


CASE REPORT

Breast metastasis from EGFR-mutated lung adenocarcinoma: A case report and review of the literature

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Key Clinical Message

Although lung cancer rarely metastasizes to the breast, we report a case of breast metastasis from lung adenocarcinoma harboring an epidermal growth factor receptor mutation. This breast metastasis was initially considered recurrent breast cancer and was later diagnosed based on histopathological and molecular examinations as metastasis from lung cancer.

KEYWORDS

breast metastasis, EGFR mutation, lung adenocarcinoma

1 | INTRODUCTION

Metastases to the breast from extramammary neoplasms are extremely rare, with an incidence ranging from 0.2% to 2.7% among reported clinical cases.^{1,2} In addition to leukemia and lymphoma, primary tumors that commonly metastasize to the breast include melanoma, rhabdomyosarcoma, and lung cancer.³ The scarcity of breast metastasis may be explained by the poor blood supply of the large amount of fibrous tissue in the breast⁴ or hormone status.⁵ Moreover, breast metastasis from lung cancer is highly unusual. In addition, it can be difficult to distinguish a metastasis from primary breast cancer when lung cancer histology indicates adenocarcinoma, and such metastases can be misinterpreted as triple-negative breast cancer. We report a case of metastases to the breast from lung adenocarcinoma. Immunohistochemical and genetic methods enabled differentiation of metastatic disease from primary breast carcinoma.

2 | CASE REPORT

A 69-year-old woman with no history of smoking underwent a lower lobectomy and lingular subsegmentectomy for an abnormal mass in her left lung in March 2013. Based on epidermal growth factor receptor (EGFR) mutational analysis, the lung specimen retrieved at surgery was identified as adenocarcinoma with an L858R mutation in Exon 21 of the EGFR gene. The cancer stage was determined to be pT2aN1M1, pStage IV. Gefitinib (250 mg/d) was initiated soon after surgery. Although treatment was effective, she discontinued therapy in August 2013 due to her financial situation and stopped coming for follow-up. The patient developed difficulties in breathing in March 2014 and again visited our department in April 2014. Chest X-ray showed pleural effusion in the left lung field that was confirmed to be malignant pleural effusion by cytology. Gefitinib was restarted. At this time, we noticed redness of the left breast, although the skin lesion gradually disappeared after reinitiation

Takayo Ota and Yoshikazu Hasegawa are contributed equally to this work.

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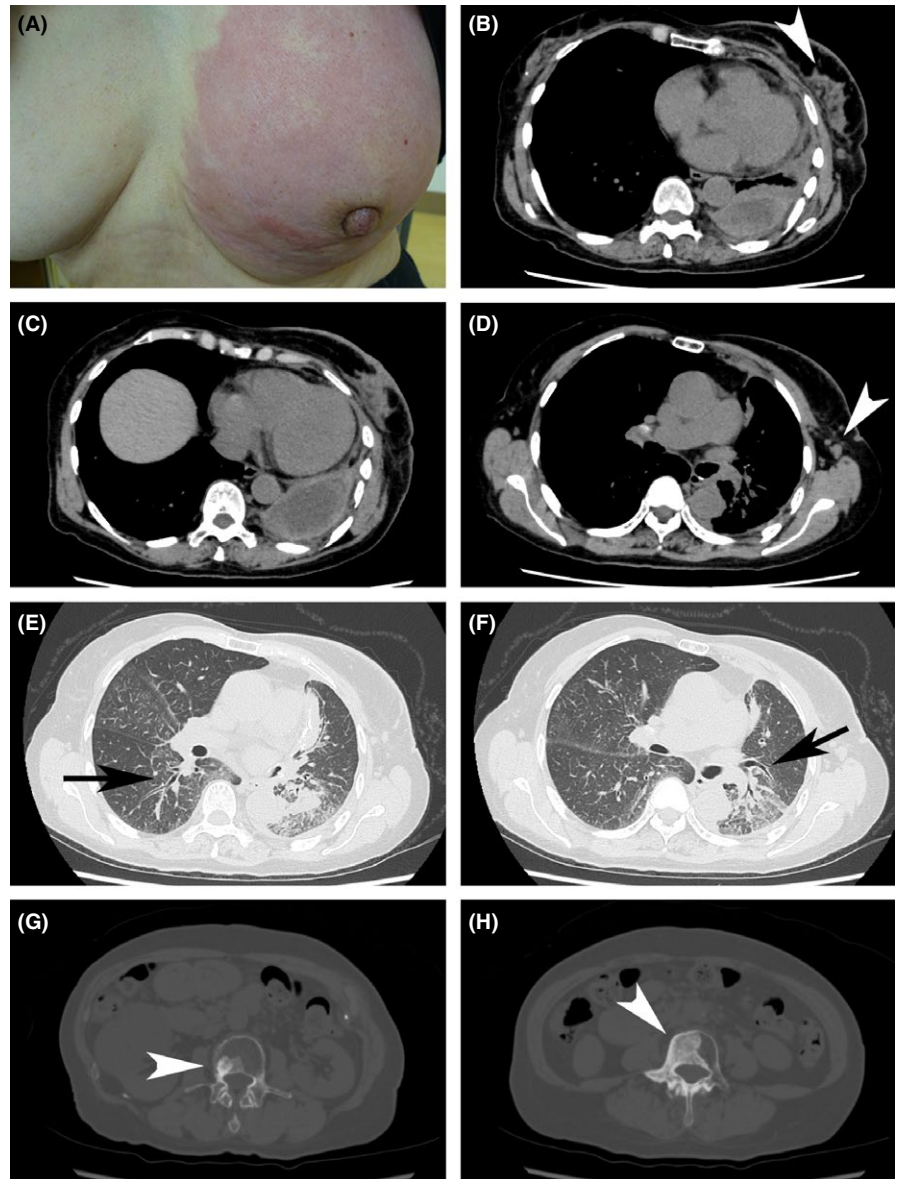


