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CASE REPORT

Pseudo- or real progression? An ovarian cancer patient under nivolumab: A case report

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Abstract

BACKGROUND

Checkpoint-Inhibition has revolutionized the treatment for several entities such as melanoma and renal cell carcinoma. The first encouraging experience in ovarian cancer was reported for nivolumab, a fully humanized anti-programmed death-1 antibody. Pseudoprogression is a new phenomenon associated with these novel immuno-oncologic agents. It can be explained by infiltrating leucocytes and edema that result in a temporary increase in tumor size and delayed subsequent shrinkage due to tumor cell destruction.

CASE SUMMARY

We report on a 47-year old patient with platinum-resistant ovarian cancer that was treated off-label with nivolumab 3mg/kg iv d1q14d. She first experienced classic pseudoprogression with inguinal lymph node swelling after cycle two and subsequent shrinkage. After 6 cycles she presented with rectal bleeding and progressive disease was diagnosed due to new tumor infiltration into the rectum.

CONCLUSION

Clinicians should be aware of pseudoprogression, its underlying mechanisms and strategies to discriminate pseudo- from real progression in ovarian cancer.

Key words: Case report; Nivolumab; Clinical oncology; Checkpoint inhibition; Gynecologic oncology; Pseudoprogression; Immunooncology

Core tip: Clinicians have to be aware of the phenomenon of pseudoprogression despite its rather rare occurrence. As both- pseudo-progression and real progression present with an increase in tumor size, the only certain way to differentiate between them is the occurrence of infiltrating growth. While the increase of tumor size in pseudoprogression

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can be explained by benign growth due to immune cell infiltration and edema, only malign growth of a real progression has the ability to infiltrate other tissues. When in doubt whether a pseudoprogression has occurred, we suggest cautious continuation of checkpoint-inhibition paired with corticoids to lower adverse effects if necessary.

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INTRODUCTION

Cancer has different techniques to evade the immune system, one of those being Programmed death-1 (PD-1) signaling. PD-1 plays an important role in antitumor immunity as it is a vital part of a set of activating and inhibitory T cell receptors called "the immune checkpoint". By binding to its ligand PD-L1, which is expressed on the tumor cell, PD-1 inhibits antigen-specific cancer immune reactions and aggravates progression of ovarian cancer by inducing host immuno-suppression[1,2]. If PD-1 and PD-L1 bind, T cell proliferation and cytokine secretion are inhibited. The regulatory T-cells (Treg) increase and so called self-tolerance is maintained[3,4].

Nivolumab is a fully- humanized immunoglobulin G4, which targets PD-1. It prevents PD-1 from binding with its ligands and blocks signaling[2]. Thus, it increases the antitumor activity of T cells[5].

Checkpoint inhibitors have shown impressive results in the treatment of melanoma and non-small-cell-lung cancer and therefore, they have become the gold standard in the management of these entities[6]. Up to this point, only sparse data exist for checkpoint-inhibition in ovarian cancer. The first experience with nivolumab in ovarian cancer patients was reported by Hamanishi and colleagues. Nivolumab as a monotherapy was proven to be active in ovarian cancer- contrary to all other approaches of immune therapies like interleukines, vaccination or dendritic cell therapy. Acknowledging these positive results, it is important to mention that these first results on the efficacy of nivolumab in ovarian cancer are not as ground-breaking as in other entities[7]. Despite these first encouraging results, the rather low response rates of 15%-25% suggest that further effort is needed to increase efficacy of this novel substance in ovarian cancer. Strategies to improve efficacy could include patient selection, combination with chemotherapy and treatment at an earlier timepoint in the management (*e.g.*, early platinum-sensible situation).

Pietzner *et al*[8] hypothesize that identifying specific patients with an immunogenic profile like BRCA mutation might lead to a better outcome. The BRCA mutation results in a DNA repair deficiency, mainly because a repair mechanism called "Homologous Recombination" is impaired, which leads to a higher mutational load. The higher the mutational load of the cancer - which includes a higher presentation of neoantigens and an overall immunogenetic profile - the higher the likelihood of success using a checkpoint inhibition therapy (CIT)[8-10].

This hypothesis is supported by data from patients with Lynch-Syndrome in colorectal cancer, which is a mismatch repair deficiency comparable to the *BRCA* mutation. Le *et al*[10] showed a strong correlation between mismatch repair deficiency and positive results under CIT.

Up until the introduction of CIT, the evaluation of therapy response followed a simple rule: If a new lesion is detected or the tumor growth increases, this process is classified as progression, and clinicians are used to stop the ongoing treatment (chemotherapy or targeted therapy) as it seems to be inefficient. This rule does not apply to the novel substance group of checkpoint inhibitors, because of a phenomenon known as pseudoprogression.

In this scenario, the increase in tumor size or the appearance of a new lesion is not related to tumor cell growth as shown in Figure 1A. Instead, it can be explained by the infiltration of immune cells into a preexisting tumor cell conglomerate as well as the consecutive edema as a response to the immune reaction[11]. Therefore, pseudo-progression initially appears like a classic progression, with subsequent decrease in size without additional treatment[6,12].

The number of patients with solid tumors undergoing immune checkpoint inhibitor therapy is rapidly growing, while pseudoprogression remains a challenge

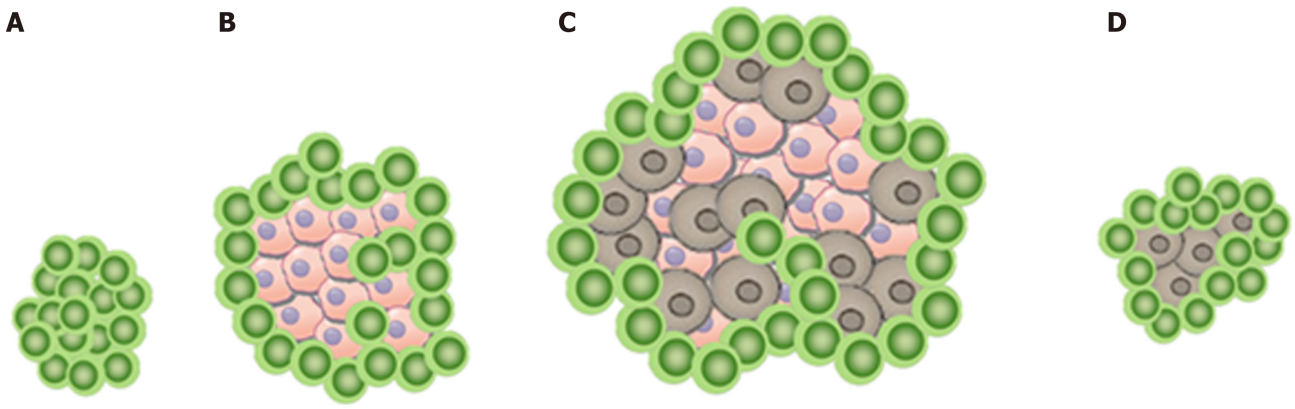

Figure 1 A schematic model of pseudoprogression in a lymph node. A: Healthy lymph node without infiltration; B: Tumor cells infiltrating the tissue, which leads to growth; C: Infiltration of tumor cells into a preexisting tumor cell conglomerate resulting in a further growth; D: Immune cells and healthy tissue cells.

for the clinician. The estimated occurrence of pseudoprogression ranges from 1.5% to 17% depending on the tumor entity and the study[6,13].

Hodi *et al*[14] conducted a study on advanced melanoma patients treated with pembrolizumab, another PDL-1 inhibitor. They were able to show pseudoprogression in 7% of the patients and found that pseudoprogression has a tendency to occur relatively early - mostly within 12 wk of treatment (62.5%, 15/24 patients), whereas pseudoprogression later than 12 wk after the beginning of PDL-1 inhibitor treatment - so called delayed pseudoprogression – was only found in 37.5% (9/24 patients)[14]. In one remarkable case early and delayed pseudoprogression could be described in one patient[15].

Under Ipilimumab, another checkpoint inhibitor, 9.7% of pseudoprogression could be found[12].

Several older manuscripts report on patients who responded to CIT after progressive disease was diagnosed: After an initial progression, they benefited from the continued CIT. As these reports were published before the introduction of the immune-related Response Evaluation Criteria in Solid Tumors (ir-RECIST) criteria, we believe that those cases report on the phenomenon we now define to be pseudoprogression, proving that this phenomenon has challenged physicians for a long time. The mechanisms behind CIT are complex and dependent on the patients' individual immunological answer, therefore the kinetics of CIT seem to be variable[16,17].

Nevertheless, it is crucial to be informed about pseudoprogression as indicates a high likelihood of > 1 year survival[18].

When considering different treatment options, practitioners and patients need to be informed about the possible occurrence of a pseudoprogression imitating real progression[6].

We present a platinum-resistant ovarian cancer patient, treated with nivolumab, who experienced both: A pseudoprogression and a real progression. We feel that this rare occurrence of both response patterns in the same patient makes this case ideal to illustrate both phenomenona and the difficulties to differentiate them.

CASE PRESENTATION

Chief complaints

We report on a 47-year-old-patient with recurrent ovarian cancer. She presented to the Emergency Department of our hospital with a swollen lymph node in her left groin.

History of present illness

Nivolumab was administered at a dosage of 3.0 mg/kg iv every three weeks for four cycles, starting December 2015 based on results from the Hamanishi *et al*[7] study. She responded with rash and pruritus to the first cycle of nivolumab which lessened under local corticoid-therapy. After the second cycle, the patient presented with typical inflammatory signs in her left groin: swelling, heat, redness and pain of an inguinal lymph node.

History of past illness

The patient was first diagnosed with high grade adenocarcinoma stage pT2b, G3,

pN0(0/29), R0, at a different institution in February 2010. She underwent radical cytoreductive surgery with hysterectomy, bilateral salpingoovarectomy, pelvine and paraaortal lymphadenectomy, omentectomy and deperitonealisation. She was treated with adjuvant chemotherapy consisting of six cycles of Carboplatin and Paclitaxel.

In June 2011, the disease relapsed for the first time and the patient was referred to our institution. Over the next four years, the patient was treated with Carboplatin/Gemcitabine as second line, pegylated liposomal Doxorubicin biweekly as third line, Carboplatin/Topotecan (Phase III "HECTOR" study) as fourth line and Paclitaxel/Bevacizumab as fifth line.

She experienced another relapse with intraperitoneal (rectum, bladder, *etc*.) and extraperitoneal manifestation (brain).

The tumor conference suggested the off-label-use of nivolumab in October 2015. The patients' health care provider granted permission for the off-label-use because of the limited options in this platinum-resistant situation and the good general health of the patient.

Personal and family history

The patient is married and lives with her husband and two children. Molecular analysis revealed *BRCA-1* mutation (p. His 1707 Arg).

Physical Examination upon admission

In the physical examination we saw a cardiopulmonary stable patient with a swollen lymph node in the left groin. In this location, a known lymph node metastasis was located, but the lymph-node nearly doubled in size initially suggesting classic progression.

Laboratory examinations

The laboratory examinations were unremarkable, including a stable tumor marker CA125.

Imaging examinations

No imaging examinations were done.

Further diagnostic work-up

Further pathologic characteristics are shown in Figure 2 and 3. Figure 3 shows the histomorphology of the patients' high-grade serous ovarian carcinoma pretreatment with solid growth pattern and pleomorphism of the tumor cells as well as frequent mitotic activity. An interesting factor are the increased tumor infiltrating lymphocytes (TILS) which have been shown to be associated with better prognosis[19]. In the biopsy after treatment the tumor still shows general features of a high-grade serous carcinoma, while TILS seem to be slightly reduced.

After the patient experienced progressive disease, lymph nodes were extracted. The mantle zone of the follicle can easily be distinguished from the increased Ki-67 positive interfollicular population, which indicates unspecific activation of the lymph node as seen in Figure 4.

This activation of the follicle combined with edema and dilated vessels are most likely caused by the nivolumab treatment.

FINAL DIAGNOSIS

A known lymph node metastasis was located in the patients' left groin, but the lymph-node nearly doubled in size initially suggesting classic progression. But the lack of evidence for additional progression, the local inflammatory signs and the stable tumor marker CA125 made a pseudoprogression the most likely diagnosis.

TREATMENT

Because the RECIST do not provide a complete assessment of immune-therapeutic agents, ir-RECIST were defined by Wolchok *et al*[12]. In this adapted recommendation, the increase in tumor size or even the appearance of a new lesion, does not automatically translate to the classification as progressive disease. While taking the potential toxicity of the treatment into consideration, continuation with the immune related therapy while persistently performing follow-up examinations to ensure the patients' safety is recommended in ir-RECIST[12]. The recommendation on the frequency of follow-up exams is four weeks, but if a rapid decline of the patients' status is observed, an earlier follow up is necessary.

