Cureus
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Open Access Case Report

Conflicting Testicular Histopathology Preceding the Diagnosis of Metastatic Male Breast Cancer: A Case Report

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Review began 10/28/2026
Review ended 11/14/2026
Published 11/17/2026

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DOI: 10.7759/cureus.119815

Abstract

Male breast cancer is a rare disease that may present with atypical clinical features. We report a case in which testicular abnormalities preceded the diagnosis of malignancy, with no primary tumor initially identified. Histopathological examination following orchiectomy was initially interpreted as showing neoplastic emboli within the lymphatic vessels of the testicular coverings, without evidence of tumor infiltration in the testicular parenchyma. However, a subsequent histopathological review did not confirm malignancy. During the initial diagnostic workup, CT also revealed a 12 mm right breast nodule that was not considered radiologically suspicious and was not investigated further. Approximately three years later, right-sided breast cancer with lung and bone metastases was diagnosed. Systemic treatment with a CDK4/6 inhibitor (ribociclib) in combination with letrozole resulted in tumor regression, followed by disease stabilization. At the reported follow-up, the patient was receiving his 27th cycle of ribociclib-based therapy, and CT demonstrated stable disease. This case report highlights the diagnostic challenges associated with atypical presentations of male breast cancer and emphasizes the importance of a broad differential approach in cases with inconclusive histopathological findings.

Categories: Urology, Pathology, Oncology
Keywords: case report, computed tomography, conflicting histopathology, immunohistochemistry, male breast cancer, neoplastic emboli, rare presentation, ribociclib, suspected testicular involvement, tunica vaginalis

Introduction

Male breast cancer is a rare clinical entity. It accounts for approximately 0.6%-1% of all breast cancer cases and about 0.3% of all newly diagnosed malignancies in men [1]. Between 2013 and 2022, an average of 19,400 new breast cancer cases were registered annually in Poland, of which 99.2% (approximately 19,250) occurred in women [2]. Current Polish experience regarding male breast cancer is limited mainly to individual case series and clinicopathological analyses. Male breast cancer most commonly presents as a painless, unilateral breast mass, typically located in the retroareolar region. Other clinical manifestations may include nipple retraction, skin changes, or nipple discharge. Invasive carcinoma of no special type (NST) is the predominant histological subtype. In advanced disease, distant metastases commonly involve the bones, lungs, and liver [3,4].

Metastatic tumors to the testes are also rare, most commonly originating from prostate cancer [5]. Metastases of breast cancer to the testes are exceptionally rare and have been described only sporadically in the literature. Such an unusual site of suspected metastatic involvement may pose a diagnostic challenge, particularly when histopathological findings are inconclusive. We report a case in which abnormalities involving the testicular coverings, initially interpreted as suspicious for malignancy but not confirmed on subsequent histopathological review, preceded the diagnosis of metastatic male breast cancer by approximately three years.

Verbal informed consent for the publication of this case report was obtained from the patient, as confirmed by the treating physician. No directly identifying patient information has been included in the manuscript.

Case Presentation

The patient was a 51-year-old male who underwent left-sided orchiectomy at a regional hospital due to testicular enlargement (Day 0). According to the available medical records, no breast-related complaints were documented at the time of the initial presentation. His medical history included diabetes mellitus and a history of tobacco smoking (10 pack-years), with no previous diagnosis of malignancy. His family history was notable for gastric cancer in his maternal uncles. The initial histopathological examination revealed a hematoma within the left testis, without evidence of malignancy in the testicular parenchyma. However, neoplastic emboli were reported in small lymphatic vessels, predominantly within the testicular coverings (tunica vaginalis). Further diagnostic investigations were therefore recommended to identify the primary tumor.

How to cite this article
Gajek A, Solka K, Wiraszka R, et al. (November 17, 2026) Conflicting Testicular Histopathology Preceding the Diagnosis of Metastatic Male Breast Cancer: A Case Report. Cureus 18(11): e119815. DOI 10.7759/cureus.119815

The diagnostic workup included gastroscopy, colonoscopy, and contrast-enhanced CT of the chest, abdomen, and pelvis, performed on Day 49. CT revealed a 12 mm nodule in the right breast, which was not considered radiologically suspicious, and a 5 mm nodule in segment 3 of the right lung. The right breast nodule identified on the initial CT examination is shown in Figure *1A*. Additional findings included thickening of the urinary bladder wall up to 13 mm, predominantly involving the right posterosuperior wall, with adjacent hyperdense strands and nodules measuring up to 4 mm. A 4 mm lesion was also identified in hepatic segment 4a; its nature could not be determined because of its small size. Immunohistochemical examination of the initially identified cells demonstrated CK7 positivity, CK20 negativity, and PSA negativity.