FIGURE 1 A, Left breast showing diffuse erythema swelling. B-D, CT image obtained with mediastinal window settings. B, Irregular mass and satellite nodules (white arrowhead). B and C, Pleural effusion/thickening. D, Axillary lymph nodes (white arrowhead). E and F, CT images obtained with mediastinal window settings showing thickened bronchovascular bundles, indicating lung cancer aggravation (arrows). G and H, CT images obtained with bone settings showing multiple bone metastases (white arrowheads)

of gefitinib. The patient had a past medical history of breast cancer, undergoing partial mastectomy of her left breast without adjuvant chemotherapy 15 years ago.

In January 2015, the patient again presented with redness of the left breast (Figure 1A), reporting that she had felt pain in the lower part of the left breast since December 2014. Physical examination revealed tenderness of the entire left breast, which was red with thickened skin. On appearance, it resembled inflammatory breast cancer. A core needle biopsy was performed on the breast, and the biopsy specimen revealed estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive ductal carcinoma (Figure 2). The patient was diagnosed with triple-negative breast cancer, which was presumed to be recurrent breast cancer. The pathological results from the mastectomy that was performed 15 years prior at another hospital were not available at the time of triple-negative breast cancer

diagnosis. As gefitinib had been effective in reducing the breast redness, we considered that the breast cancer harbored an EGFR mutation.

Chest computed tomography (CT) showed irregular masses and satellite nodules in the left breast, thickened bronchovascular bundles, and multiple bone metastases (Figure 1B-H). Blood testing revealed increased levels of carcinoembryonic antigen (CEA; 23.23 ng/mL) and cancer antigen 15-3 (CA15-3; 33.8 U/mL). As a result, she was diagnosed with double cancers, that is, lung and breast cancers associated with multiple bone metastases. The lung cancer was resistant to gefitinib, and the breast cancer was inoperable. Chemotherapy effective for both cancers was chosen: Carboplatin (AUC 5) was administered on Day 1, paclitaxel (90 mg/m²) on Days 1 and 8, and bevacizumab (15 mg/kg) on Day 1, every 21 days. Although a partial response was observed for both the lung and breast cancers, the patient suffered