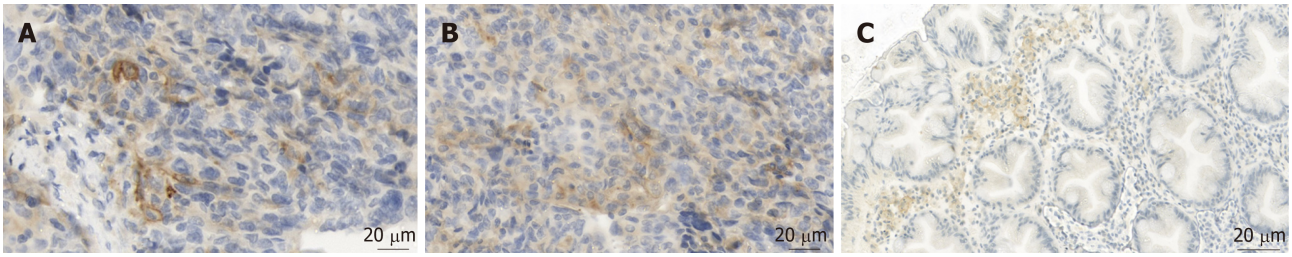

Figure 2 Posttreatment PD-L1 expression pattern in our patients' high grade serous ovarian carcinoma and in tumor infiltrating lymphocytes. A: Tumor cell with strong positive membranous staining of PD-L1; B: Tumor with artificial membranous and some cytoplasmatic staining of PD-L1 as well as some immune cells with PD-L1 expression; C: For comparison: an example of PD-L1 staining in immune cells.

Therefore, we proceeded with nivolumab treatment and the lymph node decreased in size. The shrinkage was interpreted as confirmation of pseudoprogression.

OUTCOME AND FOLLOW-UP

Three weeks after the fourth cycle of nivolumab, she presented with rectal bleeding. A cysto-rectoscopy was performed, which demonstrated new tumor infiltration into the rectum. A biopsy was taken and the pathological analysis verified new relapse with infiltration into the rectum. Three days after the cysto-rectoscopy, an operation using laparotomy by longitudinal incision was performed without any complications in order to remove the tumor. The histological findings of the biopsy of the bladder showed necrosis and atypical cells. A colostomy was done during the same procedure.

DISCUSSION

Nivolumab has been shown to be active in ovarian cancer, but the possibility of pseudoprogression imitating real progression remains[11]. This case report highlights the possibility of pseudoprogression in ovarian cancer patients undergoing nivolumab treatment and shows the challenges differentiating between pseudoprogression and real progression.

Immune-related-RECIST (ir-RC) were defined by Wolchok *et al*[12] but is important to notice that the recommended follow-up after four weeks is not evidence based and it remains unclear if another frequency of the follow-up-examinations is more beneficial.

Pseudoprogression emerges to be a challenge not only for the attending physician, but also for the radiologist: Wang *et al*[20] describe the two main differences between the ir-RC and the RECIST system: On the one hand, new lesions need to be interpreted taking into consideration the total tumor burden. On the other hand, this increase in total tumor burden has to be controlled and confirmed at least four weeks after the first event indicating possible progression[20].

If pseudoprogression is not as unambiguous as in our case, ultimately only follow-up imaging can help differentiate between pseudo- and real progression as shown in Table 1[21].

Imafuku *et al*[22] report on two cases of melanoma patients treated with nivolumab who experienced pseudoprogression. They performed sonographic imaging and computed tomography (CT) scans on both patients and found that the CT scans - in contrary to the sonographic imaging of the pseudoprogression - were not able to detect an association between tumor size and tumor blood flow. Interestingly, they describe that the lesions caused by pseudoprogression grew while simultaneously the blood flow within the lesion dropped. They therefore believe that sonographic imaging could be helpful in differentiating between pseudo- and real progression, which is intriguing because CT-imaging - especially if it has to be performed several times as the ir-RECIST requests - puts the oftentimes heavily pretreated patients at risk[22].

The patient discussed in this report is BRCA 1 positive. This mutation possibly results in a high mutational load linked to higher treatment success similar to patients with Lynch Syndrome[10]. We hypothesize that a higher immunogenic profile not only leads to higher rates of treatment success but subsequently also results in higher rates of pseudoprogression. Further investigation on patient selection, especially *BRCA*

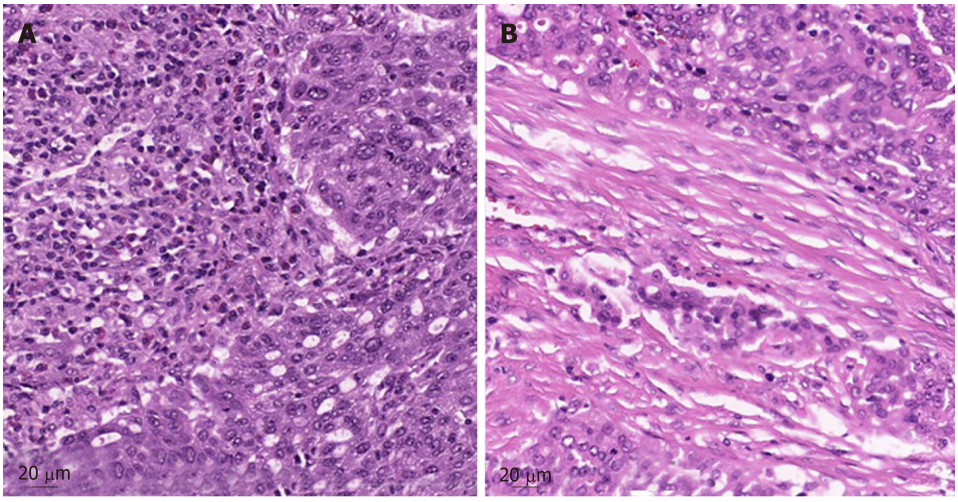

Figure 3 Tumor biopsy before and after treatment with nivolumab. A: Pretreatment tumor biopsy in 2012, HE-stain. Note the intratumoral lymphocytes (TILS); B: Posttreatment tumor biopsy of the high-grade serous carcinoma of the left colic flexure in 2016, HE-stain. Note reduced intratumoral lymphocytes.

mutation and its underlying mechanism is crucial to fully understand CIT and pseudoprogression.

Apart from pseudoprogression, another new phenomenon was noticed with the introduction of immunooncologic agents: It is notable that the progression free survival (PFS) under CIT is oftentimes not significantly lengthened: The patients relapse after a similar time compared to those who did not receive CIT, but surprisingly the overall survival (OS) of CIT patients is often prolonged. This is remarkable as the majority of other agents prolong the PFS while the OS remains unchanged.

The better OS in CIT patients indicates that the number of unreported cases of pseudoprogression might be a lot higher than the 4% suggested by Chiou *et al*[6]. The prolonged OS could possibly be explained by patients, who had a pseudoprogression that was wrongly diagnosed as a real progression. It could be hypothesized, that even though these patients received a shortened CIT treatment, they profited from it, which resulted in a benefit of the OS.

Tanizaki *et al*[23] show another interesting aspect of the durable immune reaction after CIT: They report on a Non-small-call-lung-cancer patient, whose histological evaluation of a liver metastasis showed no viable tumor cells but fibrotic tissue infiltrated by CD 3, 4 and 8 positive lymphocytes.

Tumor markers can be used as an additional source of information to differentiate between real and pseudoprogression, but - as any inflammatory process can lead to a rise of the tumor marker - a moderate increase of the tumor marker occurs in both pseudo and real progression. A rapid increase of tumor markers suggests a real progression as the more likely diagnosis. But further predictive makers for the response to immune-checkpoint inhibitors are needed.

Interestingly, interleukine-8 levels (IL-8) were shown to decrease during pseudoprogression and increase during progression. Although this was only shown in three cases so far, IL-8 monitoring might be a promising and helpful tool in the future to differentiate between pseudo- and real progression[24].

From the pathologic point of view, the overall number of TILS could be evaluated to that aspect.

Pathologic evaluation of PD-L1 remains very challenging. PD-L1 is a positive prognostic marker in ovarian carcinoma, while the predictive value for therapy response still remains doubtful[19]. Therefore, the pathologic report usually includes the percentage of PD-L1 positive tumor cells, defined as cells with a strong membranous staining of PD-L1 (Figure 2A). Cytoplasmic staining of tumor cells is considered artificial (Figure 2B). A special problem consists in tumor infiltrating immune cells (TILS). Immune cells often express some PD-L1 - either membranous or cytoplasmic (Figure 2C) - and can easily be confused with tumor cells if being intermingled as TILS.

Our patient showed positive TILS in the pretreatment biopsy.

Considering these strict criteria, our patient was negative for PD-L1 expression before treatment with nivolumab (biopsy from 2012) and showed some 3% of PD-L1 positive tumor cells in the re-biopsy (2016) after treatment. Therefore, the absence of sufficient PD-L1 expression in the pre-treatment biopsy was not predictive for a

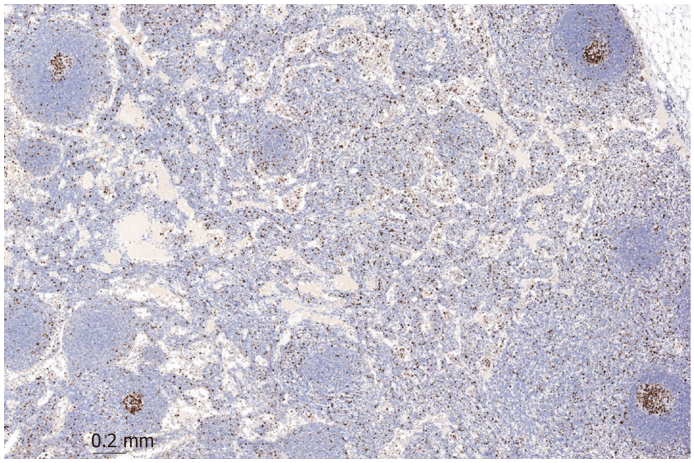

Figure 4 Biopsy of a lymph node after nivolumab treatment. Activation of a lymph node including increased Ki-67 positive interfollicular population.

negative therapy effect. Surprisingly, the tumor cells showed a positive rate of 3% after the treatment.

Although nivolumab inhibits immune checkpoints (especially PD-L1), a pretreatment evaluation is not yet required for treatment. Unfortunately, no pretreatment biomarker has been found, but it is likely that it will be necessary to also take into consideration factors like tumor genomic studies of mutational load and studies of T-cell receptors[25]. Further research is necessary to include pathologic findings as reliable markers for predictive therapeutic effects.

CIT imposes many opportunities on oncologic treatment, but also challenges our current understanding of cancer: The occurrence of pseudoprogression shows that we have to think outside the box in order to use CIT to its full potential: For decades, our understanding of cancer treatment was mainly based on data from cytotoxic agents and our definitions and statistical analysis are based on this knowledge. However, as it was necessary to introduce the ir-RECIST criteria in order to meet the novel requirements of CIT, it will likewise be necessary to adapt our statistical analysis. Possible methods to better incorporate pseudoprogression and additional new phenomena into statistics might include time-specific endpoints, immune-related endpoints, restricted mean survival time or generalized pairwise comparison[26].

As both- pseudoprogression and real progression- present with an increase in tumor size, the only certain way to differentiate between them is the occurrence of infiltrating growth. While the increase of tumor size in pseudoprogression can be explained by benign growth due to immune cell infiltration and edema, only malign growth of a real progression has the ability to infiltrate other tissues. This way to differentiate between pseudoprogression and real progression is vividly illustrated in our case report. A limitation of our case report is the lack of imaging of the left groin after pseudoprogression.

Although checkpoint inhibitor therapy is one of the most promising anti-tumor treatments yet, many questions remain unanswered: How long does the stabilizing effect after pseudoprogression last? Is pseudoprogression a predictor for progression or remission? Which symptoms are associated with pseudoprogression?

Further studies are necessary to fully characterize pseudoprogression not only translationally but also clinically and to understand its symptoms and clinical outcome.

CONCLUSION

This case illustrates not only pseudo-, but also real progression and vividly shows the main difference between the two: Only real progression has the ability to infiltrate other tissues. While the appearance of new lesions as well as the increase in size of a known lesion can be due to pseudoprogression, the new manifestation of infiltrative disease (such as the rectum infiltration in our case) is bound to be caused by real progression.

Risk factors for pseudoprogression and guidelines to diagnose pseudoprogression have yet to be investigated to ensure both the physician and the patient of the safety and efficacy of checkpoint-inhibition.

