International Journal of Surgery Case Reports 97 (2022) 107435

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

# A case of ALK-positive histiocytosis with multiple lesions in the unilateral breast: A case report

Arisa Kurita [a,b], Masayuki Yoshida [c], Takeshi Murata [a,*], Akihiko Yoshida [c], Nachiko Uchiyama [d], Shin Takayama [a]

[a] Department of Breast Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan
[b] Department of Surgery, School of Medicine, Keio University, Tokyo 160-8582, Japan
[c] Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo 104-0045, Japan
[d] Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo 104-0045, Japan

ARTICLE INFO

*Keywords:*
Case report
Diagnosis
ALK-positive histiocytosis
Breast
Multiple lesions
Non-epithelial

ABSTRACT

*Introduction and importance:* Primary ALK-positive histiocytosis of the breast is rare. Here, we report a case of ALK-positive histiocytosis with multiple unilateral breast lesions.

*Case presentation:* Our patient was a 38-year-old female with primary ALK-positive histiocytosis of the breast with multiple lesions. There were no lesions in other organs, and the patient was considered surgically resectable and underwent a left total mastectomy and sentinel lymph node biopsy. Histopathologically, there were at least three lesions in the left breast in upper inner quadrant (UIQ), upper quadrant (UQ), and upper outer quadrant (UOQ). All lesions showed spindle-shaped tumor cells that were positive for CD163 and ALK and negative for AE1/AE3. Fluorescence in situ hybridization (FISH) showed *ALK* and *KIF5B* rearrangements, suggesting the presence of the KIF5B-ALK fusion gene. In conclusion, this case was confirmed to be ALK-positive histiocytosis with multiple lesions in the unilateral breast. The patient underwent surgery and was discharged without complications.

*Clinical discussion:* Reports of ALK-positive histiocytosis are very rare, and reports of primary cases in the breast are even rarer. The basic treatment for ALK-positive histiocytosis is surgical resection; however, ALK inhibitors may be effective in unresectable or disseminated cases. Accurate diagnosis at the time of initial treatment is necessary to expand the treatment options.

*Conclusion:* This is the first case of ALK-positive histiocytosis with multiple lesions in the unilateral breast.

## 1. Introduction

ALK-positive histiocytosis is a disease characterized by abnormal proliferation of histiocytes with ALK-positive or *ALK* rearrangements [1], first reported in 2008 [2]. The basic treatment for this disease is surgical resection; however, ALK inhibitors may be effective in unresectable or disseminated cases, therefore more case reports and information about the disease are needed. The number of ALK-positive histiocytosis cases reported so far is very small, and the number of primary cases in the breast is limited to six, including this case. Most of these cases are of single lesion, and to our knowledge, our case is the first report of ALK-positive histiocytosis with multiple lesions in the breast. This case has been reported in line with the SCARE 2020 criteria [3].

## 2. Case presentation

A 38-year-old female underwent right oophorectomy, left ovarian cystectomy, and partial retinopexy for immature teratoma of the ovary. After the surgery, the patient underwent three courses of bleomycin, etoposide, and cisplatin (BEP) chemotherapy. Two years after the

*Abbreviations:* ADC, apparent diffusion coefficient; ALK, anaplastic lymphoma kinase; CNB, core needle biopsy; CT, computed tomography; DBT, digital breast tomosynthesis; ER, estrogen receptor; FISH, Fluorescence in situ hybridization; IMT, inflammatory myofibroblastic tumor; MRI, magnetic resonance imaging; NED, no evidence of disease; OQ, outer quadrant; PET-CT, positron emission tomography-computed tomography; PET-MRI, positron emission tomography-magnetic resonance imaging; PgR, progesterone receptor; RI, radioisotope; UIQ, upper inner quadrant; UOQ, upper outer quadrant; UQ, upper quadrant.

