proliferation, development and metastasis (48,49). In most cases, IPC progresses slowly and poses a low risk of local metastasis. According to Suh *et al* (50), disease-free progression can occur for >10 years under the natural history of the disease. In 2012, Liu *et al* performed a review of 284 cases of IPC and 300 cases of IDC (29). The results indicated that the rate of axillary lymph node metastasis in IPC (17.25%) was markedly lower than that in IDC (49.00%). These characteristics were associated with the pathological characteristics and gene expression of the tumors. In many studies, IPC has been reported to be smaller in size, of lower histological grade, and have higher positivity rates for ER and PR, as well as a lower Ki-67 proliferation index compared with IDC (12,51). A retrospective study in 2016 reported that patients with IPC, in comparison with patients with IDC, presented with a higher proportion of tumors that were <20 mm (67.4 vs. 63.9%) and a greater incidence of grade 1 disease (32.6 vs. 18.6%) (2). Moreover, a retrospective study conducted by Hashmi *et al* (52) reported that IPC cases exhibited a more favorable pathological profile in terms of prognostic features, including a lower Ki-67 index, tumor stage and histological grade, compared with IDC. Similarly, a higher expression of PR and a lower expression of HER2 was associated with a superior biomarker profile in IPC. Additionally, the occurrence rates of lymphovascular invasion and axillary metastasis were also lower in IPC (52). However, Terzi and Uner (53) documented a unique instance of IPC exhibiting high-grade nuclei, pronounced karyorrhexis and absence of ER or PR expression, which implied a high-grade malignancy, albeit without axillary lymph node metastasis. Furthermore, papillary neoplasms represent entities with varying biological behaviors and differential responses to treatment, suggesting that they may be driven by a few specific genomic events. It is important to note that papillary carcinoma, including EPC, SPC and IPC, may be part of the ER(+) breast cancer lineage due to their highly similar gene expression patterns (41). They are considered low-aggressive, exhibiting low levels of genes associated with cell adhesion, migration and movement (54). Moreover, research has indicated that IPC exhibits lower p53 expression, fewer gene copy number aberrations and a higher mutation rate of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α compared with IDC (55,56). A more in-depth investigation into the histopathology and genomics of IPC is necessary to gain a deeper understanding of its biological behaviors.

