Diagnostic Pathology

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Large atypical perilobular hemangioma in the breast: a potential misdiagnosis as angiosarcoma

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Abstract

Background Atypical perilobular hemangioma (APH) of the breast is a rare type of tumor. This tumor is often small, measuring no more than 2 mm in diameter, difficult to detect or palpate, and has a good prognosis.

Case presentation We report a unique case of APH in a 47-year-old female patient, which was 12 mm in diameter and characterized by tumor cell atypia. To date, six cases of APH have been reported in the literature, including the present case. The mean age of the APH patients was 49.5 years (range: 39–75 years). The majority of APHs (4/6) in the breast were initially diagnosed as angiosarcoma. The tumor in our study presented diagnostic challenges as an atypical APH due to its substantial size (12 mm), the presence of indistinct borders in certain regions, an extensive growth pattern, the hobnail appearance of endothelial cells, and the mitotic count.

Conclusion In this study, we present this case to help with proper diagnosis and treatment of the tumor, to emphasize additional characteristics of APH, to summarize the clinicopathological features of this tumor as documented in the literature, and to enhance the understanding of this tumor type, particularly the differentiation between APH and low-grade angiosarcoma.

Clinical trial number Not applicable.

Keywords Hemangioma, Breast, Atypia, Angiosarcoma, Vascular tumor

Introduction

Atypical perilobular hemangioma (APH) of the breast is a rare type of tumor. The clinical behavior, pathological features, and diagnostic criteria of APH in the breast remain largely undefined. Michael A. et al. [1] outlined the characteristics of the five APHs as follows: tumors exhibiting cytologic atypia or minimal vascular anastomosis were regarded as precursors of angiosarcoma; however, they demonstrated no evidence of progression. Given the unpredictable clinical behavior of this tumor, clinicians recommended re-excision of the biopsy site if the completeness of excision in the initial specimen was indeterminate. Tumors typically measuring no more than 2 mm in diameter, were challenging to detect or palpate, and generally had a favorable prognosis [1]. Additionally, owing to the specific morphology of APH, which displays atypical or malignant-like cellular or histological features, the pathological diagnosis of this tumor may be misinterpreted as sarcoma. When the APH exceeds 10 mm, distinguishing it from low-grade angiosarcomas can be challenging.

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In this study, we present an unusual case with a significant mass (12 mm in size) to help properly diagnose and treat the tumor, to emphasize additional characteristics of APH, to summarize the clinicopathological features of this tumor as documented in the literature, and enhance the understanding of this tumor type, particularly the differentiation between APH and low-grade angiosarcoma.

Materials and methods

The data that supported this report were obtained from the Department of Pathology, the First Affiliated Hospital, Sun Yat-sen University, China. This was a consultation case from an external hospital. All slides of hematoxylin and eosin (H&E) and immunohistochemistry (IHC) staining were obtained from the external hospital. IHC staining was conducted on tissue sections using the following antibodies: ERG (UMAB78, no dilution, ZSGB-BIO), CD34 (IR632, no dilution, DAKO), FLI-1 (G146-22, no dilution, ZSGB-BIO), CD31 (IR610, no dilution, DAKO), smooth muscle actin (SMA) (UMAB237, no dilution, ZSGB-BIO), D2-40 (dilution at 1:50, ZSGB-BIO), Desmin (IR606, no dilution, DAKO), E-cadherin (OTI1B8, no dilution, ZSGB-BIO), GATA3 (EP368, no dilution, ZSGB-BIO) and Ki-67 (UMAB107, no dilution, ZSGB-BIO). For Ki-67, nuclear staining of any intensity was evaluated. Pathologists who specialize in the diagnosis of breast and soft tissue tumors reviewed all the H&E and IHC slides and confirmed the final diagnosis.

Clinical findings

A 47-year-old female patient underwent a physical examination, which revealed a nonpalpable right breast lump that was asymptomatic in terms of significant pain. The ultrasonography examination revealed two tumors: (i) A hypoechoic nodule located near the nipple at 9–10 o'clock position in the right breast that measured approximately 10 mm×5 mm×4 mm and was situated approximately 4 mm from the epidermis. The nodule had an irregular shape with clear borders and was classified as BI-RADS category 4a (Fig. 1A). (ii) A hypoechoic nodule in the right breast located at the 10 o'clock position, which measured approximately 10 mm×4 mm in size, exhibited an oval shape with distinct borders and was classified as BI-RADS category 3 (Fig. 1B). The histological diagnosis for the first tumor was intraductal papilloma of the breast, whereas the second mass was identified as a vascular mass. Both lesions were excised.