* Corresponding author at: Department of Breast Surgery, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo ku, Tokyo 104-0045, Japan.
*E-mail addresses:* masayosh@ncc.go.jp (M. Yoshida), tamurata@ncc.go.jp (T. Murata), akyoshid@ncc.go.jp (A. Yoshida), nuchiyam@ncc.go.jp (N. Uchiyama), stakayam@ncc.go.jp (S. Takayama).

https://doi.org/10.1016/j.ijscr.2022.107435
Received 27 May 2022; Received in revised form 17 July 2022; Accepted 17 July 2022
Available online 21 July 2022

surgery, a computed tomography (CT) scan showed undeniable rib metastasis, and an 18F-FDG positron emission tomography-computed tomography (PET-CT) scan was performed. The results showed multiple abnormal accumulations in the left breast. The patient was diagnosed with an ALK-positive inflammatory myofibroblastic tumor (IMT) by needle biopsy and was referred to our hospital as a rare cancer. The patient had no other relevant medical history. The patient's maternal grandfather had a history of colorectal cancer and paternal grandfather had a history of gastric cancer.

At the initial examination, the patient had no subjective symptoms and no palpable mass in breast. Digital breast tomosynthesis (DBT) was performed in addition to 2D mammography, and DBT slice images showed a 6 × 4 mm spiculated mass in the U/O region and a 17 × 13 mm focal asymmetric density in the M region near the nipple of the left breast (Fig. 1A–C). Ultrasonography showed a 27 mm isoechoic region at the 1 o'clock position in UOQ, and a 6 mm hypoechoic mass at the 2 o'clock position of the left breast (Fig. 1D–F). Whole-body 18F-FDG positron emission tomography-magnetic resonance imaging (PET-MRI) was performed, followed by breast PET and contrast-enhanced breast MRI. Contrast-enhanced breast MRI showed multiple progressively enlarged punctate contrast nodules in UIQ to UOQ of the left breast, measuring 5 × 2 cm (Fig. 1F–K). They showed a high signal on diffusion-weighted imaging and low signal on the ADC. Fusion of breast PET images and breast MRI contrast-enhanced early phase images showed abnormal accumulation in the same area (Fig. 1L–N). There were no findings suggestive of lymph node or distant lesions.

Histologically, a needle biopsy performed by a previous physician showed proliferation of spindle cells with constricted nuclei and amphoteric foam cytoplasm within the mammary tissue. Epithelioid cells were also found surrounding the mammary glands, Touton giant cells were scattered, and there was also bundle-like proliferation of elongated reactive spindle-shaped cells of myofibroblastic phenotype (SMA-positive). There was no atypia, mitosis, or necrosis of the tumor cells. Immunostaining showed that the tumor cells were positive for CD68 (PG-M1) and ALK, and negative for AE1/3, SMA, CD34, ER (estrogen receptor), PgR (progesterone receptor), S100, desmin, STAT6, and p63. Additional immunostaining at our hospital showed that the proliferating spindle cells were positive for the histiocyte marker CD163. These histiocytes were diffusely positive for ALK (Fig. 2B, C). Fluorescence in situ hybridization (FISH) assay showed rearrangements of the *ALK* and *KIF5B* genes, suggesting the presence of a *KIF5B-ALK* fusion gene. Based on these findings, we diagnosed this case as a primary