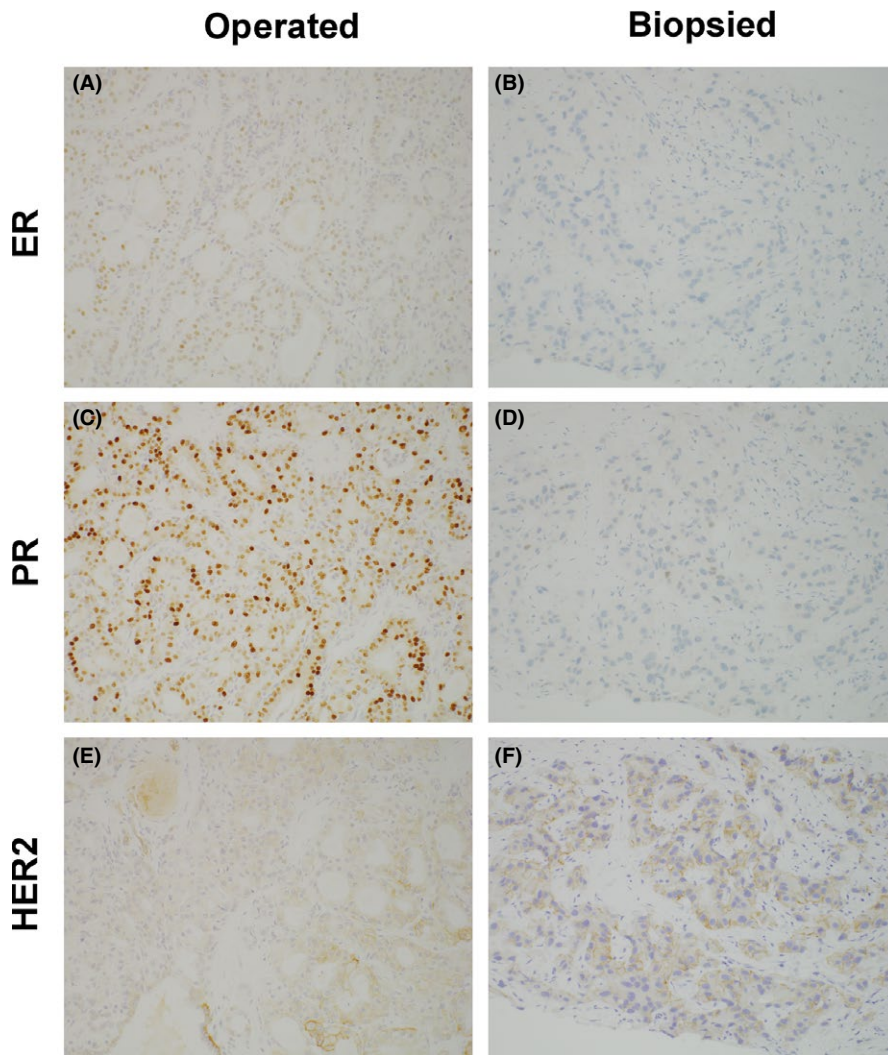


FIGURE 2 Expression of ER, PR, and HER2 in the breast cancer tissue from surgery and from core needle biopsy. (A, C, E) Breast cancer tissue from surgery ($\times 200$); (B, D, F) biopsied breast cancer tissue ($\times 200$). (A, B) ER, (B, E) PR, and (C, F) HER2. In the breast cancer tissue from surgery, ER was barely positive, PR was positive, and HER2 was 1+. In the breast cancer tissue from core needle biopsy, ER and PR were negative, and HER2 was 1+

from Grade 3 neuropathies. As a third-line therapy, carboplatin (AUC 5) was administered on Day 1, S-1 (80 mg/m² per day) on Days 1 through 14, and bevacizumab (15 mg/kg) on Day 1, every 21 days. Again, a partial response was found for both cancers; however, after two cycles, she began experiencing irrational behavior and impaired short-term memory. Magnetic resonance imaging (MRI) scan revealed carcinomatous meningitis. Although erlotinib (150 mg/d) was administered as a fourth-line therapy, her general condition gradually deteriorated, and she expired in September 2016.

After her death, we obtained breast cancer tissue specimens from the surgery performed 15 years ago at another hospital. We analyzed three specimens: breast cancer tissue from the previous surgery, lung cancer tissue from the surgery performed in 2013, and breast cancer tissue from the core biopsy performed in 2015. Although EGFR mutation was not identified in the breast cancer tissue from the previous surgery, the same EGFR mutation, namely L858R mutation in exon 21, was found in the breast cancer tissue obtained by core biopsy and in the surgically removed lung cancer

tissue. Immunohistochemical (IHC) analyses confirmed that the newly identified breast cancer was a metastasis from lung adenocarcinoma (Figures 2 and 3).