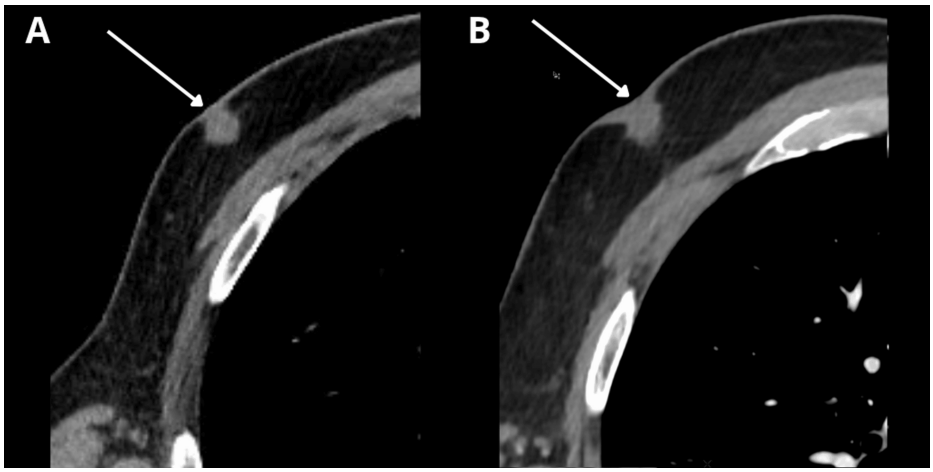


FIGURE 1: CT findings of the right breast in 2021 and 2024

(A) Cropped image from the non-contrast series of the CT examination performed on Day 49 (September 20, 2021), showing a 12 mm nodule in the right breast (arrow). (B) Cropped contrast-enhanced CT image obtained on Day 1101, showing a right retroareolar breast mass measuring 24 × 21 mm (arrow), subsequently confirmed as invasive breast carcinoma by core needle biopsy. The panels are presented at different magnifications

CT: computed tomography

A subsequent histopathological review, completed on Day 51, identified atrophic changes without evidence of neoplastic infiltration. Immunohistochemical staining demonstrated expression of calretinin, WT1, and vimentin, with Ki-67 positivity in isolated cells. These findings were interpreted as residual mesothelial cells within the inflamed and fibrotic tunica vaginalis. The second histopathological opinion, which found no evidence of malignancy, was considered sufficient by the treating surgeon to discontinue further diagnostic investigations. Despite the previously identified 12 mm right breast nodule on CT, no further evaluation of this finding or continued oncological follow-up was documented at that time. The last documented surgical consultation at our center during the initial diagnostic period took place on Day 63. The patient was subsequently seen by the same surgeon on Day 1099.

On Day 1101, the patient underwent further diagnostic evaluation because of deterioration in his clinical condition. CT demonstrated a retroareolar tumor in the right breast measuring 24 × 21 mm, approximately twice the size of the lesion previously identified, together with a cluster of pathological right axillary lymph nodes measuring 34 × 20 mm. The examination also revealed thrombi in the pulmonary artery supplying segment 5 of the right lung, with peripheral opacities consistent with pulmonary infarction. Multiple nodular lesions suggestive of metastases were present in both lungs, along with a destructive metastatic lesion involving the right sixth rib. Pulmonary embolism was diagnosed based on CT angiography. The right breast mass identified on the subsequent CT examination is shown in Figure *1B*.

Mammography revealed a spiculated retroareolar lesion in the right breast, associated with nipple retraction and classified as BI-RADS 5. A second lesion, measuring 17 mm, was identified at the margin of the examination field in the upper quadrant of the right breast and classified as BI-RADS 4C [6,7].

On Day 1124, biopsies of the breast tumor and axillary lymph nodes were performed. Histopathological examination of the breast tumor confirmed invasive breast carcinoma. Immunohistochemical analysis demonstrated estrogen receptor expression in 95% of tumor cell nuclei (Allred score: PS 5, IS 3), progesterone receptor expression in 70% (Allred score: PS 5, IS 3), HER2 expression of 1+, and a Ki-67 proliferation index of 12%.

Following the diagnosis of pulmonary embolism, anticoagulant therapy with subcutaneous enoxaparin

sodium at a dose of 1 mg/kg (100 mg) twice daily was initiated on Day 1106. After 14 days, enoxaparin was continued once daily. Cardiological treatment included metoprolol 25 mg once daily and perindopril 5 mg once daily. Bone scintigraphy performed approximately one month later confirmed metastatic involvement of the right sixth and left eighth ribs. On Day 1150, after 44 days of enoxaparin therapy, anticoagulant treatment was changed to oral rivaroxaban 20 mg once daily.