Table 1 Main differences between RECIST 1.1 and ir-RECIST, adapted from Wang *et al*[21]

	Progression	New measurable lesion	New non measurable lesion
RECIST 1.1	Increase in tumor burden on one examination	Represent progressive disease	Follow-up necessary
Ir- RECIST	Increase in tumor burden on two examinations > 4 wk apart	Are incorporated into tumor burden	Preclude complete response

RECIST: Response evaluation criteria in solid tumors.

When in doubt whether a pseudoprogression has occurred, we suggest cautious continuation of checkpoint-inhibition paired with corticoids to lower adverse effects if necessary. Increased investigation of this phenomenon is crucial to improve the management of checkpoint-inhibitors such as nivolumab.

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CASE REPORT

Reirradiation of recurrent breast cancer with proton beam therapy: A case report and literature review

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Author contributions: Lin YL performed all the research and interpretive functions for this case report.

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Abstract

BACKGROUND

Locoregional recurrence of breast cancer is challenging for clinicians, due to the various former treatments patients have undergone. However, treatment of the recurrence with systemic therapy and subsequent reirradiation of chest wall is accompanied by increased toxicities, particularly radiation-induced cardiovascular disease. Reirradiation by proton beam therapy (PBT) enables superior preservation of adjacent organs at risk as well as concurrent dose escalation for delivery to the gross tumor. This technology is expected to improve the overall outcome of recurrent breast cancer.

CASE SUMMARY

A 47-year-old female presented with an extensive locoregional recurrence at 10 yr after primary treatment of a luminal A breast cancer. Because of tumor progression despite having undergone bilateral ovarectomy and systemic therapy, the patient was treated with PBT BE total dose of 64.40 Gy to each gross tumor and 56.00 Gy to the upper mediastinal and retrosternal lymphatics including the entire sternum in 28 fractions. Follow-up computed tomography showed a partial remission, without evidence of newly emerging metastasis. At 19 mo after the PBT, the patient developed a radiation-induced pericardial disease and pleural effusions with clinical burden of dyspnea, which were successfully treated by drainage and corticosteroid. Cytological analysis of the puncture fluid showed no malignancy, and the subsequent computed tomography scan indicated stable disease as well as significantly decreased pericardial and pleural effusions. The patient remains free of progression to date.

CONCLUSION

PBT was a safe and effective method of reirradiation for locoregionally recurrent breast cancer in our patient.

Key words: Proton beam therapy; Recurrent breast cancer; Chest wall recurrence;

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Reirradiation; Pericarditis; Radiation-induced cardiovascular disease; Case report

Core tip: The treatment of recurrent breast cancer is very complex and not standardized. Patients with locoregional recurrence and gross residual tumor despite systemic therapy and surgery demand further options with potentially curative intention. Presented here is a patient with a late locoregionally recurrent breast cancer, showing significant reduction of gross tumor disease after reirradiation by proton beam therapy. In the 2 years since, the patient has remained free of tumor progression.

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INTRODUCTION

Breast cancer (BC) is the second most common cancer disease worldwide. The global cancer research project GLOBOCAN 2012 reported an approximate 1.67 million new cases diagnosed in 2012, accounting for 25% of all cancers in women and ranking 5th among the total cancer-related deaths. At the initial diagnosis of BC, the likelihood of locoregional and distant recurrence and overall prognosis can be assessed according to clinicopathological features, such as tumor size, grading, lymph node (LN) involvement, expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), and proliferation index Ki-67. The incidence rate of local recurrence at 10 years after breast conserving therapy ranges from 10% to 22% and that for mastectomy from 5% to 15%, occurring on average within the first 5 years after the primary treatment. Furthermore, local recurrence is associated with increased appearance of regional LN and distant metastases, namely in 10%-30% of patients after breast conserving therapy and in 30%-50% of those after mastectomy[1].

BC recurrence is a real challenge for clinicians owing to the variety of previous treatments a patient can undergo [*i.e.*, breast conserving therapy, mastectomy, neoadjuvant or adjuvant systemic therapy, and radiotherapy (RT)] as well as the co-existence of LN and distant metastases. Patients with recurrent BC, even in the absence of distant metastasis, suffer from severe mental and corporal stress related to the local tumor progression and which, particularly the latter, can manifest ulceration, hemorrhage, stench, pain, brachial plexus palsy, and lymphedema. Thus, multidisciplinary treatment approaches are required, consisting of breast and plastic surgery, medical and radiation oncology, pathology, radiology, psycho-oncology, and specific wound management for ulcerating tumors.

Based on the favorable physical property of the Bragg peak[2], proton beam therapy (PBT) enables an optimal planning of reirradiation for locoregional recurrence of BC. This technology not only spares adjacent uninvolved breast tissue and other organs at risk (OAR), such as heart, esophagus, lungs, spinal cord and brachial plexus, but also allows for dose escalation of the irradiation to partial breast and chest wall (CW).

CASE REPORT

Chief complaints

A 47-year-old female presented with a progressive locoregional recurrence at 10 years after the initial diagnosis of a luminal A BC. As to her clinical symptoms, she complained only of intermittent pain in the parasternal area on both sides.

History of present disease

The breast magnet resonance imaging (MRI) performed in May 2014 primarily showed suspicious sternal metastasis, but the sternum biopsy did not reveal any malignancy. The subsequent mammography of both breasts also excluded local recurrence. Over a year later, in July 2015, a computed tomography (CT) scan

revealed a tumor mass in the right para- and presternal area (between the 2nd and 5th rib) with invasion of cartilage and ventral pleura, and extending to the subcutis and contralateral parasternal region. Moreover, several enlarged mediastinal LN were detected, along with a pleural lesion in the anterior segment of right upper lobe and bony metastasis in the sternum body. Biopsy of the CW recurrence confirmed a moderately differentiated invasive carcinoma with ER 8, PR 8 (according to Allred score), HER2 negativity, and Ki-67 10%.

After a laparoscopic ovarectomy (both sides) was performed, the patient chose to participate in the MONALEESA-3 study investigating efficacy of fulvestrant in combination with ribociclib (*vs* placebo). In addition, she commenced biphosphonate therapy with zoledronic acid. In February 2016, she dropped out of the study due to progressive disease with newly-occurring parasternal LN metastases and slowly growing pleural metastasis; her endocrine therapy was switched to letrozole. However, the parasternal CW recurrence on the right side continued to grow, reaching roughly 30 mm × 50 mm × 20 mm in size. The patient participated in consults for both cyber knife therapy in another clinic and PBT at the Rinecker Proton Therapy Center, and eventually decided to undergo the latter.

History of past disease

At the age of 37, the patient had been diagnosed with a multifocal invasive ductal carcinoma, presenting as four cancerous lesions measuring up to 1.6 cm, as well as an extended ductal carcinoma *in situ* of the right breast. She underwent, first, a segment resection with axillary LN dissection. In the second session, she underwent an ablation of the right breast. The postoperative tumor stage was pT1c(m) pTis(4cm) G2 pN1a(2/23) cM0 L0 V0 R0. The receptor status (according to Allred score) was ER 8, PR 8, HER2-negative.

After completing 6 cycles of postoperative chemotherapy with docetaxel, doxorubicin and cyclophosphamide, the patient received adjuvant RT with photon beams to the right CW and supraclavicular, axillary and retrosternal lymphatic drainage pathways (at a total dose of 50 Gy in 25 fractions). A sequential electron boost treatment (providing a further 10 Gy in 5 fractions) was given to the tumor bed in the lower and inner quadrants over the period of June to July 2006. Under endocrine therapy with zoladex (until June 2009) and tamoxifen (until July 2012), there was no sign of tumor recurrence in the follow-ups. Consequently, the patient underwent a breast reconstruction with deep inferior epigastric perforator flap in January 2011.

Physical examination

Beside lymphedema of her right arm, a tumor conglomerate was noted on the right parasternal CW; although, the skin surface was still intact and without ulceration. The common clinical examination of cardiopulmonary and neurological status did not reveal any pathological findings.

Laboratory examinations

No special laboratory test was arranged.

Imaging examinations

Prior to the PBT, the patient underwent positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) PET/CT at our center, displaying intensively increased uptake in the LN stations of the right armpit, upper mediastinum, aortic arch on the left, and retrosternal in front of the right heart ventricle, as well as in the corpus sterni and on the CW in the right parasternal area with invasion of right breast, subcutis and mediastinum (Figure 1). Over and above that, pleural metastases with aspect of lymphangiosis carcinomatosa were detected in the right upper lobe, with adhesion on the interlobe of the right lower lobe apex (Figure 2).

MULTIDISCIPLINARY EXPERT CONSULTATION

This approach was not specified according to the unequivocal histopathological and ^{18}F-FDG PET/CT findings.

FINAL DIAGNOSIS

Recurrent BC.

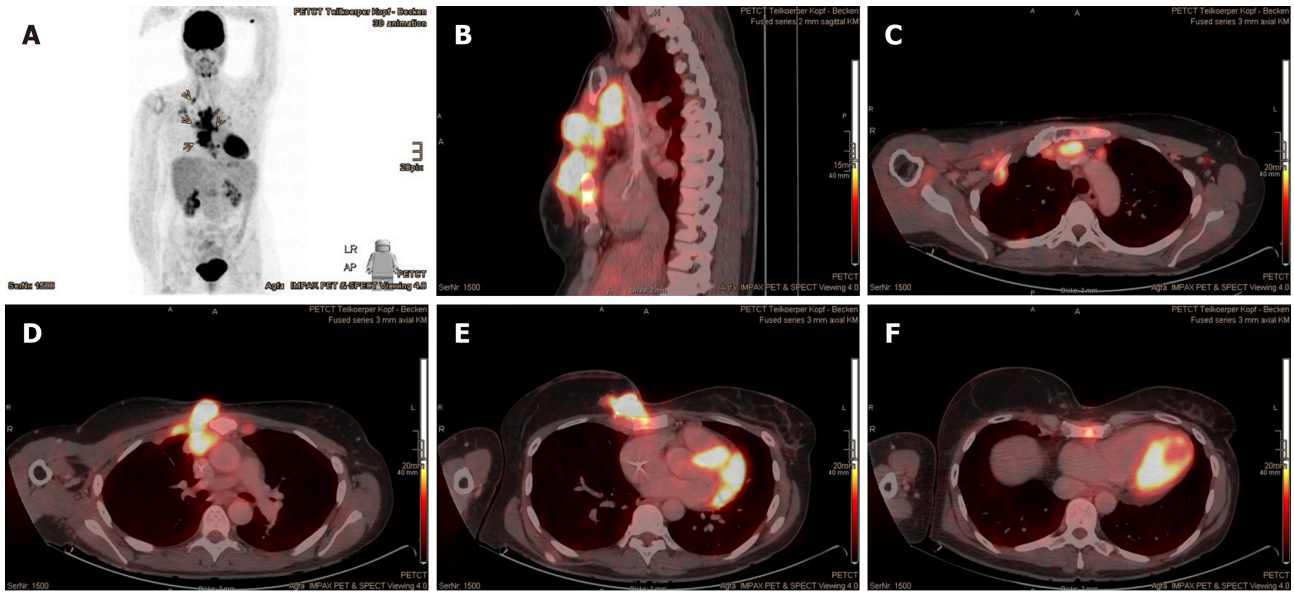

Figure 1 **^{18}F-FDG PET/CT performed immediately prior to proton beam therapy in October 2016.** A: Overview of multilocular tumor recurrences with increased FDG uptake (marked with arrows); B: Sagittal plane; C-F: Axial plane. ^{18}F-FDG PET/CT: 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography/computed tomography.

TREATMENT

The patient was treated at the Rinecker Proton Therapy Center from November to December 2016. The PBT was delivered in 28 fractions (at a total dose of 64.40 Gy; relative biological effectiveness (referred to as RBE)) to the tumor lesions on the right CW, including the adjacent pleura, LN metastases in the right axillary, parasternal and mediastinal area and sternum metastasis. The superior mediastinal and retrosternal lymphatic drainage pathways and the entire sternum also received 56 Gy (RBE) in 28 fractions, concurrently (Figure 3). For the purpose of accurate reproduction of the target, the patient was positioned with custom immobilization devices, consisting of vacuum cushion, breastboard and Beekley Spots as fiducial markers. To estimate the deviation of the target by respiratory motion, the patient underwent CT simulation in flat and free breathing states during the planning stage, as well as weekly CT scans (performed as controls) during the treatment and including fusion with the planning CT. We used only one irradiation field, from the 352 degree gantry angle with a field size of 22.8 cm in width and 28.8 cm in length. The irradiation direction was chosen in the best way to compensate the difference of chest wall in anterior-posterior direction due to respiratory motion. The pencil beam scanning technique, depriving energy of 75-250 MeV from a superconducting cyclotron at our center, enables an intensity modulated proton therapy, which was employed with the anticipation of homogeneous target volume coverage, sparing of uninvolved surrounding tissue and OAR, as well as certain dose escalation.