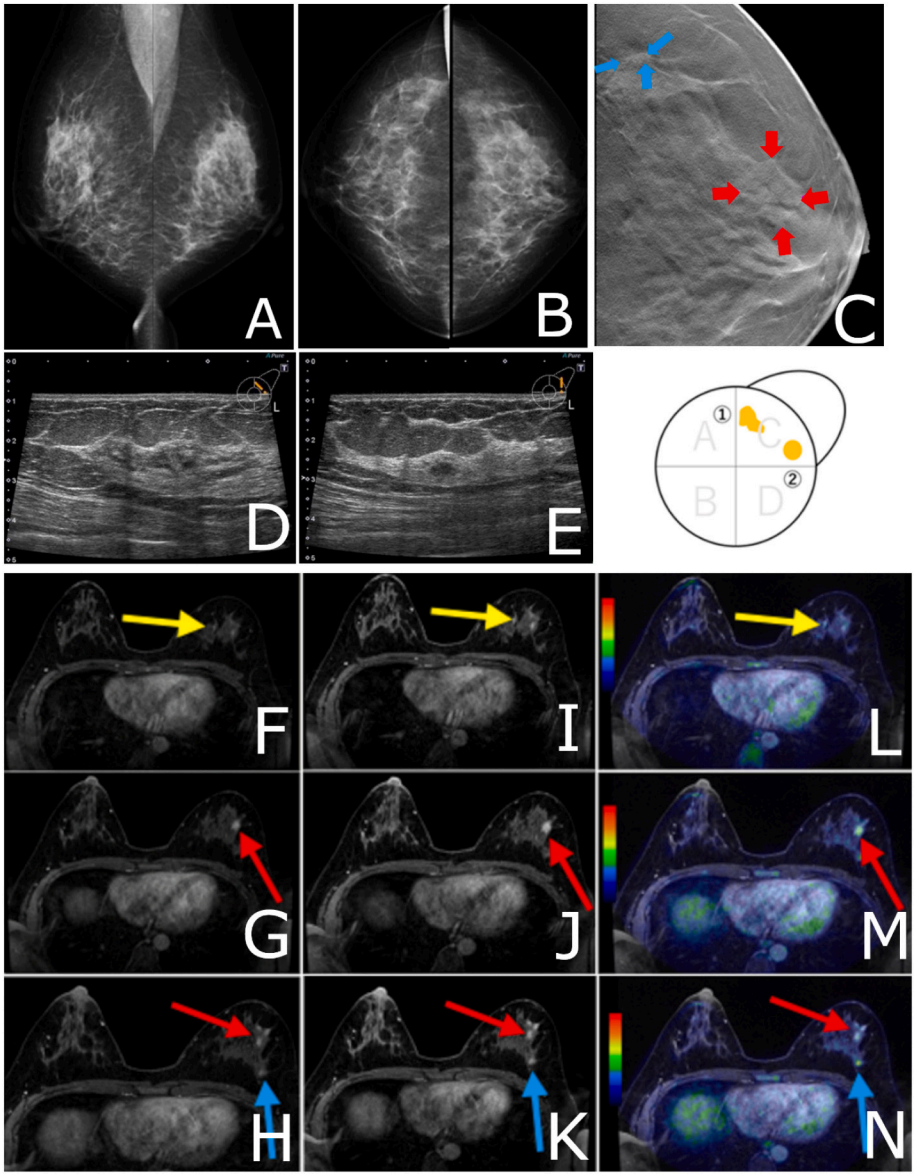


**Fig. 1.** Preoperative imaging
Mammography
Left: Digital breast tomosynthesis (DBT) showing a 6 × 4 mm spiculated mass in the U/O region (C-5) and focal asymmetric density in the M region near the nipple in the range of 17 × 13 mm.
Right: No abnormality (C-1), 2D-MLO view (A), 2D-CC view (B), DBT-CC view (C)
Mammary ultrasound
Left UOQ (at 1 o'clock), isoechoic region at approximately 5 cm NTD, 27 × 8 mm area, map-like to mottled, indistinct borders, some clear and slightly coarse. Mixed internal hyperechogenicity. Posterior echo-invariant blood flow signal (-) (D).
Left UOQ (at 2 o'clock), hypoechoic mass of 6 × 3 × 3 mm in size, approximately 5 cm NTD. Oval, borderline indistinct, posterior echo-invariant blood flow signal (−) (E).
Contrast-enhanced breast MRI and breast PET-MRI
Contrast-enhanced breast magnetic resonance imaging (MRI) showed multiple nodules and masses with progressive contrast enhancement in UIQ to UOQ of the left breast and abnormal accumulation in the same area on breast positron emission tomography (PET)-MRI fusion images. There was no suspicion of a lymph node lesion (early phase, F-H; delay phase, I-K; and PET-MRI fusion images, L-N).