On Day 1159, systemic treatment with ribociclib was initiated in combination with letrozole. At that time, the patient's Eastern Cooperative Oncology Group (ECOG) performance status was 1, and baseline electrocardiography showed a corrected QT (QTc) interval within normal limits, fulfilling the eligibility criterion for ribociclib therapy. Systemic therapy was initiated 58 days after the diagnosis of pulmonary embolism. In accordance with cardiology recommendations, an approximately one-month waiting period was observed, during which disease restaging was performed. The pulmonary embolism did not alter the choice of anticancer regimen, and anticoagulation was continued concurrently with systemic treatment for approximately six months. Ribociclib was administered for 21 consecutive days followed by a seven-day treatment interruption in each 28-day cycle. Letrozole was administered continuously at a dose of 2.5 mg daily. Treatment response was evaluated on serial CT examinations according to the RECIST 1.1 criteria, as required by the national drug program.

Approximately three months after the initiation of systemic therapy, follow-up CT demonstrated regression of the right breast tumor from 24 × 21 mm to 12 × 12 mm. The thickness of the overlying skin decreased from 4.5 mm to 3 mm. Regression of thrombi in the pulmonary artery supplying segment 5 of the right lung was also observed, with only residual changes remaining. Although the overall number of pulmonary lesions was unchanged, some had decreased in size. Subsequent CT performed approximately five months after treatment initiation confirmed further regression of pulmonary lesions, including a reduction from 8 mm to 6 mm in segment 3 of the left lung and from 8 mm to 5 mm in segment 4 of the right lung. The primary breast lesion remained stable.

Further imaging assessments performed approximately eight and 11 months after treatment initiation demonstrated continued regression of pulmonary metastases, with the largest residual lesions measuring 4 mm. At that stage of follow-up, the patient was receiving his 13th cycle of ribociclib, with a sustained favorable response to treatment. Brain magnetic resonance imaging performed approximately 12 months after treatment initiation revealed no evidence of central nervous system metastases. Serum CA 15-3 concentrations were monitored throughout systemic therapy (Figure *2*). Before treatment initiation, on Day 1155, the CA 15-3 level was 202.0 U/mL; it peaked at 219.9 U/mL on Day 1190, approximately one month after the start of ribociclib and letrozole. Thereafter, the marker declined markedly to 98.41 U/mL on Day 1246 and 54.42 U/mL on Day 1365, and subsequently remained stable, fluctuating between 41.3 and 59.46 U/mL. The most recent measurement, on Day 1869, was 42.2 U/mL.

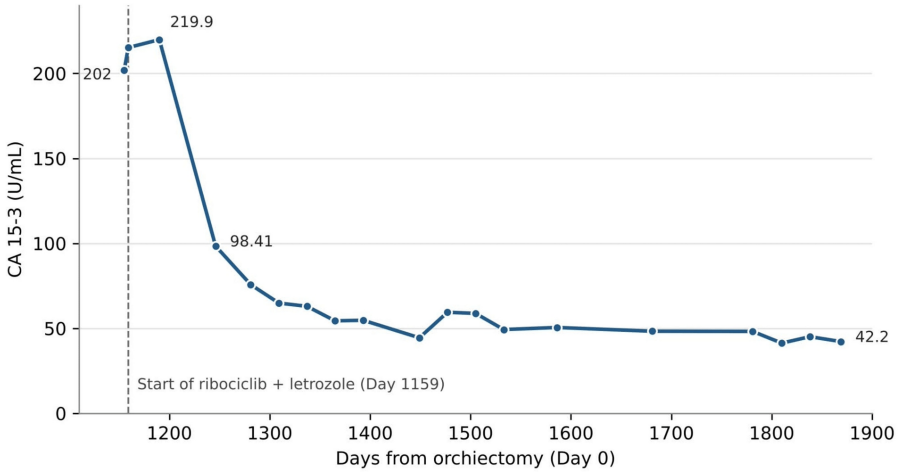


FIGURE 2: Changes in serum CA 15-3 levels during systemic therapy

Serial serum CA 15-3 measurements (U/mL) from Day 1155 to Day 1869, showing a marked decline following the initiation of ribociclib and letrozole, followed by stabilization. The dashed vertical line indicates the initiation of systemic therapy on Day 1159. Time is expressed in days from orchiectomy (Day 0)

On Day 1877, follow-up CT of the chest, abdomen, and pelvis demonstrated stable disease (SD). At the follow-up visit on Day 1894, the patient was receiving his 27th cycle of ribociclib-based therapy. Throughout the treatment period, ribociclib-based therapy was well tolerated, and the patient's ECOG performance status remained 1, with no treatment interruptions or dose modifications documented in the medical

records. No laboratory abnormalities requiring dose adjustment according to the summary of product characteristics were observed. A chronological summary of the clinical course is presented in Table 1.