3 | DISCUSSION

Metastases to the breast from lung cancer are extremely rare. Indeed, only 43 cases were identified in literature from 1989 to 2013.⁶ Eighteen additional cases with detailed clinical information from 2013 to 2017 were identified in our literature search of the PubMed database (Table 1).⁷⁻²² Of these 18 cases, four involved male patients and 14 female patients, with ages ranging from 40 to 74 years (average, 56.5 years). Among the cases, including one in which adenocarcinoma transformed into small cell carcinoma following tyrosine kinase inhibitor treatment, 11 were adenocarcinomas and two small cell lung carcinomas.¹⁸

Metastases to the breast from extramammary neoplasms can spread via both hematologic and lymphatic routes.^{5,23} The former most commonly present as palpable,

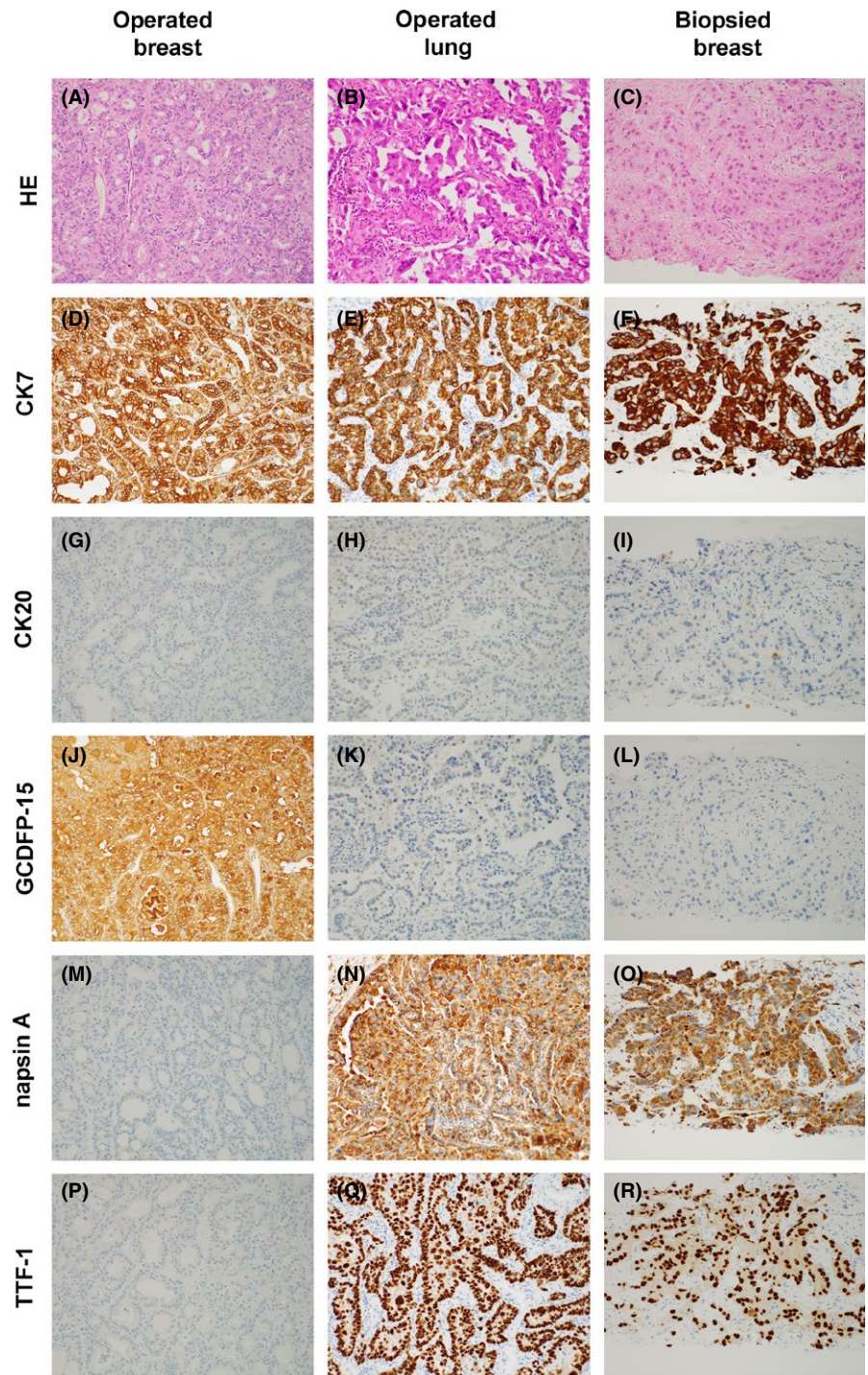


FIGURE 3 IHC analyses of the breast cancer tissue from surgery, lung cancer tissue from surgery, and breast cancer tissue from core needle biopsy. (A, D, G, J, M, P) Breast cancer tissue from surgery ($\times 200$); (B, E, H, K, N, Q); lung cancer tissue from surgery ($\times 200$); (C, F, I, L, O, R) breast cancer tissue from the core needle biopsy ($\times 200$). (A, B, C) HE, (D, E, G) CK7, (G, H, I) CK20, (J, K, L) GCDFP-15, (M, N, O) napsin A, and (P, Q, R) TTF-1. HE; hematoxylin and eosin. As shown in figure, the IHC staining pattern of the breast cancer tissue from core needle biopsy was the same that of the lung cancer tissue from surgery but was not the same as that of the breast cancer tissue from surgery

well-circumscribed painless solitary masses. The metastases are found in the upper outer quadrant and despite their superficial location, they do not exhibit skin or nipple retraction. In contrast, lymphatic metastases to the breast appear as reddening and swelling of the breast and are difficult to distinguish from primary inflammatory breast cancer; such metastases have been reported from gastric and ovarian carcinomas.⁵ As in the present case, lymphatic metastases to the breast can also originate from lung cancer, although they are uncommon.