OUTCOME AND FOLLOW-UP

The patient tolerated the PBT well and reported only dysphagia with reflux and cough now and then, defined as grade 2 by the Common Terminology Criteria for Adverse Events (commonly known as CTCAE). The skin showed radiation dermatitis of grade 2 CTCAE, with dry desquamation in the parasternal and submammary locations. Because of the remarkable radiation dosage to the lungs, a regimen of ciprofloxacin (10 d), prednisolone and omeprazole (6 wk) was recommended as prevention against radiation pneumonitis. Already in the course of the treatment, a diminution of the parasternal tumor nodules was observed clinically and radiographically by the weekly-performed controls with low-dose CT scan (Figures 4-6).

In the first follow-up, at 3 mo after the PBT, the CT scan revealed significant regression of the CW recurrence and the LN metastases (Figure 7A). Subjectively, the patient complained of consistent skin hyperpigmentation with itching, in spite of frequent skin care. Furthermore, she reported coughing with clear sputum, but felt generally sound and undisturbed. The difficulties in swallowing had completely

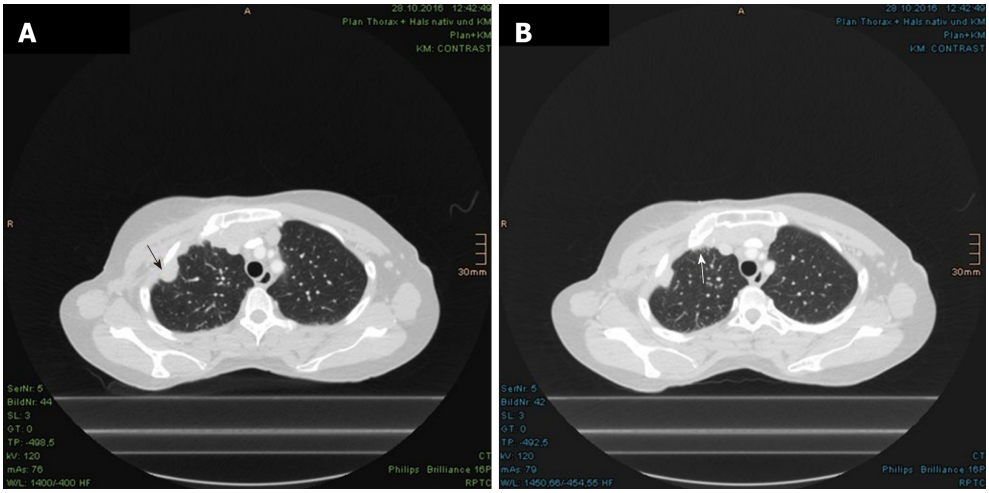

Figure 2 Pleural metastases with aspect of lymphangiosis carcinomatosa in the right upper lobe. A: Pleural metastasis; B: Lymphangiosis carcinomatosa (both marked with arrows).

diminished. She was able to move her right arm better and had less pain. The lymphedema, which had existed since the axillary LN dissection, did not deteriorate after the PBT but was reportedly improved by movements like swimming. Regarding the most concerned brachial plexus palsy due to reirradiation of the extended locoregional recurrence, a mere tingling paresthesia of the right arm had occurred at 8 mo after the end of the PBT treatment and ameliorated spontaneously within 1 mo. In this time period, the arm strength was not impaired and the lymphedema of right arm remained unchanged. Subsequently, the patient only reported subtle paresthesia on the fingertips and heaviness of the right arm, and she underwent regular lymphatic drainage. Apart from the chronic cough with difficulties in expectorating due to stiffness of the neck, there was no other clinical complaint.

The CT scans of thorax and abdomen, taken at the 9th and 13th mo after PBT, demonstrated further reduction of the tumor mass at right of the sternum, as well as constant postradiogenic changes in both paramediastinal regions and in the right lung apex (Figure 7B and C), excluding any new metastasis. Early 2018, the patient indicated dysphonia with occasional dyspnea and cough stimulated by cold in winter. The examination by a staff otolaryngologist exhibited laryngeal edema with soreness, excluding vocal cord paralysis. The patient attended and completed speech therapy, and no further treatment was recommended for this condition. Aside from persisting lymphedema of the right arm, the patient reported tension of the right shoulder muscles, which the fibrosis contributed to as well. The skin continued to appear discreetly flushed, consistent with teleangiectasia. There was no tumorous proturbance that was visible, but the right breast remained in its slightly swollen state since the PBT.

In July 2018, the follow-up CT scan showed an increase in pericardial and pleural effusion on the right (Figure 8). Assessment of the pericardial effusion (about 4 cm wide) by a staff cardiologist found no evidence of hemodynamic compromise. Instinctively, the patient reported overall stable general condition, except for burden of dyspnea, corresponding to class II in the New York Heart Association (commonly known as NYHA) classification system. Otherwise, the dysphonia, coughing and shoulder tension were bettered by physiotherapy and speech therapy. In addition, a newly-appeared soft tissue augmentation in the right parasternal area (Figure 9A and B) prompted referral to the Breast Cancer Institute by her oncologist. Nevertheless, the pericardial and pleural effusions became gradually significant thereafter. A cardiac MRI performed after the first puncture revealed acute pericarditis without myocardial involvement or cardiac wall motion abnormalities.

In the following months, a total amount of 1650 mL of pericardial effusions and 3000 mL of pleural effusions were drained, all sans evidence of malignancy. Starting with the first drainage, the patient had been treated with colchicine, ibuprofen and torasemide. According to the reproduction of effusions in the interval of 2 wk and ruling-out of other differential diagnoses, such as rheumatic diseases, a probationary treatment with corticosteroid was initiated. From this time forward, the pericardial and pleural effusions distinctly declined (Figure 10).

In the most recent CT scan, taken in October 2018, there was no definite sign of tumor progression. Considering the stable size of the right parasternal soft tissue

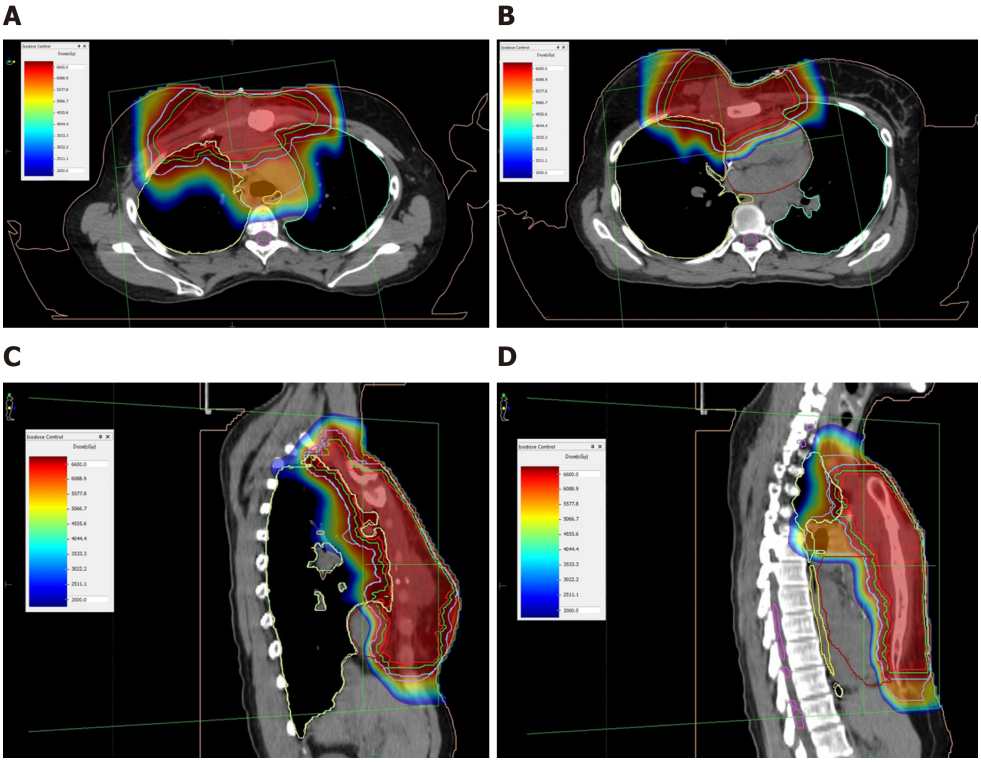

Figure 3 Treatment plan of proton beam therapy with isodose distributions. A and B: Axial plane; C and D: Sagittal plane. Red line: Gross tumor volume; Green line: Clinical target volume; Blue line: Planning target volume of gross tumors; Lilac line: Planning target volume of gross tumors including adjacent regional lymphatics and sternum.

density (Figure 9C), no further investigations (*i.e.*, biopsy and ^{18}F-FDG PET/CT) were arranged by the Breast Cancer Institute. The patient continued the present systemic therapy with letrozole and denosumab. She experienced incremental advances in physical ability and appetite, and even reported a noticeable reduction in the lymphedema in her right arm, which allowed her to begin swimming anew.

DISCUSSION

Recognition and appreciation of the various biological subtypes of BC can help clinicians predict the recurrence pattern and determine the most appropriate and effective treatment concept[3]. In the literature, several approaches to analyze hormone receptor status as a predictor of outcome in BC patients have been reported. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results program (commonly known as SEER; 1992-2002), ER-negative and ER-positive cases rendered very different consequences in hazard rates of cancer-specific death. Specifically, at 17 mo the ER-negative hazard rates peaked at 7.5% per year and thereafter declined, while the ER-positive hazard rates had no distinct early peak but showed a consistent rate of 1.5%-2% per year. The falling ER-negative and constant ER-positive hazard rates finally traversed at 7 years. Thereupon, the prognosis seemed to be better for the ER-negative cases[4].

Intriguingly, the recurrence rate is significantly higher in ER-negative cases for the first 2 years of follow-up and is associated with rising emergence of visceral and soft tissue metastases. ER-positive tumors, in contrast, metastasize more frequently to bone[5]. With regard to this, Campbell *et al*[6] proposed a new combined endocrine receptor immunohistochemistry scoring system as a more powerful predictor of patient outcome, being especially important for early BC with positivity for ER.

A retrospective study of 300 patients with recurrent disease concluded that hormone receptor-positive and HER2-negative BC had higher risk of recurrence later than 5 years from the initial treatment or after diagnosis, particularly concomitant with high ER titer (> 50%) and low nuclear grade, and predominantly spread to the bone; larger (> 2 cm), node-positive and HER2-positive tumors were predicted for early recurrence[7]. A recent Dutch study demonstrated that the risk of first recurrence was highest in the second year after BC diagnosis, including a second peak around years 8-9[8]. In that study, young age (< 40 years), tumor size, positive LN metastases,

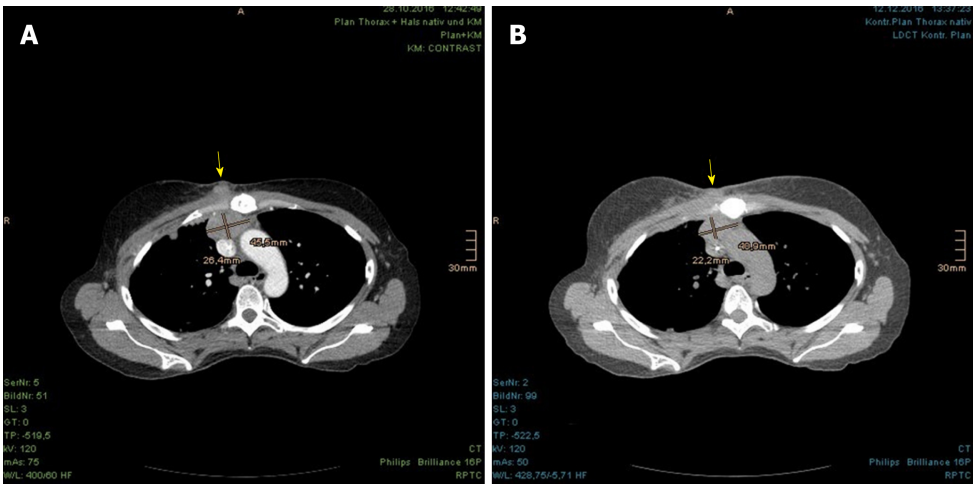

Figure 4 Incipient size reduction of right parasternal metastasis (with size measurement) and chest wall recurrence (marked with arrow) during the proton beam therapy. A: In planning computed tomography (CT) prior to proton beam therapy; B: In control CT at 26th fraction of treatment.

tumor grade 2-3, multifocality, and lack of systemic therapy were identified as prognostic predictors for first recurrence. Interestingly, another study by Lynch *et al*[9] could not define multifocal or multicentric BC as an independent risk factor for locoregional recurrence. Those patients with multifocal or multicentric disease showed a comparable locoregional control rate as those with unifocal tumor, regardless of treatment type (*i.e.*, breast conserving therapy or mastectomy, or mastectomy with postmastectomy RT)[9].