Pathological findings

The excisional tissue exhibited irregularity, with a cut section revealing a reddish-colored mass measuring 12 mm×5 mm×3 mm. The mass was circumscribed and had a cavernous shape.

Microscopically, the tumor presented as multiple nodules or clusters. Most nodules were circumscribed with well-defined borders, whereas some nodules presented irregular borders. The nodules with irregular borders were inadequately separated from the adjacent adipose tissue (Fig. 2A and B). The nodules were composed of proliferating thin-walled blood vessels of varying sizes. In certain regions, the vessels exhibited a thin, slit-like morphology characterized by a nondilated and unfilled lumen; they resembled lobulated capillary hemangiomas (Fig. 2C). The vessels proliferated significantly within the lobular alveoli of the mammary gland, demonstrating an infiltrative growth pattern, while the lobular architecture of the mammary gland was preserved (Fig. 2D). The

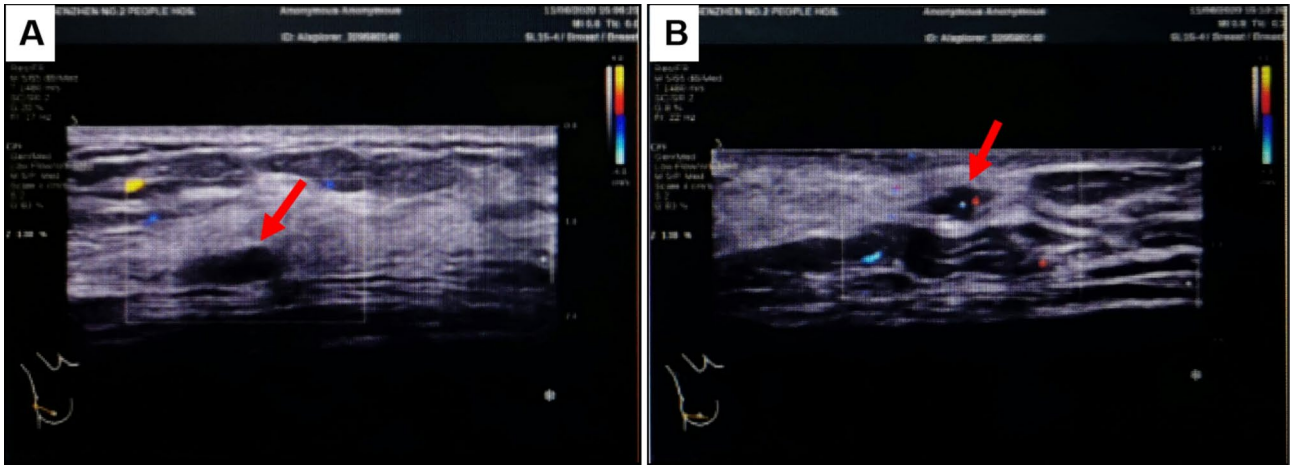

Fig. 1 (**A**) A hypoechoic nodule located near the nipple at 9–10 o'clock position in the right breast measuring approximately 10 mm×5 mm×4 mm and situated approximately 4 mm from the epidermis. The nodule exhibited an irregular shape with clear borders and was classified as BI-RADS category 4a. (**B**) A hypoechoic nodule in the right breast located at the 10 o'clock, measuring approximately 10 mm×4 mm in size and exhibiting an oval shape with distinct borders, classified as BI-RADS category 3.