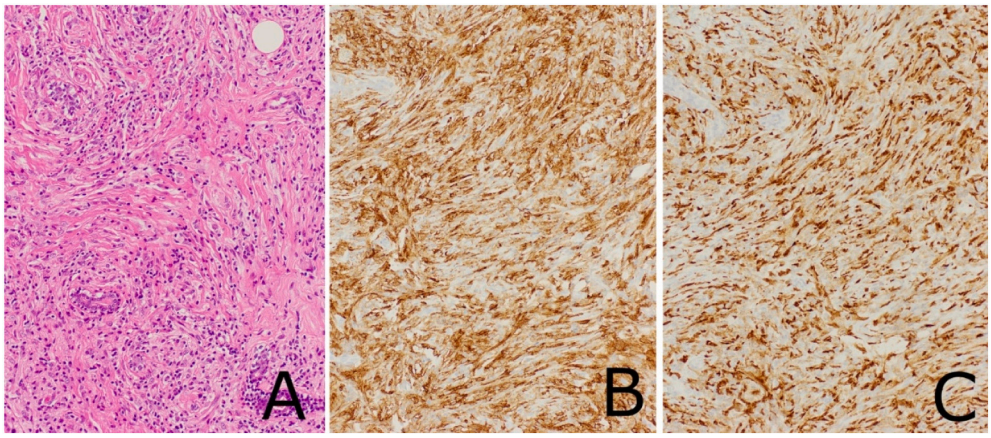


**Fig. 2.** Preoperative pathology (needle biopsy)
Hematoxylin and Eosin staining
Proliferation of elongated spindle-shaped tumor cells. There is little atypia and no evidence of mitosis or necrosis (A).
Immunostaining
The histiocyte marker CD163 is positive (B), similar to that of ALK (C).

ALK-positive histiocytosis of the breast. Comparison of the right ovarian specimen from the previous doctor with the present specimen showed no morphological similarity between the ovarian teratoma and breast ALK-positive histiocytosis, and the relationship between the two was not clear.

The patient underwent left total mastectomy and sentinel lymph node biopsy. Postoperative pathology revealed three lesions with indistinct yellow-to-yellowish-white mottled borders in the mammary tissue: UIQ (12 × 8 × 5 mm), UQ (11 × 11 × 5 mm), and UOQ (11 × 9 mm) (Fig. 3A, B). The continuity of the three lesions was unclear. Histologically, all lesions showed proliferation of predominantly spindled histiocytic tumor cells with no cellular atypia and mitotic figures, similar to preoperative needle biopsy. Immunostaining showed that tumor cells were positive for CD163 and ALK, and negative for AE1/AE3 (Fig. 3E–G). There were no lesions in the sentinel lymph nodes (0/2). Postoperative adjuvant therapy was not administered. Five months postoperatively, no recurrence or other organ lesions were observed. The patient will be followed-up periodically with mammography, ultrasonography, and CT scans.

## 3. Clinical disccusion

ALK-positive histiocytosis can occur in multiple organs aside from the breast, such as liver, spine, skin, and brain [4]. However, to our knowledge, this is the first report of primary ALK-positive histiocytosis with multiple lesions in the unilateral breast (Table 1). In the present case, at least three lesions were found in the left breast. There was no subjective symptom, and it was incidentally discovered on PET—CT. If the lesion is only in the breast, it is unlikely to be fatal, but if it is in another organ, it can be lethal. For example, there have been reports of epileptic seizures in patients with intracranial lesions [1]. We decided to perform a surgical resection considering the possibility of future invasion into other organs. The presence of multiple lesions was predicted using preoperative imaging, and total mastectomy was selected as the surgical procedure. There have been reports of cases with lymph node involvement [5], and we performed sentinel node biopsy, similar to breast cancer surgery. Two sentinel lymph nodes were identified, both of which were ALK-negative.

ALK-positive histiocytosis was originally reported as a systemic disease of infancy [2], and the spectrum of the disease has recently expanded to include localized disease in older children and young adults [6]. Although it is a very rare disease, the number of cases has gradually increased in recent years since the concept of the disease has become more widespread. Kemps et al. reported 39 cases of ALK-positive histiocytosis [4]. In addition to the breast, the disease can occur in any part of the body, including brain [1,7], liver [2,6,8], skin [2,6], intestinal tract [6,9], mesentery [10], and peripheral nerves [11], thus symptoms vary depending on the site of origin. Primary ALK-positive histiocytosis of breast is difficult to detect because of the lack of subjective symptoms other than mass awareness. Histologically, breast lesions often show spindle-shaped histiocytic cells, rather than conventional epithelioid cells [1]. Immunostaining shows that the tumor cells are positive for histiocytic markers CD4, CD68, and CD163 and negative for markers such as CD1a and Langerin [1]. FISH assays show fusion of *ALK* with partner genes, mostly *KIF5B*, but *TPM3* and *COLIA2* have also been reported [6].