Correlated to this knowledge, our case presented herein yielded several adverse prognostic factors, including young age, multifocality, large tumor size and axillary LN metastases at the initial diagnosis of BC. The ER and PR status of our patient was highly positive, while the HER2 status was negative. She had received the adjuvant endocrine therapy for a total of 6 years, but developed unresectable tumor recurrence at 3 years after ending the tamoxifen therapy. The review published by Wimmer *et al*[10] validated the benefit of prolonged endocrine therapy beyond 5 years on recurrence-free and disease-free survival for patients with hormone receptor-positive BC, particularly when tamoxifen was followed by an aromatase inhibitor. The updated version of the American Society of Clinical Oncology clinical practice guideline in 2014 recommended a prolongation of adjuvant endocrine therapy with tamoxifen, from 5 years to 10 years, in pre- and perimenopausal patients; for those with postmenopausal status, after 5 years of adjuvant therapy, the tamoxifen should be switched to an aromatase inhibitor or the patient should continue on tamoxifen for another 5 years[11]. Consequently, our patient should be a candidate benefiting from extended adjuvant endocrine therapy of 10 years.

Unfortunately, the elongated treatment is associated with aggravated adverse effects, namely thromboembolic events, bone density loss and additional risk for endometrial cancer. Apart from the well-known risk factors for tumor recurrence like nodal-positive and large tumors, feasible predictive markers are required to evaluate patients who are most likely to benefit from protracted endocrine therapy. Sestak *et al*[12] pointed out the importance of identifying BC patients with high risk of late (distant) recurrence precisely by use of prognostic and predictive biomarkers or multi-gene signatures or liquid biopsies. The improved expertise of molecular markers will enable a planning of individualized therapies for patients[12].

Beyond that, the early and accurate detection of recurrent disease is of essential importance. In comparison to conventional imaging, such as sonography, mammography, CT, MRI and bone scintigraphy, ^{18}F-FDG PET/CT is more comprehensive and less time consuming. It has shown distinctly higher predictive values for determination of locoregional and systemic BC recurrence, and consequently has a higher impact on therapeutic management as well as prognostication of survival[13,14]. The maximum standardized uptake value (commonly referred to as the SUVmax) of ^{18}F-FDG PET/CT has been shown to serve incidentally as a useful predictor of postoperative relapse-free survival and overall survival in patients with luminal-type BC[15].

The patient in our case report had not received ^{18}F-FDG PET/CT at the beginning of clinical suspicion. As the diagnosis was confirmed at more than 1 year later, she already presented a locally advanced, unresectable locoregional recurrence with distant metastases. Leastways prior to PBT, she was referred to undergo ^{18}F-FDG

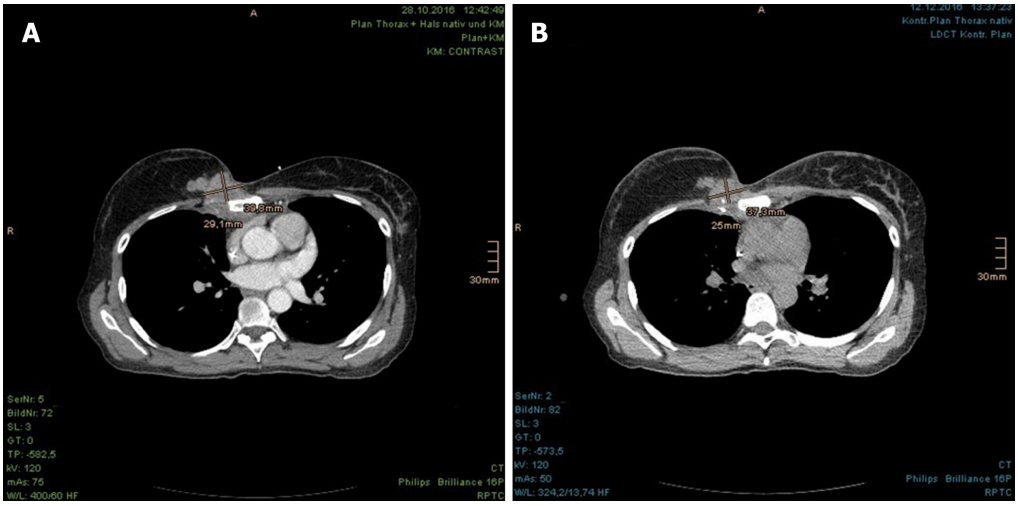

Figure 5 Incipient size reduction of chest wall recurrence (with size measurement) during the proton beam therapy. A: In planning computed tomography (CT) prior to proton beam therapy; B: In control CT at 26th fraction of treatment.

PET/CT to obtain a more precise localization of all cancerous manifestations. However, although the ^{18}F-FDG PET/CT was recommended by us (owing to the later noted right parasternal soft tissue augmentation), her supervising oncologist and referring BC institute did not regard it as necessary because of the observed stability in size from July to October 2018.

Concerning the management of locoregional BC recurrence, the treatment is not standardized and demands a multidisciplinary approach[1,16,17]. The German Society of Radiation Oncology updated the radiotherapeutic guidelines and considered RT (*e.g.*, external beam RT, brachytherapy, or intraoperative RT) as an essential part of multimodality treatment in addition to systemic therapy, surgery and hyperthermia[18]. However, it remarked that the largest experience on reirradiation was based on multi-catheter brachytherapy and that prospective clinical trials were required to define the selection criteria, long-term local control, and toxicity.

A multi-institutional review of repeat irradiation of breast and CW for locally recurrent BC (median dose of the first and second course of RT being 60 Gy and 48 Gy) found the overall complete response rate to be 57%; strictly speaking, the rates were 67% and 39% with and without concurrent hyperthermia, respectively. The 1-yr local disease-free survival rate for patients with gross disease was 53%, while the rate for those short of gross disease reached 100%[19]. In another study of radiation-naive patients with isolated locoregionally recurrent BC after mastectomy, the presence of residual gross disease at the time of RT was recognized as the most crucial prognostic factor for any outcome, as well. Even a 10% dose escalation (54 Gy to complete CW and regional lymphatics, and 12 Gy boost to CW flap and any other recurrent sites) did not exhibit any remarkable improvements in locoregional control and survival[20].

Siglin *et al*[21] reviewed the literature on reirradiation for locally recurrent BC, which had been demonstrated as feasible for its toxicity and response rates. Nonetheless, the increased risk of toxicity in repeat CW radiation with cumulative dose of ≥ 100 Gynamely, skin ulceration, lymphedema, brachial plexopathy, soft-tissue and bone necrosis, rib fracture, pneumonitis and cardiomyopathynecessitates this procedure to be undertaken with caution. In our case report, the patient received a cumulative dose from partial CW treatments ranging from 106 Gy to 124.40 Gy. The dose burden of OAR in the second course of our treatment with PBT is listed in Table 1. Even though there was an interval of 10 years between both courses of RT, the recovery and tolerance of our patient's OAR remained varied and unreliable.

In general, the acutely reacting tissues (skin, mucosa, lung) are deemed to repair radiation damage within a few months and can tolerate a repeat RT. On the other hand, late responding organs (brain, heart and kidney) do show none or limited long-term recovery[22,23]. Applying to the patient herein, the acute and late toxicities of skin, esophagus, brachial plexus and lungs were largely moderate but a radiation-induced pericardial disease became relevant at 19 mo after the PBT. This is known as one of the most common and earliest variants of radiation-induced cardiovascular disease, beside coronary heart disease, cardiomyopathy, valvular dysfunction and conduction abnormalities, and appears if a significant portion of heart volume sustains a critical radiation dose.

According to the data from the Quantitative Analysis of Normal Tissue Effects in

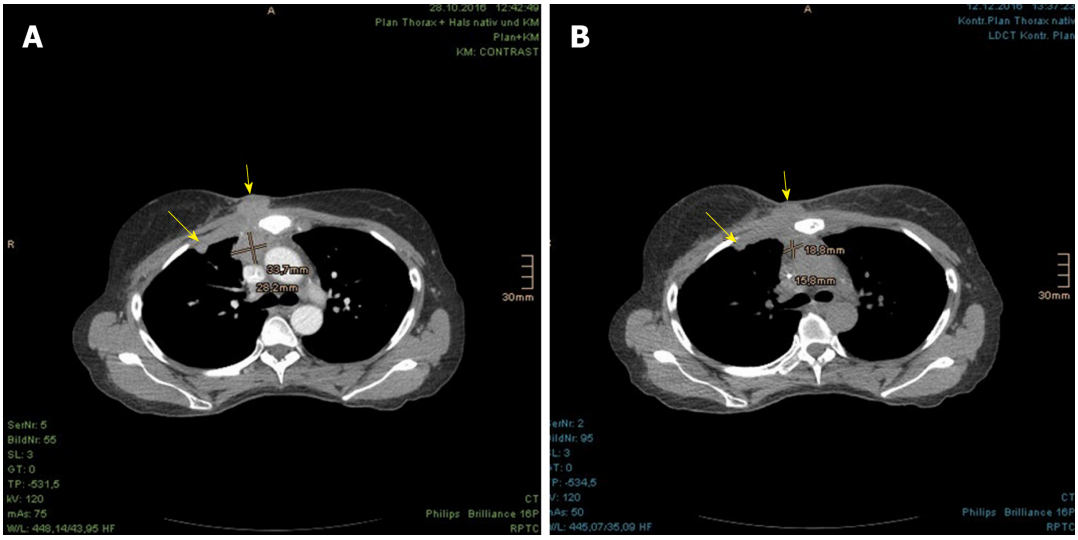

Figure 6 Incipient size reduction of right parasternal metastasis (with size measurement) as well as chest wall recurrence and pleural metastasis (both marked with arrows) during the proton beam therapy. A: In planning computed tomography (CT) prior to proton beam therapy; B: In control CT at 26th fraction of treatment.

the Clinic (referred to as QUANTEC) effort, the likelihood of pericarditis is less than 15% in compliance with the following dose constraints: mean heart dose < 26 Gy and V30 < 46 %. The mean heart dose of our patient treated with PBT was 13.06 Gy, and the heart volume receiving ≥ 30 Gy was 20% (Figure 11). Even if both the QUANTEC recommended heart dose restrictions were not exceeded, a limited recovery of the heart from the former RT would be expected. Furthermore, the consequence of previous and present systemic therapies, particularly those with established cardiotoxic side effects such as anthracyclines and trastuzumab, should also be taken into account. Indeed, a retrospective cohort study found comparable risk of cardiac ischemia and stroke among the tamoxifen-only and aromatase inhibitor-only users but detected, unexpectedly, an association between the sole and sequential use of an aromatase inhibitor and increased risk of other cardiac events (*i.e.*, heart failure, cardiomyopathy, dysrhythmia, valvular disease and pericarditis)[24].

Since publication of the supposed proportionally growing rate of ischemic heart disease at the mean dose to the heart by 7.4% per gray[25], clinicians have been appealed to contemplate cardiac dose and risk factors in choosing the appropriate RT technique for BC patients. PBT evidently offers a refinement of cardiopulmonary events in comparison to conventional RT with photon and electron beams. The treatment planning comparison studies have verified the dosimetric advantage in use of PBT for locally advanced and left-sided BC, with respect to homogeneous target volume coverage and reduction of radiation dose exposure to surrounding uninvolved tissue, in favor of decreasing the cardiopulmonary toxicities and radiation-induced second malignancies[26,27].

Although most of the clinical experience has been based on passive scattering and uniform scanning technique, pencil beam scanningused on our patientfacilitates a faster treatment delivery with a single irradiation field and certain degree of skin sparing[28]. However, both PBT and conventional RT are confronted with inter- and intrafraction uncertainty due to breath and heart motions and set-up inconstancy. Techniques like deep inspiration breath-hold and respiratory gating were developed to reduce the position variability of target and OAR[29]. In a recent comparative treatment planning study on the use of deep inspiration breath-hold technique for Hodgkin's lymphoma patients, plans with intensity modulated proton therapy showed superior results in decrease of all dose/volume parameters of the OAR compared to those with intensity modulated RT in the form of volumetric modulated arc therapy[30].

Still, in our experience of practical implementation, these techniques postulate training and compliance of patients beforehand, as well as compatibility between respiratory control devices and PBT facilities and consistent beam delivery to abbreviate the breath-hold time and daily treatment duration. Mostly, the latter remains challenging for larger centers, which need to share the beam among several gantries.

