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Case report

Epithelioid myofibroblastoma of the breast: A case report and review of the literature

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ABSTRACT

Introduction: Mammary myofibroblastoma (MFB) is a rare tumour. Its clinical and pathologic characteristics have been only sporadically described. A case of epithelioid variant of MFB is reported with the diagnostic tips, the differential diagnoses, and a discussion on the possible pathogenesis.

Presentation of case: A 74 year-old woman presented with a painless nodule in the left breast. Core needle biopsy (CNB) revealed a tumour primarily composed of epithelioid cells. Despite epithelioid appearance of the tumour cells, ductal/lobular components were absent within the tumour. As cell lineage of the epithelioid cells could not be determined with CNB, lumpectomy was performed to obtain definitive diagnosis and, at the same time, to remove the lesion. Histologically, the tumour consisted of multiple epithelioid cell nests that were spread over fibrous stroma infiltrated with adipose tissue. Spindle cells were also present, but they were fewer than epithelioid cell clusters. Occasionally, the tumour cells showed nuclear atypia. It was difficult to determine whether this tumour was benign or malignant solely with Hematoxylin-eosin stain. However, with the aid of immunohistochemical analyses, we could make a histodiagnosis of epithelioid subtype of myofibroblastoma.

Discussion: The differential diagnoses of epithelioid MFB include ductal, lobular, metaplastic carcinomas and mesenchymal tumours. Comprehensive knowledge of classic and variant MFB is necessary for the correct diagnosis.

Conclusion: Pathologic diagnosis of epithelioid variant of MFB requires careful evaluation of histology and the use of a panel of immunohistochemistry. Female phenotype of breast stroma may play a role in the pathogenesis of MFB.

1. Introduction

Myofibroblastoma (MFB) of the breast was originally described as a benign fibroblastic and myofibroblastic tumour [1]. Clinically, it develops as a painless slowly growing tumour. MFB is typically depicted as a well-defined, solid nodule on imaging [2–12]. Macroscopically, MFB presents as a sharply demarcated tumour devoid of capsule [1,6] and, histologically, as a tumour composed of spindle cell proliferation. The MFB tumour cells usually lack nuclear atypia, necrosis, and mitotic figures. However, with the accumulation of MFB cases, variant forms have been reported. Some of these may show hypercellularity, non-spindle cell appearance, and nuclear atypia. Theses subtypes need careful differential diagnoses from other lesions with similar histology.

We report here a case of an epithelioid variant of MFB, which required careful histological examination and use of panels of immunostaining to obtain the correct histodiagnosis. Diagnostic pitfalls, differential diagnoses, useful tips for the accurate pathologic diagnosis, and possible histogenesis of MFB are discussed with a review of pertinent literature.

This report is in line with the SCARE/PROCESS criteria [13,14].

2. Presentation of case

A 74-year-old Japanese woman had been followed for a nodule in the

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upper outer quadrant of the left breast, which grew gradually over five years. Initially, the tumour was discovered incidentally with patient's selfpalpation. At the first visit to our hospital, imaging studies suggested mammary hamartoma. Fine needle aspiration cytology was negative. Thereafter, she had been under close observation as an outpatient. Although thought as clinically benign, we were warned by the slow but steady growth of the tumour. The latest re-taken mammography demonstrated a dense, round to oval solid nodule with clearly defined border in the upper lateral quadrant (Fig. 1A, B). Ultrasound revealed a 27 × 24 × 11 mm-sized tumour composed of mixed hyperechoic and hypoechoic regions (Fig. 2). Her past history included diverticulitis of the rectum with perforation. She had no drug, smoking, alcohol history. Her physical figure was small (137 cm, 39 kg, BMI 20.8 kg/m^2). Her family history was not remarkable. There were no cases of breast cancer or ovarian cancer in her relatives.