Time point	Event	Key findings and management
Day 0	Left-sided orchiectomy at a regional hospital due to testicular enlargement	Hematoma within the left testis, without malignancy in the testicular parenchyma. Initial histopathological assessment reported neoplastic emboli in small lymphatic vessels, predominantly within the tunica vaginalis. Further diagnostic investigations were recommended
Day 49	Contrast-enhanced CT of the chest, abdomen, and pelvis (workup also included gastroscopy and colonoscopy)	12 mm right breast nodule, not considered radiologically suspicious; 5 mm nodule in segment 3 of the right lung; urinary bladder wall thickening up to 13 mm; 4 mm indeterminate lesion in hepatic segment 4a. IHC of the initially identified cells: CK7-positive, CK20-negative, PSA-negative
Day 51	Second histopathological opinion	Atrophic changes without neoplastic infiltration; calretinin, WT1, and vimentin expression; Ki-67 in isolated cells. Interpreted as mesothelial cell remnants in an inflamed, fibrotic tunica vaginalis. Diagnostics discontinued; no oncological follow-up
Day 63	Surgical consultation	Last documented surgical consultation during the initial diagnostic period
Day 1099	Surgical consultation	The patient was seen again by the same surgeon, approximately three years after the initial diagnostic workup
Day 1101	Further diagnostic evaluation due to clinical deterioration; CT and CT angiography	Retroareolar right breast tumor 24 × 21 mm; right axillary lymph nodes 34 × 20 mm; multiple bilateral pulmonary metastases; destructive lesion of the right 6th rib; pulmonary embolism with infarction (segment 5, right lung). Metoprolol and perindopril started. Enoxaparin 1 mg/kg (100 mg) s.c. twice daily from Day 1106, once daily after 14 days
Before Day 1124	Mammography	Spiculated retroareolar lesion, BI-RADS 5; second 17 mm lesion in the upper quadrant of the right breast, BI-RADS 4C
Day 1124	Core needle biopsy of the breast tumor and axillary lymph nodes; diagnosis of breast cancer	Invasive breast carcinoma: ER 95% (Allred PS 5, IS 3), PR 70% (Allred PS 5, IS 3), HER2 1+, Ki-67 12%
Approx. 1 month after PE diagnosis	Bone scintigraphy	Metastases in the right 6th and left 8th ribs. On Day 1150, anticoagulation was switched to rivaroxaban 20 mg once daily
Day 1159	Initiation of systemic therapy	Ribociclib (21 days on, 7 days off, 28-day cycles) with letrozole 2.5 mg daily; anticoagulation continued for a total of approx. 6 months
Approx. 3 months after treatment initiation	Follow-up CT	Breast tumor regression from 24 × 21 mm to 12 × 12 mm; skin thickness from 4.5 mm to 3 mm; regression of pulmonary artery thrombi; some pulmonary lesions smaller
Approx. 5 months after treatment initiation	Follow-up CT	Further regression of pulmonary lesions (left lung segment 3: 8 to 6 mm; right lung segment 4: 8 to 5 mm); breast lesion stable
Approx. 8 and 11 months after treatment initiation	Follow-up imaging	Continued regression of pulmonary metastases, with the largest residual lesions measuring 4 mm. The patient was receiving his 13th cycle of ribociclib at the later assessment
Approx. 12 months after treatment	Brain MRI	No central nervous system metastases

initiation		
Day 1877	CT of the chest, abdomen, and pelvis	Stable disease (RECIST 1.1)
Day 1894	Follow-up visit	Ongoing 27th cycle of ribociclib-based therapy; treatment well tolerated, without documented interruptions or dose modifications

TABLE 1: Timeline of the clinical course from orchiectomy to the most recent follow-up

Day 0 corresponds to the date of orchiectomy (August 2, 2021)

CT: computed tomography; IHC: immunohistochemistry; BI-RADS: Breast Imaging Reporting and Data System; PE: pulmonary embolism; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; MRI: magnetic resonance imaging; RECIST: Response Evaluation Criteria in Solid Tumors; s.c.: subcutaneous

Discussion

Male breast cancer remains a rare clinical entity, which translates into a limited amount of data regarding its clinical course, particularly in atypical presentations [3,4]. Only a limited number of clinicopathological analyses concerning this group of patients are also available in the Polish literature [8].