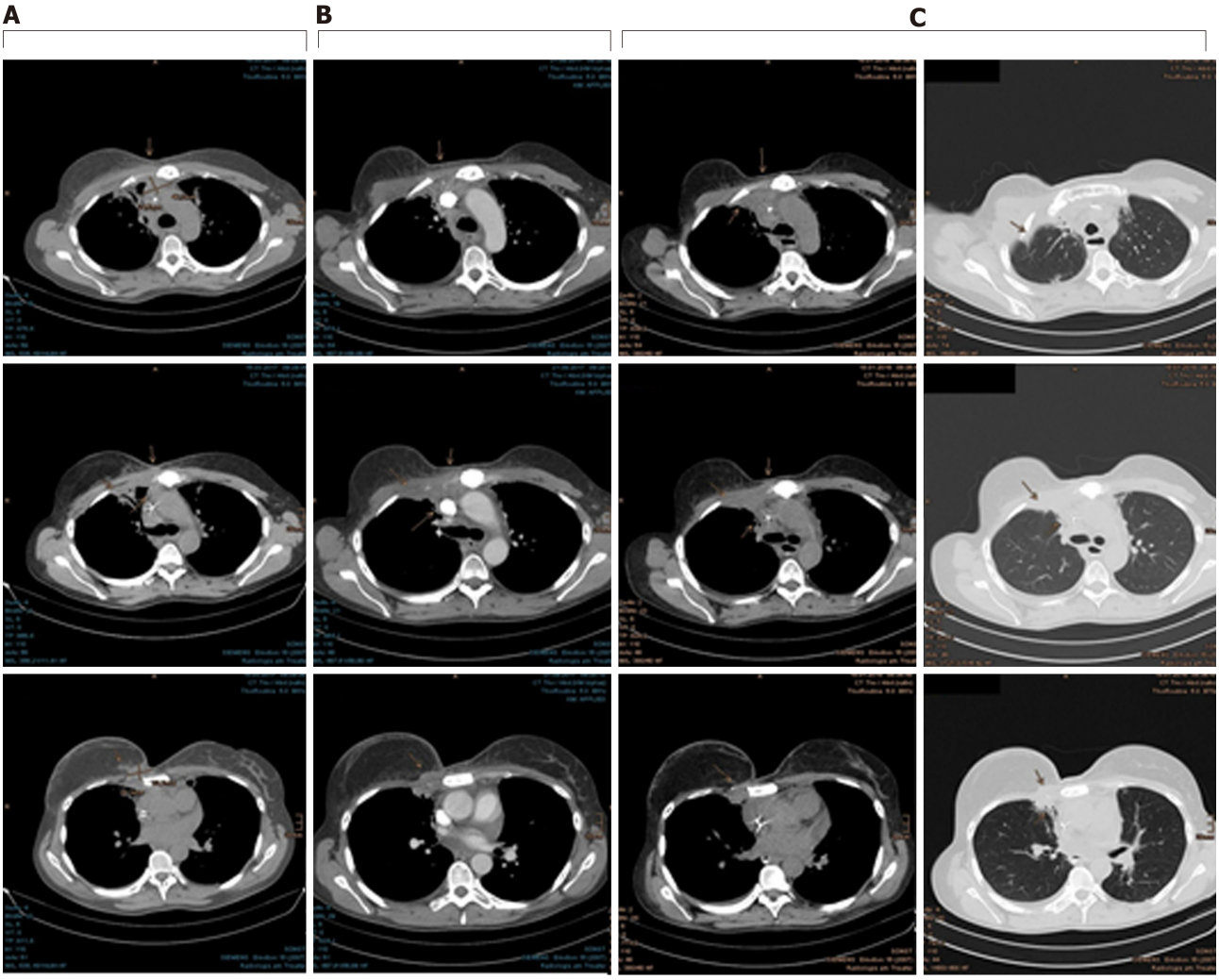

Figure 7 Continuous shrinkage of the chest wall recurrence, right pleural metastases and parasternal lymph node metastases, which are marked with arrows. A: Follow-up computed tomography (CT) at 3 mo after proton beam therapy; B: Follow-up CT at 9 mo after proton beam therapy; C: Follow-up CT at 13 mo after proton beam therapy.

CONCLUSION

This case report demonstrates that even patients with locally advanced recurrent BC can benefit from a local treatment with PBT. Apart from later arising pericardial and pleural effusions that were successfully treated by drainage and corticosteroid, the acute toxicities as well as the locoregional control, progression-free survival, cosmetic result and quality of life at 2 years after PBT are satisfactory and encouraging. Since gross residual disease despite prior surgery and systemic therapy represents an essential factor for locoregional control and survival outcome, further comprehensive investigations into the simultaneous use of radiosensitizers, such as hyperthermia, with PBT become compelling above all.

EXPERIENCES AND LESSONS

The patient demonstrates acceptable acute and late side effects after a dose-escalated reirradiation of a vast tumor recurrence, followed by a progression-free survival of 2 years since the treatment. Although a radiation-induced pericardial disease occurred at 19 mo, it was successfully treated by drainage and corticosteroid. PBT serves as a safe and effective therapy for locoregionally recurrent BC and improves the outcome of gross tumor disease significantly.

Table 1 Dose of organs at risk in the second course radiation therapy with proton beam therapy

Organ at risk	Minimum dose, Gy	Maximum dose, Gy	Mean dose, Gy
Spinal cord	0	1.37	0.06
Right brachial plexus	0.20	61.57	43.70
Heart	0	65.56	13.06
Left lung	0	65.60	7.38
Right lung	0	67.55	14.79
Esophagus	0	58.04	22.89

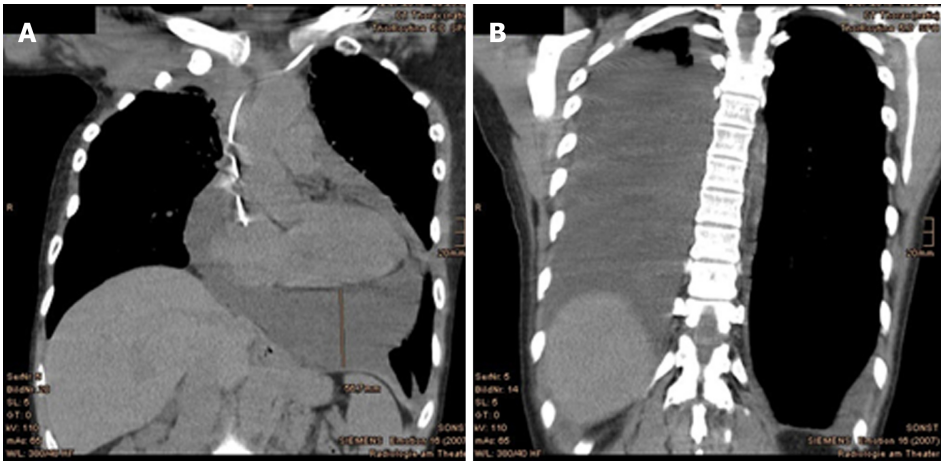

Figure 8 Relevant pericardial and pleural effusions emerged at 19 mo after proton beam therapy. A: Pericardial effusion; B: Pleural effusion in the coronal plane.

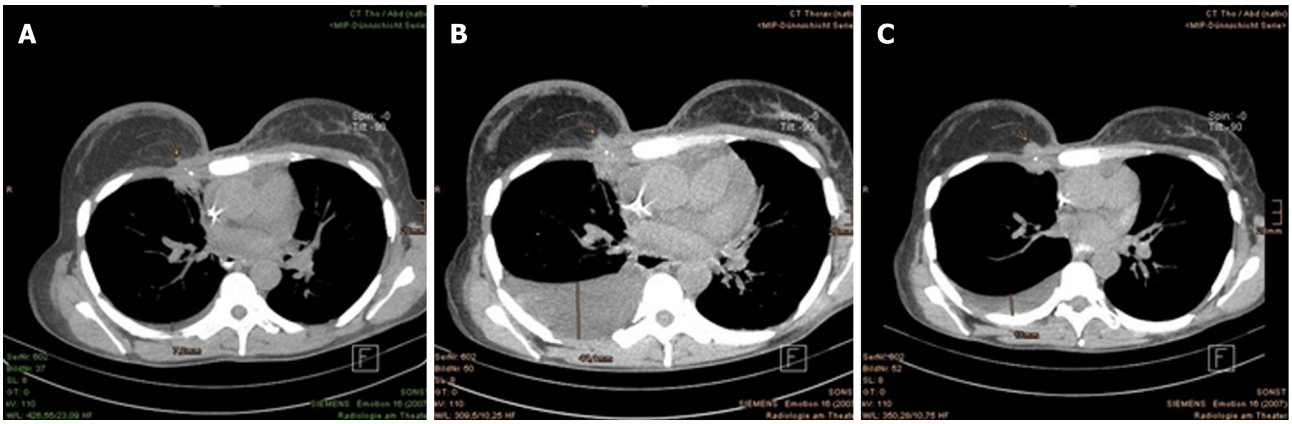

Figure 9 A soft tissue augmentation occurred in the right parasternal area at 19 mo after proton beam therapy. A: Continuously reduced chest wall recurrence at 13 mo after proton beam therapy; B: Discreet augmentation of right parasternal soft tissue and significant pleural effusion on the right at 19 mo after proton beam therapy; C: Consistent size of right parasternal soft tissue and decrease of pleural effusion at 22 mo after proton beam therapy. The tumor is marked with arrows.

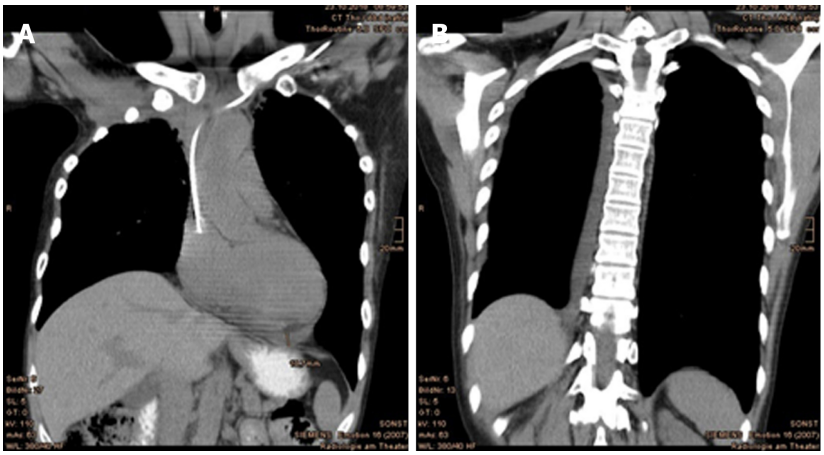

Figure 10 Follow-up computed tomography at 22 mo after proton beam therapy showed significantly improved findings of (A) pleural effusions and (B) pericardial effusions.

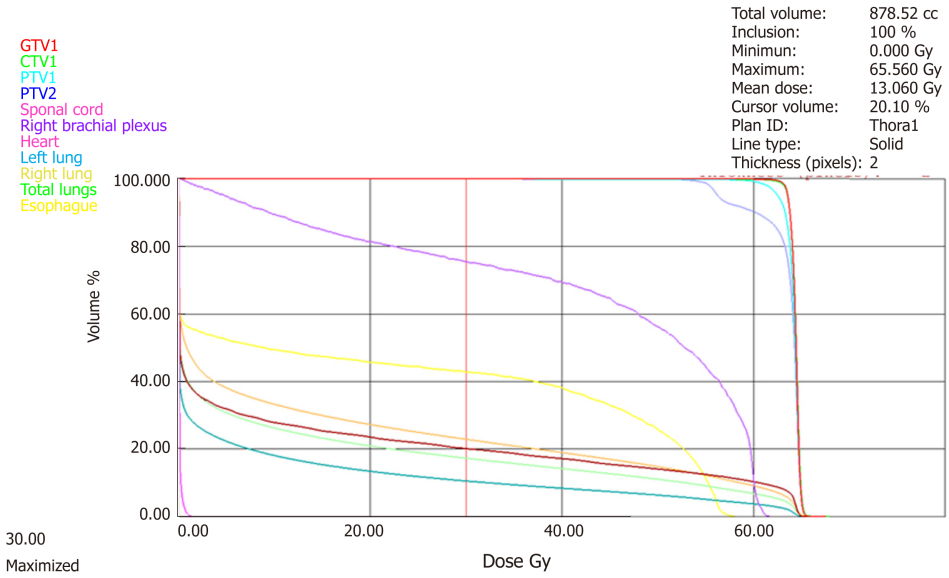

Figure 11 Dose-volume-histogram of the target volumes and organs at risk.