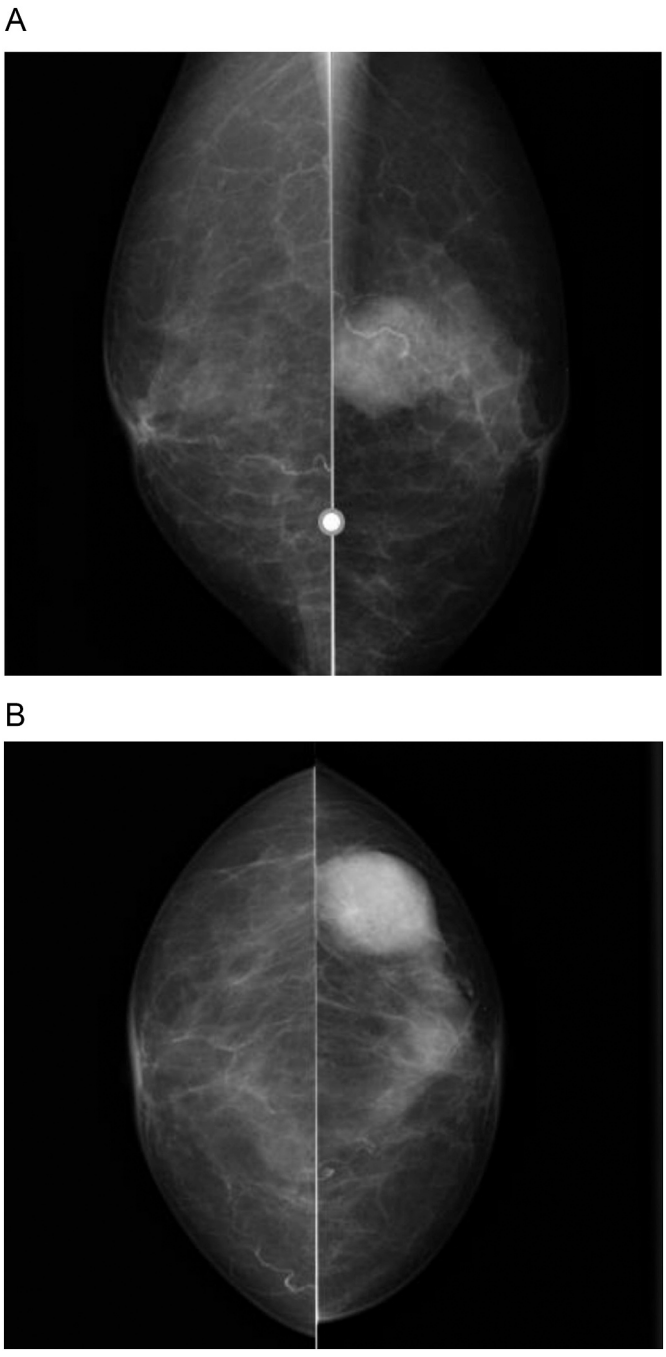

Fig. 1. Mammography of the breast. Note that homogeneously dense nodule with clearly defined contour. This image obviously suggests a benign tumour.

Histology of the core needle biopsy (CNB) performed in the Nagoya Memorial Hospital revealed a tumour composed of epithelioid cells (Fig. 3). The tumour cells formed multiple nests, which diffusely grew in an adipo-fibrous stroma. However, stromal reaction was absent. Nuclear atypia was subtle and mitotic figures were sparse. Ki-67 (MIB-1) positive cells were less than one per high power field (not shown). These findings indicated that this tumour was likely benign. Mammary lobules or ducts were not observed within the tumour. Immunohistochemically, these tumour cells were negative for cytokeratin (CK) AE1/AE3, CK7, α-smooth muscle actin (SMA), p63, CD10, CD117, and synaptophysin. Vimentin (+) and S-100 were positive. Oestrogen receptor (ER) was positive, but progesterone receptor and HER-2 were negative (not shown). These findings suggested that, despite its epithelioid appearance, these tumour cells were not of mammary epithelial origin. This tumour was presumed to be benign, but its exact histodiagnosis could not be determined with certainty.