Surgical resection is the standard treatment for this disease in adulthood [1]. In contrast, the ALK inhibitors alectinib [1] and crizotinib [6] have been successful in some unresectable cases. Accurate diagnosis of ALK-positive histiocytosis is important for expanding the therapeutic options. However, because the concept of the disease is relatively new and not well known, it has been misdiagnosed as other diseases in many cases. The most common differential diagnosis for ALK-positive histiocytosis is inflammatory myofibroblastoma (IMT). IMT is a soft tissue lesion in which spindle-shaped myofibroblasts proliferate [12]. IMT of the breast is rare [13], however, this case was diagnosed as IMT at the previous hospital, and the diagnosis was revised as additional staining revealed histiocytic nature of the spindle cells. Unlike ALK-positive histiocytosis, the spindle cells in IMT show myofibroblastic differentiation. The similarities in the morphology of proliferating cells, both of which are spindle-shaped, and the proliferation of inflammatory lymphoid cells in the background are the reasons for this misdiagnosis. For an accurate differential diagnosis of ALK-positive histiocytosis, it is necessary to confirm that the tumor cells are both histiocytic (positive for CD4, CD68, or CD163) and ALK-positive. In a previous case at our hospital, double immunostaining was performed, and the same cells were confirmed to be positive for both CD163 and ALK, leading to the diagnosis [1].

The number of ALK-positive histiocytosis cases reported so far is very small, and the number of primary cases in the breast is limited to six, including this case [1,6,14] (Table 1). Five cases were localized and one was systemic, suggesting the presence of a *KIF5B-ALK* fusion gene. All patients underwent surgical resection of the breast lesions, and one patient with lesions in other organs was treated with ALK inhibitor. Due to the small number of reported cases, the exact prognosis of this disease is unknown. However, no recurrence was observed in any of the six cases. When accurately diagnosed and treated, the prognosis is considered good.

## 4. Conclusion

To our knowledge, this is the first case of ALK-positive histiocytosis with multiple lesions in the unilateral breast. More case reports are needed to understand the characteristics of the disease and to increase the options for surgical resection and targeted therapy, such as ALK inhibitors.