Ipsilateral breast metastasis from lung adenocarcinoma might also occur via lymphatic routes. Huang et al²⁴ proposed that lung cancer cells may seed on the pleura, invade axillary lymph nodes, and metastasize to the ipsilateral breast through retrograde lymphatic vessels. Such patients present with ipsilateral pleural effusion/thickening, axillary lymph node enlargement, and ipsilateral breast metastasis. In the present case, we also detected pleural effusion and axillary lymph node enlargement on the same side as the breast metastasis (Figure 1B-D). Diffuse-type breast

TABLE 1 Clinical findings in patients with metastases to the breast from lung cancer

| Author | Year | Age | Sex | Primary lung cancer | Breast mets | Metachronous | Ipsilateral | Initial stage (lung) | EGFR mutation |
|----------------------------------|------|-----|--------|-------------------------|-------------|--------------|-------------|----------------------|---------------|
| Liam et al ⁷ | 2013 | 70 | Female | Adenocarcinoma | Nodule | Yes | Yes | IV | Positive |
| Sousaris et al ⁸ | 2013 | 55 | Female | Adenocarcinoma | Mass | Yes | Yes | IV | NA |
| Wang et al ⁹ | 2014 | 40 | Female | LCNEC | Mass | No | Yes | IV | NA |
| | | 49 | Female | Small | Mass | No | Yes | IV | NA |
| Jeong et al ¹⁰ | 2014 | 47 | Female | Adenocarcinoma | Nodule | Yes | No | IB | NA |
| Hachisuka et al ¹¹ | 2014 | 60 | Male | Adenocarcinoma | Mass | No | Yes | IV | NA |
| Bhattarai et al ¹² | 2015 | 48 | Male | Non-small | Mass | No | No | IV | NA |
| Dansin et al ¹³ | 2015 | 52 | Female | Adenocarcinoma | Mass | No | Yes | IV | Positive |
| Papa et al ¹⁴ | 2015 | 59 | Female | LCNEC | Nodule | No | Yes | IV | NA |
| Lee et al ¹⁵ | 2015 | 49 | Female | Non-small | Diffuse | Yes | Yes | IIIA | Positive |
| Shen et al ¹⁶ | 2015 | 52 | Female | Adenocarcinoma | Mass | No | Yes | IV | NA |
| Erhamamci et al ¹⁷ | 2016 | 74 | Male | Adenocarcinoma | Mass | No | Yes | IV | NA |
| Lin et al ¹⁸ | 2016 | 49 | Male | Adenocarcinoma to small | Mass | Yes | No | IV | Positive |
| Ninan et al ¹⁹ | 2016 | 67 | Female | Adenocarcinoma | Diffuse | Yes | Yes | IIIB | NA |
| Fujita et al ²⁰ | 2017 | 66 | Female | Pleomorphic carcinoma | Mass | No | No | IV | NA |
| Zagurovskaya et al ²¹ | 2017 | 51 | Female | NET | Mass | Yes | Yes | IIIA | NA |
| Cserni ²² | 2017 | 60 | Female | Adenocarcinoma | Mass | Yes | No | Not known | NA |
| Current case | | 69 | Female | Adenocarcinoma | Diffuse | Yes | Yes | IV | Positive |