Lumpectomy under general anaesthesia was carried out in the Nagoya Memorial Hospital to obtain specific histological diagnosis and, at the same time, to extirpate the lesion. The excised nodule was well defined and measured 22 × 12 mm in size. Its cut section was solid and whitish (not shown). In low power view, the tumour was composed of multiple cell nests spread over fibrous stroma associated with fat infiltration. There were no foci of haemorrhage, necrosis, or calcification (Fig. 4A). Most of the tumour nests consisted of epithelioid cell clusters (Fig. 4B). However, spindle cell nests were also observed occasionally (Fig. 4C). The number of spindle cell nests was less than 20 % of the all tumour cell clusters. The nuclei of both types of the tumour cells were oval to round, and the nucleoli were inconspicuous. Mitotic figures were scanty and hyperchromasia was absent. However, some of the epithelioid tumour cells had large, pleomorphic nuclei with prominent nucleoli, though they were rare (Fig. 4D). There were no ductal epithelial cells or myoepithelial cells within the tumour. The patient has been unremarkable after the operation.

The immunohistochemical profiles were essentially the same as the CNB specimens. These results were largely compatible with previous reports of the immunophenotype of MFB [3,5,7,11,12,15–19].

While nuclear atypia was seen in some part of the tumour, this tumour lacked haemorrhage, tumour necrosis, increased mitotic counts, and vascular/capsular invasion. Although spindle cells were seen in some part of the tumour, majority of the tumour cells showed epithelioid appearance. These findings supported a histodiagnosis of epithelial variant of MFB.

3. Discussion

MFB was first descried as a benign neoplasm of mesenchymal origin, which is composed of mixed proliferation of myofibroblasts, collagen fibres, and adipocytes [1]. The immunohistochemical markers utilized in the diagnosis of MFB are CD34, desmin, vimentin, α-SMA, ER, and bcl-2 [3,5,7,11,12,15–20]. CD34 and vimentin are often positive, and other antibodies become sometimes stained positive to variable degrees. The epithelial markers are always negative. These antibodies are useful for the histodiagnosis of MFB.

The differential diagnoses of breast MFB include other spindle cell tumours such as pseudo-angiomatous stromal hyperplasia (PASH), fibromatosis, nodular fasciitis (NF), solitary fibrous tumour (SFT), spindle cell lipoma, leiomyoma, and metaplastic spindle cell carcinoma [21]. Inflammatory myofibroblastic tumour (IMT) should also be raised as a differential diagnosis [22]. Of these, PASH and IMT are both myofibroblastic tumours macroscopically appears as a sharply defined, non-encapsulated mass as MFB. Histologically, PASH is composed of a myofibroblastic proliferation associated with epithelial components. Typically, the background stroma has characteristic anastomosing slit-like spaces, which is a helpful finding for the differential diagnosis