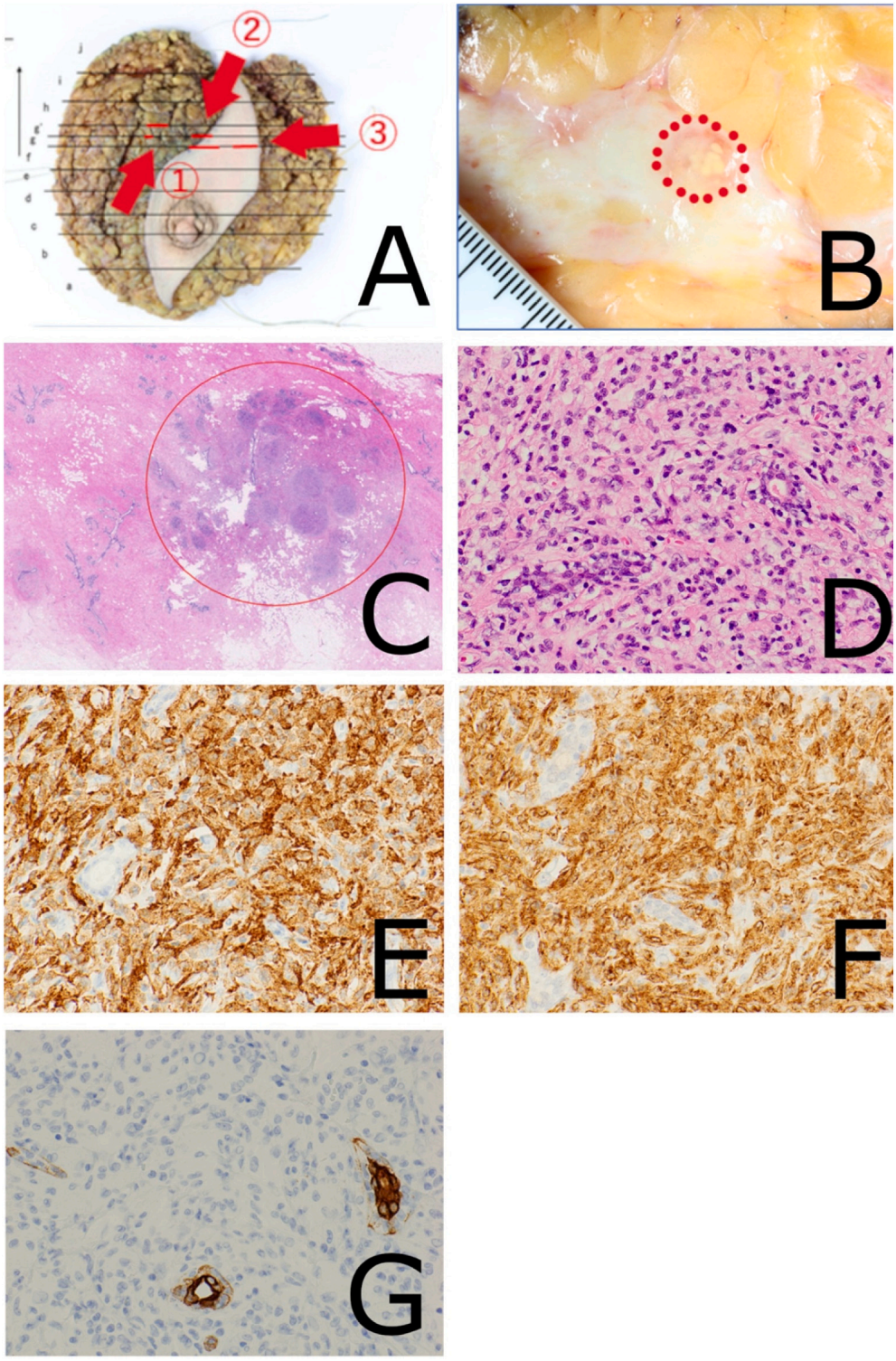


**Fig. 3.** Histological and immunohistochemical findings of the tumor.
Gross image of the left mastectomy specimen (A)
There were lesions in three areas, UIQ, UQ, and UOQ.
Cut surface of the left mastectomy specimen (B)
There was a mass with indistinct borders in the yellow-to-yellowish-white mottled lesion (red dotted line).
Hematoxylin and Eosin (HE) staining (C, Low magnification; D, High magnification)
Spindle-shaped histiocyte-like cells were proliferating in bundles.
Immunostaining (E, CD163; F, ALK; G, AE1/AE3)
Tumor cells were positive for the histiocyte markers CD163(E) and ALK (F) and negative for AE1/AE3, a marker for epithelial cells (G). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Sources of funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Ethical approval**

This case report was approved by the internal review board of the National Cancer Center, Tokyo, Japan (no. 2017-278).

**Consent**

Written informed consent was obtained from the patient for the publication of the case report.

The patient shares her perspective on the treatments she received.

**Research registration**

This manuscript is a case report, not a research.

**Table 1**
Primary ALK-positive histiocytosis of the breast (based on Ref. 1 with modifications and additions).

| Case No. | Age | Site | Single or multiple lesion in the breast | Size (cm) | Other Tumor Sites | Positive IHC | Negative IHC | Gene Fusion | Treatment | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 [1] | 45 | R, UIQ | single | 1.6 | None | CD163, CD68, CD4, CD45, ALK | S100, CD30, desmin, AE1/AE3 | KIF5B-ALK | Surgery | NED (1 mo) |
| 2 [1] | 16 | R, UOQ | single | 2.1 | Brain, lungs, pancreas, | CD163, CD68, CD4, ALK | S100, CD1a, langerin, desmin, AE1/AE3 | KIF5B-ALK | Surgery, ALK inhibitor (alectinib) | NED (44 mo) |
| 3 [1,14] | 38 | R, OQ | single | 1.7 | None | CD163, S100, ALK | CD1a, langerin, desmin | KIF5B-ALK | Surgery | NED (1 mo) |
| 4 [14] | 45 | L UIQ | single | 1.3 | None | CD163, CD68, CD13, CD45RO, ALK | CD1a, langerin, desmin, BRAF V600E, CD3、CD20、PAX5, cytokeratin | KIF5B-ALK | Surgery | NED (13 mo) |
| 5 [6] | 40 | Unknown | Unknown | Unknown | None | CD163, CD68, ALK | CD1a, langerin, BRAF V600E | KIF5B-ALK | Surgery | NED (3.5 y) |
| 6 (the present case) | 38 | L, UQ | multiple | ①1.2 ②1.1 ③1.1 | None | CD163, ALK | AE1/AE3, SMA, CD34, ER, PgR, S100, desmin, STAT6, p63 | KIF5B-ALK | Surgery | NED (4 mo) |

## Guarantor

Masayuki Yoshida
Takeshi Murata
Arisa Kurita

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## CRediT authorship contribution statement

Arisa Kurita: First author. Surgeon who assisted the surgery. Resident with 2 years of surgical specialty training.