LCNEC, large cell neuroendocrine carcinoma; NA, not assessed; NET, neuroendocrine tumor.

metastasis is always ipsilateral; however, as ipsilateral breast metastasis presents as a solid mass or a diffuse type (Table 1), lymphatic routes alone may not explain the laterality of metastases from lung cancer.

Differentiating between primary breast cancer and breast metastases is challenging, particularly when the metastases are identified as adenocarcinoma. Thus, histological examination and IHC analyses are important for distinguishing between metastases to the breast and primary breast carcinoma.^{1,25}

In the present case, we first diagnosed the patient with recurrent triple-negative breast cancer based on tissue morphology. Later, we compared the following three specimens using IHC methods: breast cancer tissue from the previous surgery, lung cancer tissue from surgery, and breast cancer tissue from a core needle biopsy. Analysis of cytokeratin (CK) 7 and CK20 expression has diagnostic value for determining the origin of metastatic lesions,²⁶ and in the present case, sections of all three tissues were CK7 + /CK20-, strongly indicating that all of the samples were either of breast or lung origin.²⁶ Although thyroid transcription factor-1 (TTF-1) is expressed in 68%-76% of lung adenocarcinomas, positivity in breast adenocarcinoma has never been reported.²⁷ Napsin A is expressed in 84% of primary lung adenocarcinomas but not in other types of adenocarcinoma.²⁸ In addition, gross cystic disease fluid protein-15 (GCDFP-15) is used as a marker for primary breast cancer; however, its expression is also observed in lung adenocarcinoma.²⁹ In our case, the biopsied breast cancer tissue was positive for napsin A and TTF-1 but not for GCDFP-15, suggesting that the biopsied breast cancer originated from the lung.

Estrogen receptor is expressed at very low levels in lung cancer.³⁰ Typical IHC findings for lung adenocarcinoma were obtained for the biopsied breast cancer tissue in the present case. Expression of both ER and PR confirmed that the biopsied breast cancer tissue was not recurrent primary breast cancer.

Epidermal growth factor receptor mutations in triple-negative breast cancer are inconsistently reported. Four studies have reported that approximately 3%-11% of triple-negative tumors harbor EGFR mutations,^{31,32} whereas other studies have found no activating EGFR mutations in triple-negative breast cancer patients.³³⁻³⁵ As discussed, variability in results might be due to the processing methods used or to geographic or ethnic differences. Also, we assessed EGFR mutations in patients with triple-negative breast cancer at our hospital (Data S1), and none of the nine tumor sections examined exhibited EGFR mutations within Exons 18-21. This observation strengthens the previous findings of a lack of EGFR mutations in triple-negative breast cancer.

In summary, we report a case of breast metastasis from lung adenocarcinoma that was mistakenly diagnosed as

triple-negative breast cancer. With respect to pathology, if histology indicates adenocarcinoma, it is difficult to distinguish between primary breast cancer and breast metastasis. Therefore, clinical history and IHC analyses are essential for definitive diagnosis. The fact that EGFR mutations are not frequent in triple-negative breast cancer may help in achieving a correct diagnosis.

4 | CONSENT

Because the case reported patient herself was unable to provide consent, her daughter provided written informed consent for publication of this case report and any accompanying images. A copy of the consent form has been made available for review by the Editor-in-Chief of this journal.

CONFLICT OF INTEREST

None declared.

AUTHORSHIP

TO: wrote the manuscript. YH, KS, TS, KY, RS, KS, and MF: involved in patient management. AO: provided pathological analysis of samples. All authors: provided editing and review of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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