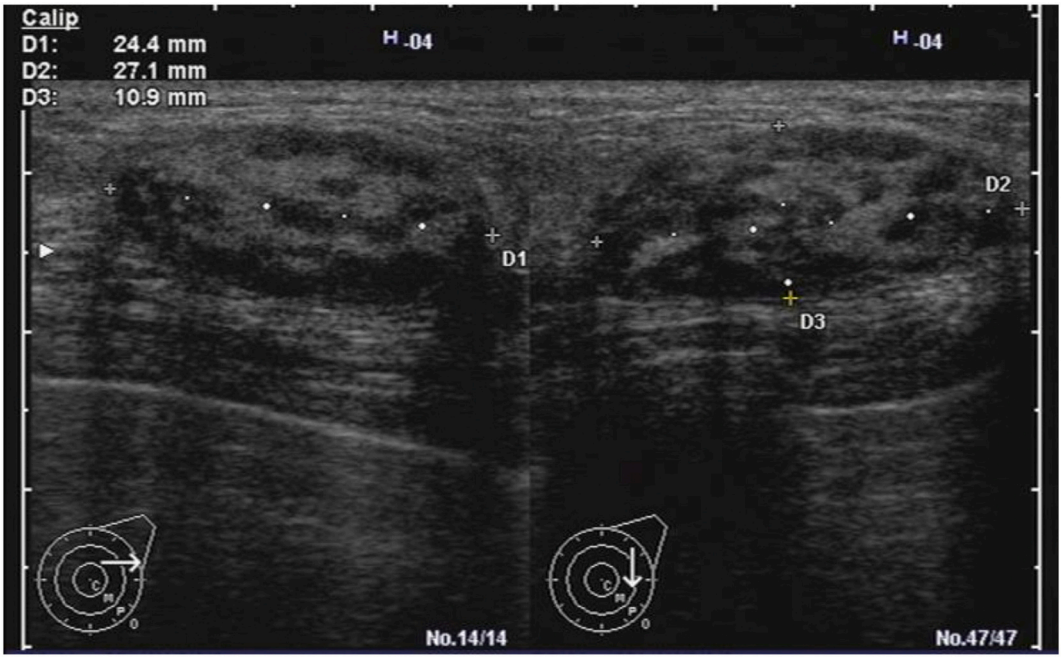

Fig. 2. Ultrasonography of the breast. A 27 × 24 × 11 mm-sized oval tumour was depicted. The tumour was composed of mixed hypoechoic and hyperechoic regions.

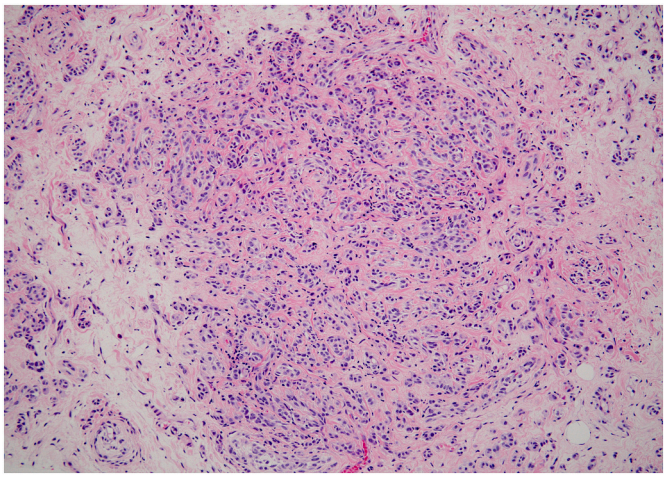

Fig. 3. Histology of the core needle biopsy. Note proliferation of epithelioid cells as multiple foci (Hematoxylin-eosin [HE] stain, ×100).

[23]. IMT is a myofibroblast tumour that usually arises from visceral/soft tissue in the paediatric and young cases. IMT of the breast is very rare, but it should be reminded as a differential diagnosis. As the name implies, abundant inflammatory cells, the majority of which are plasma cells, are present within the lesion.

Fibromatosis, NF, and SFT comprise fibroblasts/myofibroblasts growth. Fibromatosis shows an infiltrative proliferation of fibroblasts/myofibroblasts. Compared with MFB, fibromatosis is poorly demarcated, and histologically less cellular and rich in collagen-fibres. NF of the breast is very rare. The fibroblasts/myofibroblasts proliferation in the NF occurs as randomly fascicular manner, and lymphocytes and plasma cells are often associated within the lesion [24]. SFT is characterized with sclerotic growth of fibroblasts/myofibroblasts and shows immunohistochemical profiles similar to MFB (CD34 and vimentin positive). Stag-horn shaped vessels with peri-vascular hyalinization are often seen within the fascicular growth of myofibroblasts. These findings are rarely seen in MFB. SFT with fat formation is reported [25], which histologically mimics spindle cell lipoma and lipomatous MFB. Spindle cell lipoma consists largely of mature adipocytes and occasional interspersing bland spindle cells. Proliferation of adipocytes is the major constituent of the tumour and spindle cells with collagen bundles run across the lipoma as minor element. This helps to delineate MFB. Leiomyoma shows proliferation of spindle cells as intersecting fascicles, and the spindle cells have ample eosinophilic cytoplasm.

Metaplastic spindle cell carcinoma exhibits high-grade nuclear atypia and epithelial markers are positive. Furthermore, GATA binding protein 3 (GATA-3) is expressed significantly higher in metaplastic spindle cell carcinoma compared with other spindle cell lesions [26], which may be useful for the differential diagnosis.

As the number of reported cases of MFB has been accumulated, histological subtypes of MFB such as cellular [6,19], infiltrating [7], collagenized/fibrous [5,7,27], lipomatous [5,7,27], myxoid [6,8,9,11,28], deciduoid-like [7], and palisaded variant [2] have been reported.