Masayuki Yoshida: Second author. Pathology Instructor (Data collection). Data interpretation.

Takeshi Murata: Corresponding author. Breast specialist who performed the surgery. Data interpretation.

Akihiko Yoshida: Pathology Instructor (Data collection). Data interpretation.

Nachiko Uchiyama: Radiographic Instructor (Data collection). Data interpretation.

Shin Takayama: Breast specialist. Data interpretation.

## Declaration of competing interest

None.

## Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

## References

[1] J. Kashima, M. Yoshida, K. Jimbo, K. Izutsu, T. Ushiku, K. Yonemori, A. Yoshida, ALK-positive histiocytosis of the breast: a clinicopathologic study highlighting spindle cell histology, Am. J. Surg. Pathol. 45 (2021) 347–355, https://doi.org/10.1097/PAS.0000000000001567.
[2] J.K. Chan, L. Lamant, E. Algar, G. Delsol, W.Y. Tsang, et al., ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy, Blood 112 (2008) 2965–2968, https://doi.org/10.1182/blood-2008-03-147017.
[3] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230, https://doi.org/10.1016/j.ijsu.2020.10.034.
[4] P.G. Kemps, J. Picarsic, B.H. Durham, Z. Hélias-Rodzewicz, L.S. Hiemcke-Jiwa, et al., ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition, Blood 139 (2022) 256–280, https://doi.org/10.1182/blood.2021013338.
[5] Y. Tian, J. Li, B. Liu, H. Xie, M. Zheng, W. Yao, ALK-positive histiocytosis with disseminated disease responded to alectinib: a case report, Ann. Palliat. Med. 10 (2021) 10095–10101, https://doi.org/10.21037/apm-21-2117.
[6] K.T.E. Chang, A.Z.E. Tay, C.H. Kuick, H. Chen, E. Algar, et al., ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion, Mod. Pathol. 32 (2019) 598–608, https://doi.org/10.1038/s41379-018-0168-6.
[7] C.G. Lucas, A. Gilani, D.A. Solomon, Xiayuan Liang, O.M. Maher, et al., ALK-positive histiocytosis with KIF5B-ALK fusion in the central nervous system, Acta Neuropathol. 138 (2019) 335–337, https://doi.org/10.1007/s00401-019-02027-7.
[8] Huiya Huang, G. Gheorghe, P.E. North, M. Suchi, Expanding the phenotype of ALK-positive histiocytosis: a report of 2 cases, Pediatr. Dev. Pathol. 21 (2018) 449–455, https://doi.org/10.1177/1093526617740784.
[9] G.K. Gupta, L. Xi, S.D. Pack, J.B. Jones, S. Pittaluga, M. Raffeld, E.S. Jaffe, ALK-positive histiocytosis with KIF5B-ALK fusion in an adult female, Haematologica 104 (2019) e534–e536, https://doi.org/10.3324/haematol.2019.230094.
[10] T.A.N. Tran, K.T.E. En Chang, C.H. Kuick, J.Y. Goh, C.-C. Chang, Local ALK-positive histiocytosis with unusual morphology and novel TRIM33-ALK gene fusion, Int. J. Surg. Pathol. 29 (2021) 543–549, https://doi.org/10.1177/1066896920976862.
[11] O.I. Jaber, D.Al. Jarrah, M. Hiasat, M.Al. Hussaini, ALK-positive histiocytosis: a case report and literature review, Turk. Patoloji Derg. 37 (2021) 172–177, https://doi.org/10.5146/tjpath.2020.01507.
[12] I. Leuschner, Inflammatory myofibroblastic tumor, Pathologe 31 (2010) 106–108, https://doi.org/10.1007/s00292-009-1262-9.
[13] X. Mao, H. Liu, J. Du, N. Yu, L. Chen, L. Zhang, Imaging findings of inflammatory myofibroblastic tumor in breast: a case report, Medicine (Baltimore) 97 (2018), e11804, https://doi.org/10.1097/MD.0000000000011804.
[14] T. Osako, A. Kurisaki-Arakawa, A. Dobashi, Y. Togashi, S. Baba, et al., Distinct clinicopathologic features and possible pathogenesis of localized ALK-positive histiocytosis of the breast, Am. J. Surg. Pathol. 46 (2022) 344–352, https://doi.org/10.1097/PAS.0000000000001794.