The most unusual element was the initial suspicion of malignancy involving the testicular coverings. Metastatic tumors to the testes are rare and most commonly originate from prostate cancer, and less frequently from other internal organ malignancies [9]. The initial report of neoplastic emboli in the lymphatic vessels of the tunica vaginalis, despite the absence of malignancy in the testicular parenchyma, contrasted with the subsequent histopathological review, which identified reactive mesothelial cells within the inflamed and fibrotic testicular coverings rather than neoplastic infiltration. The conflicting histopathological interpretations complicated the diagnostic assessment, particularly given the additional abnormalities identified during the initial diagnostic workup. In such circumstances, an additional review at a reference pathology center may be considered when the initial suspicion of malignancy is not confirmed by subsequent examination. No further histopathological consultation at a reference center was undertaken, and the original tissue specimens are no longer available for re-evaluation. Consequently, the discrepancy between the two histopathological interpretations cannot be resolved retrospectively.

It was only the clinical progression after approximately three years and the development of generalized neoplastic disease that allowed for the diagnosis of breast cancer. It is worth noting that a breast lesion was already present on the initial CT examination; however, in the radiologist's opinion, its characteristics did not raise oncological concern. This finding illustrates the diagnostic challenges associated with atypical presentations of male breast cancer, particularly when an initially detected lesion is not considered radiologically suspicious [4].

The immunohistochemical profile initially reported in the testicular coverings (CK7-positive, CK20-negative, PSA negative) may be compatible with several epithelial malignancies, including breast carcinoma, but is not specific for the primary site. Since the second histopathological assessment did not confirm malignant infiltration, metastatic involvement of the testicular coverings could not be established conclusively.

The available literature describes isolated cases of breast cancer metastases to the testes, most commonly in the advanced stages of the disease; however, presentation as a lesion preceding the diagnosis of the primary focus is exceptional [5]. To the best of our knowledge, no analogous cases involving male breast cancer have been reported in the Polish literature; only isolated reports of testicular metastases originating from other primary malignancies, mainly prostate cancer, have been published [10].

In the analyzed case, multiple distant metastases were identified, involving the lungs and the skeletal system, as well as a complication in the form of pulmonary embolism. Despite the advanced stage of the disease, systemic treatment with ribociclib and letrozole was associated with regression of the breast lesion and pulmonary metastases, followed by stable disease on subsequent imaging. Treatment response was assessed according to RECIST 1.1 criteria, as required by the national drug program. The use of CDK4/6 inhibitors in men with advanced hormone receptor-positive, HER2-negative breast cancer is supported by ASCO guidelines [11], while evidence for the efficacy of ribociclib combined with letrozole comes primarily from clinical trials involving women [12].

This case report emphasizes the need for careful diagnostic evaluation when histopathological findings are inconclusive and highlights the relevance of considering unusual sites of suspected metastatic involvement. Although it remains uncertain whether further investigations at the initial presentation would have led to an earlier diagnosis, the previously identified breast lesion illustrates the potential value of continued

evaluation of unexplained findings.

Furthermore, this report indicates that male breast cancer can remain minimally symptomatic for a long period, and its diagnosis may only occur once generalized disease has developed. Therefore, maintaining oncological vigilance is crucial, even when presented with atypical clinical symptoms.

Conclusions

Male breast cancer may present with atypical clinical features, which can complicate timely diagnosis. The described case illustrates the diagnostic challenges associated with testicular abnormalities preceding the diagnosis of breast cancer. Although metastatic involvement of the testicular coverings was initially suspected, it could not be confirmed because of conflicting histopathological findings. Such cases highlight the importance of further diagnostic evaluation when findings remain inconclusive, particularly in the presence of additional abnormalities requiring investigation; in such situations, an independent review of the histopathological material at a reference pathology center should be considered. Despite the advanced stage of the disease, systemic treatment with ribociclib and letrozole was well tolerated and was associated with tumor regression and a marked decline in serum CA 15-3 concentrations, followed by sustained radiological disease stability.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Aleksandra Gajek, Robert Wiraszka, Karolina Solka, Iwona Drab-Mazur

Drafting of the manuscript: Aleksandra Gajek, Karolina Solka

Concept and design: Robert Wiraszka

Critical review of the manuscript for important intellectual content: Robert Wiraszka, Iwona Drab-Mazur

Supervision: Robert Wiraszka

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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