Of these, the diagnosis of the epithelioid variant requires careful examination. Epithelioid variant of MFB often shows variable degrees of nuclear atypia [6,7] as seen in our case (Fig. 2D). Bi- and multinucleated tumour cells are also seen [6,8]. These findings may be misinterpreted as carcinoma. Despite nuclear atypia, close examination would demonstrate that hyperchromasia, higher mitotic count, coarsely condensed chromatins, conspicuous nucleoli, invasion (stromal reaction), and necrosis are not observed. In addition, the epithelioid variant of MFB may mimic invasive lobular carcinoma, especially when the tumour cells are associated with nuclear atypia [7,21,30]. The epithelioid subtype of MFB is defined that the more than half of the tumour cells appear as epithelioid cells [7]. Spindle cells may be present somewhere within the lesion, though the amount of spindle cells might be small. When spindle cells are identified, ILC may be an unlikely diagnosis. Immunostaining of epithelial markers also helps to differentiate ILC from epithelioid MFB.

Another subtype of MFB, the lipomatous variant, is associated with wide-spread fat infiltration across the lesion, which may imitate fatty invasion [5,15,27]. Among the various variants of MFB, WT1 cytoplasmic immunostaining is restricted to the epithelioid subtype [31], and is a useful marker for the diagnosis.