Breast cancer is a diverse group of diseases with varying histological and clinical characteristics. Treatment options are primarily based on the more prevalent types, such as non-specific IDC. However, for the rarer types of breast cancer, treatment guidelines are not always clear, and options are often inferred from comparisons with the more common types (57). There is no clear consensus on the treatment of IPC, a rare type of breast cancer (52). Due to its prevalence in postmenopausal elderly women and the favorable pathological characteristics and biological behaviors of tumor, it is generally recommended to avoid overtreatment (4). Local surgical intervention can not only prevent breast cancer progression but also improve the quality of life of patients with locally advanced disease (58,59). Arora *et al* (60) reported a case of a 62-year-old male patient with IPC who underwent a simple mastectomy. The patient remained disease-free at the 1-year follow-up. For comprehensive evaluation and treatment, it is necessary to completely remove IPC tumors and perform a sentinel lymph node biopsy (61,62). When cystic structures are present, neoadjuvant therapy should be considered for tumor reduction and skin graft or flap metastasis, as IPC tend to be larger in size. Additionally, due to the low malignancy of IPC and the low risk of metastasis recurrence, breast-conserving surgery combined with radiation therapy may be appropriate (63). Furthermore, IPC is an invasive carcinoma, and a systematic adjuvant treatment plan needs to be determined based on characteristics such as recurrence risk and tumor molecular classification. Patients with IPC with low recurrence risk may be more suitable for endocrine therapy compared with chemotherapy. The toxic and side effects of chemotherapy may affect its use, especially in postmenopausal elderly female patients who are commonly affected by IPC (64). Combination therapy or sequential therapy with multiple chemical drugs may cause liver function damage, digestive tract damage and leukocyte reduction (65). The integration of gene expression profiling, chemotherapy benefit and toxicity prediction tools is expected to better inform chemotherapy decisions in this population (66). Conversely, whilst IPC often expresses HR, HER-2 expression is often negative, and the Ki-67 index is low, which may result in poor efficacy of chemotherapy (67,68). However, endocrine therapy has lower toxicity and side effects, improved patient adherence, and is particularly effective for patients who are HR(+). Furthermore, the use of CDK4/6 inhibitors in combination with endocrine therapy has brought new hope to patients with HR(+)/HER-2(-) breast cancer (69). In 2016, a case of HR(+)/HER-2(-) invasive papillary carcinoma in an 83-year-old postmenopausal female patient was reported in Japan. The patient achieved a pathological complete response after undergoing neoadjuvant endocrine therapy with letrozole at a dosage of 2.5 mg/day for 12 months (70). In the present case, due to financial constraints, the patient underwent aromatase inhibitor therapy solely with anastrozole, administered at a daily dosage of 1 mg for 5 years post-surgery, whilst eschewing adjunctive therapies like radiotherapy and chemotherapy. Notably, anastrozole, letrozole and exemestane all belong to the class of aromatase inhibitors, and their efficacy in treating hormone-sensitive breast cancer is equivalent (71). Liu *et al* (29) demonstrated that IPC was associated with a higher 5-year overall survival rate (92.77%) and disease-free survival rate (87.95%) compared with IDC (87.95 and 80.72%, respectively). IPC typically exhibits favorable pathological features and biological behaviors; however, further evidence-based medical research is required to determine its true prognosis. A recent large retrospective study compared IPC and IDC and reported similar 5-year overall survival rates for both (86.8 vs. 88.7%). The study further reported that age (ranging from 80 to 90 years), locally advanced disease and the lack of radiation therapy are independent risk factors for poor prognosis in patients with IPC (30). Zheng *et al* (2) reported that, after adjusting for confounders, patients treated with IPC did not have a significant survival advantage over those treated with IDC. In the present case, the patient received telephone follow-ups every 3 months post-surgery, primarily to communicate about the post-surgical recovery progress, discuss medication side effects and assess for any signs of metastasis or recurrence of breast cancer. To date, the patient has reported no discomfort during this period, and self-examination has not revealed any significant masses in the affected chest wall, axilla, contralateral breast or axilla. Further observation, along with comprehensive assessments using imaging and other auxiliary examinations, is necessary to determine the long-term prognosis of the patient.

The present study reports a rare case of giant IPC and not only highlights the benign pathological characteristics and indolent growth behavior typically associated with this tumor, but also provides valuable data for the study of IPC treatment and prognosis. Due to the economic limitations of the patient, the follow-up was unable to include comprehensive auxiliary examinations and laboratory tests. Therefore, the absence of recurrence or metastasis in the patient cannot be fully confirmed. However, despite the 2-year duration from the self-discovery of the mass by the patient to treatment, and the large size of the tumor with extensive skin involvement, no axillary lymph node or distant metastasis was detected after surgery. Furthermore, the patient has maintained a good quality of life for 2.5 years following the operation. Based on previous research, it is believed that the current status of the patient is positive, although the true prognosis still requires longer-term and more comprehensive follow-up observations.

In conclusion, IPC is a rare type of breast cancer and its favorable prognosis is attributed to its pathological features and biological behaviors. Accurate diagnosis and avoidance of overtreatment are crucial in clinical management. Due to the limited clinical data and absence of clear treatment guidelines, doctors must exercise caution and individualize treatment plans. Endocrine therapy may be an effective treatment modality, but further prospective clinical studies are necessary.

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Availability of data and materials

The datasets generated in the present study may be requested from the corresponding author.

Authors' contributions

SW, XM, QZ and TZ contributed to the study design, writing and revisions of this manuscript. SW and XM confirm the authenticity of all the raw data. All authors reviewed the results and have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the present case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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