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CASE REPORT

Breast metastasis from primary lung adenocarcinoma in a young woman: A case report and literature review

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Author contributions: Enrico D performed study design, review, writing, and analysis and interpretation of data, figures, tables, and statistics; Saucedo S and Bravo I contributed to cytological, histopathological, immunohistochemical and molecular analyses.

Informed consent statement: The patient provided informed written consent prior to the case review.

Conflict-of-interest statement: The authors reported no proprietary or commercial interest in any product mentioned or discussed in this article.

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Abstract

BACKGROUND

Breast metastasis from extra mammary malignancies is rare. An incidence of 0.2%-1.3% has been reported in the literature, including that from different types of malignant neoplasms.

CASE SUMMARY

We present a case of a 29-year-old nonsmoking woman with breast metastasis from lung adenocarcinoma. Computed tomography revealed atelectasis in the right middle lobe of the lung and ipsilateral pleural effusion. Additionally, on physical examination, a small mass was noted in her right breast. The patient underwent bronchoscopy, needle thoracentesis, and breast biopsy. Following cytology, histology and immunohistochemistry, primary lung adenocarcinoma with metastasis to the breast was diagnosed. Only 63 cases, including our patient, have been reported in the literature since 2000, and this is the second in a woman under 30 years of age.

CONCLUSION

This atypical presentation may cause a significant diagnostic dilemma, but the contribution of immunohistochemistry is crucial to the accuracy of the final diagnosis.

Key words: Lung cancer; Breast metastasis; Immunohistochemistry; Lymphatic spreading; Case report

Core tip: We present the second case of lung adenocarcinoma with metastasis to the breast in a patient under 30 years of age. This is a rare entity in oncology and even more

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so in this age group. There have only been 63 reported cases of breast metastasis from lung adenocarcinoma over the last eighteen years. A clear correlation between the side of primary lung cancer and the side of breast metastasis can be identified. Due to the infrequency of this phenomenon, the diagnosis may cause a significant dilemma. Nevertheless, immunohistochemistry plays a key role in the final diagnosis.

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INTRODUCTION

Primary breast cancer is the most common malignancy in adult females. However, metastatic involvement of the breast is a rare phenomenon, with a reported frequency of approximately 0.2%-1.3%[1]. A variety of neoplasms have been reported to metastasize to the breast, including malignant melanoma, lymphoma, lung, ovary, prostate, kidney, stomach, ileum, thyroid, and cervical cancer[2]. Despite its rarity, metastatic breast disease from lung adenocarcinoma poses a significant diagnostic dilemma.

Lung cancer is the leading cause of cancer death, with one of the highest incidences. However, to date, there have been a few published cases of lung adenocarcinoma metastasizing to the breast. We report the case of a patient with breast metastasis from primary lung adenocarcinoma. To the best of our knowledge, this is the second report of this entity in a woman under 30 years of age.

CASE PRESENTATION

Chief complaints and history of illness

A 29-year-old nonsmoking nurse presented with a 3-wk history of dry cough to the Eva Perón General Hospital, San Martín (Buenos Aires), Argentina.

Imaging examinations and physical examination

Routine chest X-ray followed by computed tomography (CT) revealed atelectasis in the right middle lobe of the lung, ipsilateral pleural effusion, and enlarged lymph nodes in the mediastinum and right hilum (Figure 1). On physical examination, a small mass was noted in the upper outer field quadrant of her right breast. Axillary and cervical chain lymph nodes were not palpable. Mammography did not reveal any suspicious images. However, ultrasonography (US) satisfactorily showed a hypoechoic solid nodule (11.6 mm x 6.6 mm x 8.9 mm) in the right breast, which was biopsied with a trucut needle (Figure 2).

The patient underwent bronchoscopy, which revealed submucosal infiltration causing a about 50% obstruction of the right middle lobe bronchus. During the bronchial procedure, washing, brushing and biopsies were obtained. Furthermore, needle thoracentesis was performed.

Based on all this information, the main differential diagnoses considered were a primary breast tumor with lung and pleural metastasis or two synchronous primary tumors.

Cytological findings

All the cytological specimens (pleural effusion, bronchial washing, and bronchial brushing) were stained using the Papanicolaou technique, and the diagnosis of adenocarcinoma was suggested.

Histopathological and immunohistochemical findings

Hematoxylin-eosin (HE) staining and immunohistochemistry (IHC) were performed on formalin-fixed paraffin embedded tissues from bronchoscopy biopsy and core-needle breast biopsy. On both biopsies (bronchial mucosa and breast), HE-stained paraffin sections revealed infiltration by adenocarcinoma (Figure 3). Additionally, no evidence of in situ carcinoma was observed on the breast specimen. IHC (performed

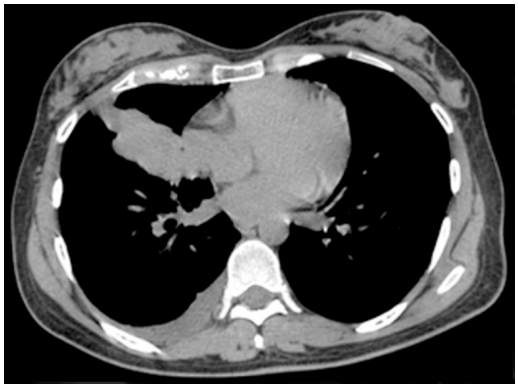

Figure 1 Chest computed tomography scan. Atelectasis in the right middle lobe of the lung, ipsilateral pleural effusion, and enlarged lymph nodes in the mediastinum and right hilum.

on a BenchMark XT autostainer, Ventana Medical Systems Inc, Tucson, AZ) of lung and breast specimens revealed strong immunoreactivity for anti-pancytokeratin AE1AE3, cytokeratin 7 (CK7), thyroid transcription factor-1 (TTF-1), and napsin A. The neoplastic cells lacked expression of cytokeratin 20 (CK20), P63, estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and GATA3 (Figure 3).

Molecular findings

Epidermal growth factor receptor mutations in exons 19 to 21 were negative (PCR-based pyrosequencing assay), as was EML4-ALK rearrangement by fluorescence *in situ* hybridization (FISH).

FINAL DIAGNOSIS

The histology and immunohistochemical staining pattern were strongly consistent with metastasis to the breast from primary lung adenocarcinoma.

TREATMENT

In February 2016, the patient was started on treatment with cisplatin and pemetrexed. After an initial response, she experienced lung progression, and docetaxel was used as a second-line therapy to achieve stable disease.

OUTCOME AND FOLLOW-UP

Due to the deterioration of her clinical conditions, a third-line therapy was not feasible, and she continued with palliative supportive care. Her overall survival was 20 mo.

DISCUSSION

Literature review

Since 2000, 63 cases of breast metastasis from a lung adenocarcinoma have been reported in the literature, including our patient (Table 1)[1,3-44]. The median age was 56 years (SD 13.4), and as expected, the majority were female (82.5%), while only 8 (12.7%) patients with breast metastasis were men.

Of the 43 patients with data about the side of disease, 35 (81.4%) had evidence of disease in both lung and breast on the same side, while 6 (14%) had contralateral and 3 (7%) had bilateral breast involvement. A statistical correlation was observed between the side of the primary lung cancer and the side of the breast metastasis ($P < 0.001$).

The distribution of immunohistochemical markers in the literature is shown in Figure 4. The most frequent markers analyzed were TTF-1, CK7, CK20, napsin A, ER, PR, HER2, GCDFP-15, mammaglobin, and GATA3. There were six cases with negative TTF-1, three with negative napsin A, and only one with negative CK7.

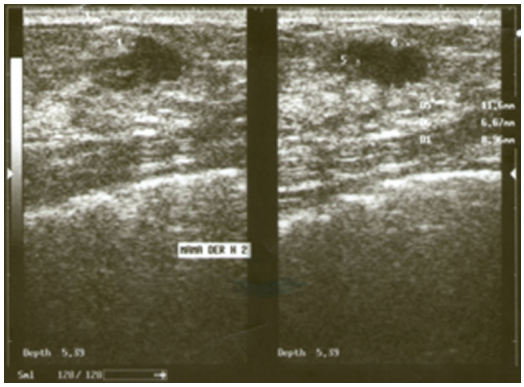

Figure 2 Right breast ultrasound. Hypoechoic solid nodule (11.6 mm x 6.6 mm x 8.9 mm).

Discussion

The most common sites of lung cancer metastasis are the bones, lungs, brain, adrenal glands, liver, and extrathoracic lymph nodes, in descending order[45]. However, autopsy series have revealed that lung cancer may metastasize to nearly any organ. Williams *et al*[46] published the most extensive series, which included 169 cases of metastases to the breast from extra mammary solid tumors and reported that the most common histological type was malignant melanoma.

Distinguishing a breast metastasis from a primary breast cancer, based on mammography, may be extremely difficult since metastasis can mimic a primary malignancy or even a benign lesion. The absence of micro calcifications is considered a characteristic of metastatic lesions to the breast, with the exception of ovarian cancer[47]. On mammography, usually single lesions are observed, but sometimes multiple well-circumscribed lesions may be present [13]. In our case, there were no mammographic findings, and the breast lesion was discovered by ultrasonography. Although most of the lesions do not show any specific histological features, some authors have described different characteristics of breast metastasis from extra mammary malignancies. These features include a circumscribed tumor with multiple satellite foci, the presence of many lymphatic emboli and the absence of an intraductal component, which is the most relevant characteristic[1].

As outlined above, the distinction between metastasis from lung adenocarcinoma and primary breast adenocarcinoma may cause a diagnostic dilemma. For this, the contribution of immunohistochemistry is crucial. There is no single marker with 100% sensitivity and specificity that can solve this problem, hence an immunohistochemical panel is needed. Both breast and lung adenocarcinomas have overlapping CK7+/CK20- immunoprofiles in most cases. The frequency of ER expression in lung adenocarcinoma has been reported to vary from 7.6% to 27.2%, depending on the antibody used[48]. TTF-1 is positive in 73%–88% of lung adenocarcinoma cases, and there are very few reports of its positivity in breast cancer (less than 3% at least weakly or focally)[49]. Napsin A staining has been reported to be positive in 80%-90% of lung adenocarcinoma cases. This marker is usually negative in breast cancer, even though it has been found to be positive in less than 3% of breast adenocarcinoma cases[50]. Although TTF-1 is a reliable marker for lung adenocarcinoma, napsin A is more sensitive and specific. The combination of both markers provides the maximum benefit. On the other hand, 67%-95% of breast cancer cases express GATA3 (43%–73% of triple-negative cases), and its expression in lung adenocarcinomas is less than 10%[51].

Our patient had metastasis to her right breast, which is the same side affected by the malignant pleural effusion, consistent with the hypothesis by Huang *et al*[25]. To this end, they considered a stepwise mechanism involving parietal pleural seeding, followed by invasion into chest wall lymphatic vessels draining to ipsilateral axillary lymph nodes and retrograde lymphatic spreading to the breast. This mechanism of breast metastasis could be supported by findings of enlarged homolateral axillary lymph nodes. Moreover, Barber *et al*[52] demonstrated lymphatic communication between the breast and mediastinal lymphatic channels. These hypotheses could be confirmed by the fact that almost 80% of the cases reported from 2000 to date had ipsilateral lesions. Another potential type of spread could be hematogenous. However, if lung cancer spreads through this route, both breasts should have the same probability of being affected. This is not reflected in the reviewed cases, where only 5.4% of patients had bilateral breast involvement. The last possible explanation could be direct tumor invasion through the chest wall to the breast, but chest CT scans