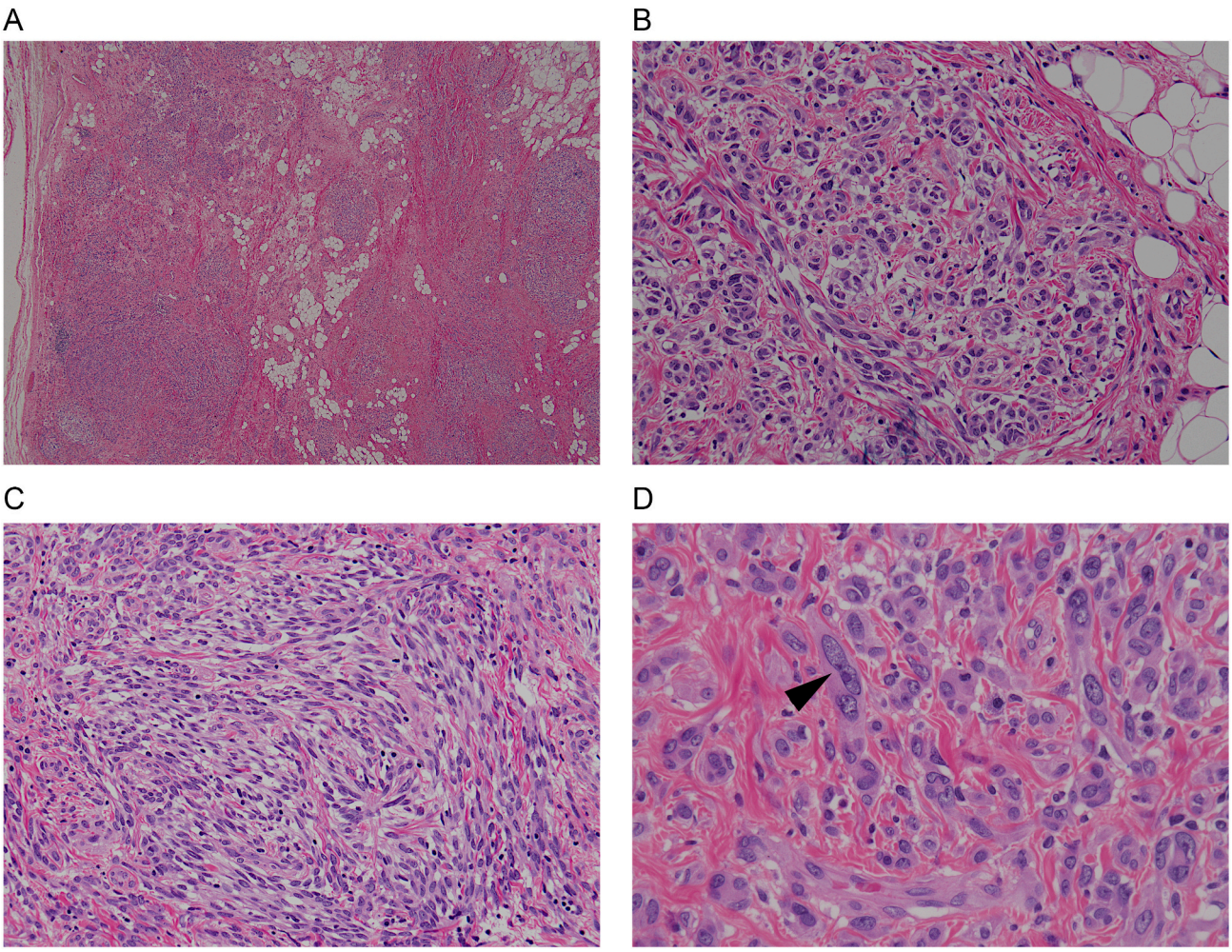

Fig. 4. A Low-power view of the resected tumour. Note that abundant fat infiltration into the tumour is present (HE stain, ×40). B Tumour nests composed of epithelioid cells. Note that tumour cells with nuclear atypia proliferate as multiple nests. Also note that adipose tissue is located very adjacent to the tumour (HE stain, ×200). C Cluster of spindle cells. Note that monotonous spindle cells proliferate in a randomly oriented manner (HE stain, ×200). D Nuclear atypia was occasionally observed in the epithelioid tumour cell nests. Note a bizarre nucleus with large nucleolus (arrowhead) (HE stain, ×400).

Although MFB was first described as a benign tumour of mammary stromal origin [1], its histogenesis of MFB is not clearly elucidated. MFB is believed to arise from myofibroblasts, but the pathologic mechanism that leads to neoplastic proliferation of myofibroblasts remains unclear.

MFB is an unusual breast tumour in that it arises in almost equally both sexes. In fact, in the first report of MFB, 11 among 16 cases (68.8 %) were men [1]. Subsequently, male cases have been reported [2–5,9–11,16,18,19,32–34]. This is in contrast to mammary carcinomas, in which women are affected far more frequently than men. Interestingly, male cases of MFB are often associated with gynaecomastia [1,3,4,11], which suggests that change of male breast stroma to female characteristics may play an important role in the development of MFB. Immunohistochemical analyses in the male breast have shown that, in case of gynaecomastia, peri-ductal connective stromal cells are highly positive for CD34 (93.8 %). On the other hand, in the male breast carcinoma, CD34 staining of peri-ductal stromal cells was seen only in 8.3 % [35]. In the female breast, interlobular stromal cells are CD34+ [36]. This suggests that the conversion of male breast connective stromal cells to CD34-positive phenotype may be the initial step of the histogenesis of MFB.

The prognosis of MFB is generally favourable, so lumpectomy with enough resection margins is the treatment of choice. To achieve proper management of MFB, it is essential to correctly recognize its benignity. In the typical MFB, in which the tumour is composed of bland spindle cells, it would be straightforward to recognize the lesion as benign with careful histological observation. In case of epithelioid variant, epithelioid appearance of the MFB cells may be confusing with carcinomas including ILC, especially when associated with nuclear atypia. Lipomatous subtype may mimic fat invasion. However, meticulous observation and immunohistochemical analyses would help to make a diagnosis of MFB.

4. Conclusion

A case of epithelioid variant of breast MFB is reported. Detailed descriptions of histological findings, confusing pitfalls in the histodiagnosis, the use of panels of immunohistochemistry, differential diagnoses are presented, and possible pathogenesis of MFB are discussed with a review of pertinent literature. Awareness of various forms of MFB subtypes and meticulous histopathological observation are useful for the correct diagnosis and proper management of the patient. A review of the possible pathogenesis may be informative in the understanding of MFB.

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Ethical approval

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

Not applicable.

Guarantor

Takahiko Sakuma.

Provenance and peer review

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CRediT authorship contribution statement

T Inaishi and T Fukuoka were responsible for the patient care and surgical intervention.

T Sakuma and S Ichihara made pathologic analyses and diagnosis

T Sakuma and T Inaishi wrote the manuscript

S Ichihara supervised this paper:

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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