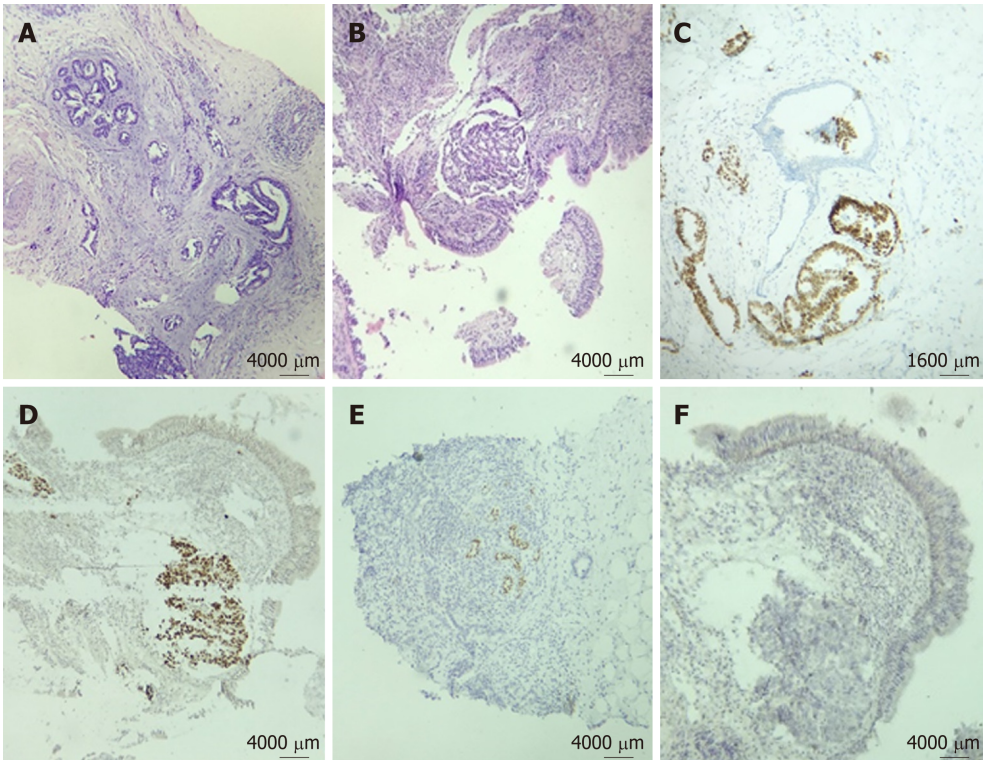

Figure 3 Breast biopsy showed adenocarcinoma infiltrating into the adjacent parenchyma. A: Ducts were not involved by the tumor, and no evidence of in situ carcinoma was obtained (x 40); B: Bronchoscopy biopsy (HE) showed poorly differentiated adenocarcinoma (x 40); C, D: Immunohistochemical staining for thyroid transcription factor-1 was positive on both breast (C) and lung specimens (D); E, F: GATA3 staining was negative in both breast (E) and lung tissue (F).

did not reveal this alteration in the reported cases. Therefore, lymphatic spreading might be the most reasonable mechanism of lung cancer dissemination to the breast.

CONCLUSION

Here, we present a rare case of synchronous isolated metastasis to the breast from lung adenocarcinoma in a young patient. This is the second report, together with that by Wang *et al*[14], in a woman under 30 years of age. Due to the infrequency of this phenomenon, the diagnosis may cause a significant dilemma. Clinical examination, radiological assessment, and pathological evaluation are essential. Nonetheless, in our opinion, immunohistochemistry makes a difference, playing a key role in the accuracy of the final diagnosis.

Table 1 Breast metastasis from primary lung adenocarcinoma: Literature review 2000-2018

Ref.	Sex/age	Lung cancer	Breast metastasis	IHC markers of breast biopsy
Lee *et al*[3], 2000 (2 cases)	NA/NA	NA	NA	NA
Masmoudi *et al*[4], 2003	Female/54	NA	NA	NA
Ramar *et al*[5], 2003	Male/56	Right	Right	CK7-; CK20-; CAM 5.2-; ER-; PR-; CDP-
Yeh *et al*[6], 2004	Female/44	NA	Right	NA
Komorowski *et al*[7], 2005	NA/48	NA	NA	NA
Gómez-Caro *et al*[8] , 2006	Male/65	Left	Left	CK4+; CK7+; TTF-1-
Lee[1] , 2007	Female/64	NA	NA	NA
Ucar *et al*[9], 2007	Male/63	Left	Left	CK7+; TTF-1-
Ho *et al*[10], 2007	Male/71	Right	Left	NA
Rimner *et al*[11], 2007	Female/81	Left	Left	TTF-1+; ER-; PR-; HER2-
Fulciniti *et al*[12], 2008	Female/59	Right	Right	TTF-1+; ER-; PR-
Klingen *et al*[13], 2009	Female/79	NA	Left	CK7+; TTF-1+
	Male/70	NA	Right	CK7+; TTF-1+
Wang *et al*[14], 2009	Female/26	Right	Bilateral	TTF-1+
Babu *et al*[15], 2009	Female/51	NA	Left	CK7+; TTF-1+; ER-; PR-
Maounis *et al*[16], 2010	Female/73	Left	Left	TTF-1+; SP-A+; CEA+; CD15+; ER-; GCDFP15-; Mammaglobin-; CK 5/6 -; Calretinin -; CA125-; Thyroglobulin -
Yoon *et al*[17], 2010	Female/42	Left	Left	TTF-1+; E-cadherin+; ER-; PR-; p53-; HER2-
Nasit *et al*[18] ,2011	Female/42	Right	Bilateral	TTF-1+; CK7+; CEA+; GCDFP15-; ER-, PR-; CK5/6-; Thyroglobulin-
Fukumoto *et al*[19], 2011	Female/65	Left	Left	TTF-1+; ER-
Li *et al*[20], 2011	Female/53	Left	Left	TTF-1+; ER-; PR-
Ko *et al*[21], 2012	Female/47	Right	Right	TTF-1+; ER-; PR-; Mammaglobin-
Branica *et al*[22], 2012	Female/55	Left	Left	TTF-1+; CK7+; CK20-
Sato *et al*[23], 2012	Female/57	Right	Right	TTF-1+; CK 7+; SP-A+; MUC1+; ER-; PR-; MUC2 -; CK20-; GCDFP15-; HER2-
Ji *et al*[24], 2012	Female/49	Right	Left	TTF-1+; ER-; PR-; HER2-; Mammaglobin-; GCDFP15-
	Female/40	Left	Right	TTF-1+; ER-; PR-; HER2-; Mammaglobin-; GCDFP15-
Huang *et al*[25], 2013	Female/70	Left	Left	TTF-1+; ER-; PR-; GCDFP15-
	Female/48	Right	Right	NA
	Female/43	Right	Right	NA
	Female/54	Left	Left	NA
	Female/52	Left	Left	NA
	Female/43	Left	Left	NA
Sanguinetti *et al*[26], 2013	Female/43	Left	Left	TTF-1+; SP-A+; ER-; GCDFP15-; Mammaglobin-
Liam *et al*[27], 2013	Female/70	Right	Right	TTF-1+; ER-; PR-; HER2-
Sousaris *et al*[28], 2013	Female/55	Left	Left	TTF-1+; Napsin A+ER-; PR-
Jeong *et al*[29], 2014	Female/47	Left	Left	TTF-1+; CK7+; Napsin A+; ER-; PR-; HER2-; GCDFP15-; ALK-
Mirrielees *et al*[30], 2014	Female/58	Left	Left	TTF-1+; ER+; PR-; HER2-
Hachisuka *et al*[31], 2014	Male/60	Left	Right	TTF-1-; Napsin A-; ER-; PR-; HER2-; SP-A-; GCDFP15-
Dansin *et al*[32], 2015	Female/52	Left	Left	TTF1+; ER-; PR-; HER2-; GATA3-; GCDFP15-; PAX8-
Venkatesulu *et al*[33], 2015	Female/30	Right	Right	TTF1+; ER-; PR-; HER2-

Shen *et al*[34], 2015	Female/52	Right	Right	TTF-1+; CK7+; Napsin A+; ER-; PR-; GCDFP15-; Mammaglobin-
Gao *et al*[35], 2016	Female/45	Right	Right	TTF-1+; CK7+; Napsin A+; ROS1+; ER-; PR-; GCDFP15-; Mammaglobin-; HER2-; P63-; CK 5/6-; GATA3-
	Female/43	Right	Right	TTF-1+; CK7+; Napsin A+; ALK+; ER-; PR-; GCDFP15-; Mammaglobin-; HER2-; P63-; CK 5/6-; GATA3-
Bhanu *et al*[36], 2016	Female/30	Right	Right	TTF-1+; GCDFP15-; Mammaglobin-
Erhamamci *et al*[37], 2016	Male/74	Right	Right	NA
Ninan *et al*[38], 2016	Female/67	Right	Right	CK7+; TTF-1+; Napsin A+; GCDFP15-; GATA3-
Ozturk *et al*[39], 2017	Male/63	Left	Left	TTF-1+; Napsin A+; Mucin +; P63-
Cserni[40], 2017	Female/60	Right	Left	CK7+; TTF-1+; Napsin A+; ER+; PR-; HER2-; GCDFP15-; Mammaglobin-; GATA3-; P63-
Zahedi *et al*[41], 2017	Female/45	Left	Right	CK7+; TTF-1+; Napsin A+; ER-; PR-; HER2-; GCDFP15-; CK20-; Mammaglobin-; Calretinin-; WT1-; CDX2-; Thyroglobulin-
Al-Zawi *et al*[42], 2017	Female/84	Left	Left	CK7+; TTF-1+; CK5-; P63-; ER-; PR-; GCDFP15 -; HER2-; ALK-
Ali *et al*[43], 2017	Female/64	NA	NA	TTF-1-; ER-; HER2-
	Female/70	NA	NA	TTF-1+; Napsin A+; ER+; HER2-
	Female/72	NA	NA	TTF-1+; Napsin A+; ER-; HER2-
	Female/59	NA	NA	TTF-1+; ER-; HER2-
	Female/63	NA	Bilateral	TTF-1+; Napsin A+; ER-; HER2-
	Female/45	NA	NA	TTF-1+; Napsin A-; ER-; HER2-
	Female/65	NA	NA	TTF-1+
	Female/70	NA	NA	ER-
	Female/69	NA	NA	TTF-1+; Napsin A+; ER-; HER2-
	Female/65	NA	NA	TTF-1-; ER-
	Female/64	NA	NA	TTF-1-; Napsin A-; ER-; HER2-
Ota *et al*[44], 2018	Female/69	Left	Left	CK7+; CK 20-; TTF-1+; Napsin A+; ER-; PR-; HER2-; GCDFP15-
Our case	Female/29	Right	Right	AE1AE3+; CK7+; TTF-1+; Napsin A+; P63-; CK20-; ER-; PR-; GATA3-; HER2-

IHC: Immunohistochemistry; NA: Not available; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epithelial growth factor receptor 2; TTF-1: Thyroid transcription factor 1; CK7: Cytokeratin 7; CK20: Cytokeratin 20; CK4: Cytokeratin-4; GCDFP15: Gross cystic disease fluid protein 15; SP-A: Surfactant A; CK5/6: Cytokeratin 5/6; MUC1: Mucin 1; MUC2: Mucin 2; ALK: Anaplastic lymphoma kinase; GATA3: GATA-binding protein 3; PAX8: Paired box gene 8; P63: Transformation-related protein 63.

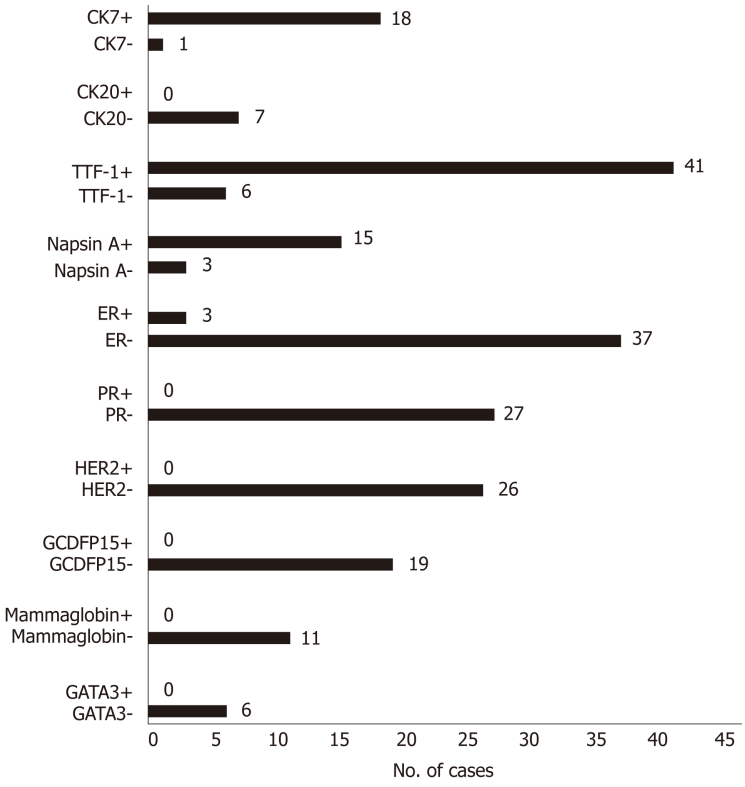

Figure 4 Distribution of immunohistochemical markers on the breast biopsies in the reviewed cases (including ours). ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epithelial growth factor receptor 2; TTF-1: Thyroid transcription factor 1; CK7: Cytokeratin 7; CK20: Cytokeratin 20; GCDFP15: Gross cystic disease fluid protein 15; GATA3: GATA-binding protein 3.

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