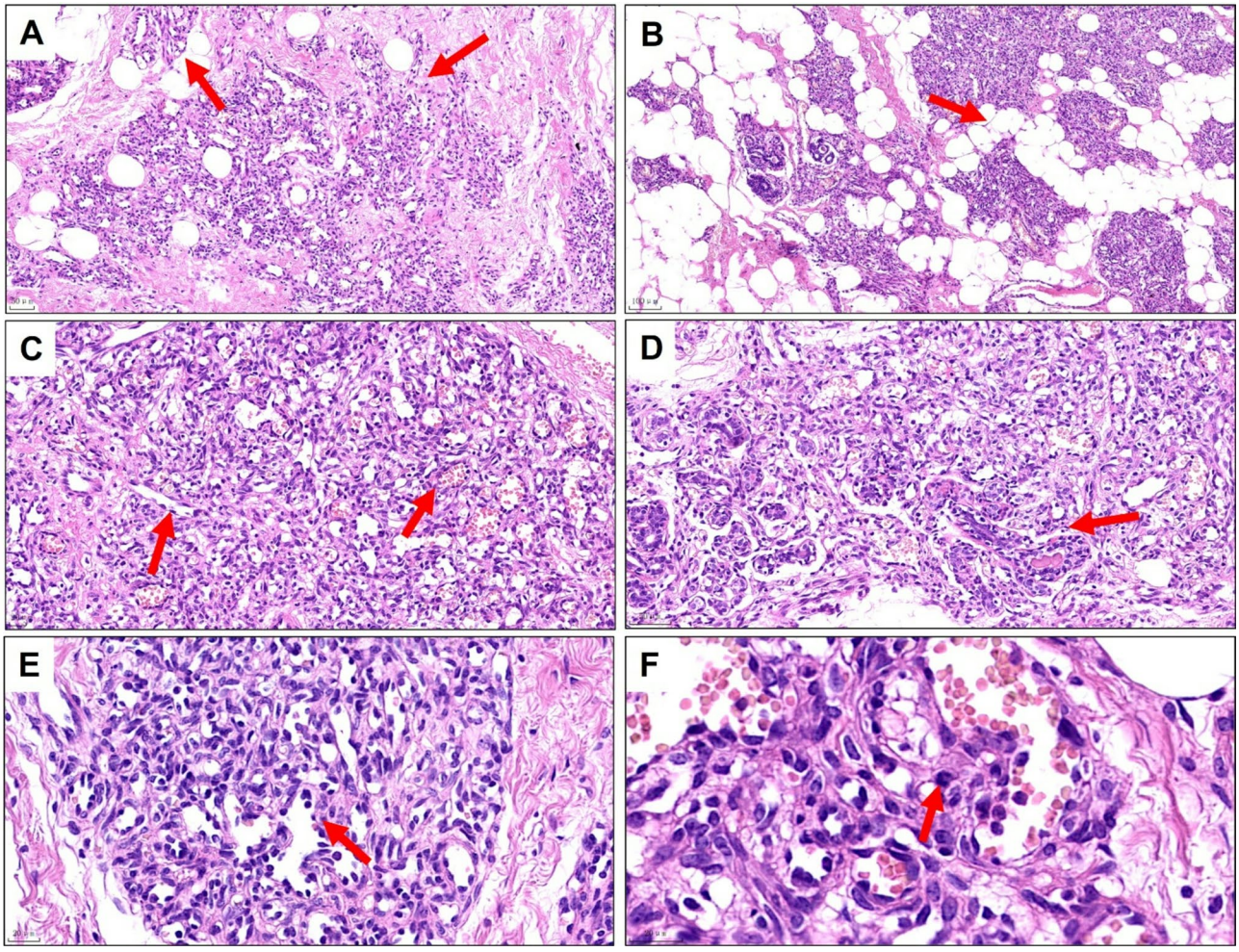

Fig. 2 Histopathology: (**A**) Nodules or small clusters exhibited variability in size and displayed irregular borders in certain regions. (**B**) The tumor nodules with irregular borders were inadequately separated from the adjacent adipose tissue, with some tumor tissue appearing mixed with the adipose tissue. (**C**) The nodules consisted of thin-walled blood vessels of varying sizes, with some vessels exhibiting dilated lumens filled with red blood cells. In certain regions, the vessels exhibited a thin, slit-like morphology and characterized by a nondilated and unfilled lumen resembling lobulated capillary hemangiomas. (**D**) The epithelial components of the breast may be discernible between the tumor nodules. The vessels developed extensively among the lobular alveoli of the mammary gland, exhibiting an infiltrative growth pattern, whereas the lobular architecture of the mammary gland remained intact. (**E**) Most of the tumor cells displayed mild atypia, whereas in other regions the tumor endothelial cells presented significantly large nuclei with a hobnail appearance. (**F**) A mitotic figure was observed.

vascular channels were interconnecting but nonanastomosing and resembled capillaries in some regions. In localized regions where the vascular lumens exhibited round or oval shapes, lacking a distinct boundary and seemingly destroying the adipose tissue. This infiltration pattern was distinct from that of conventional well-differentiated angiosarcoma. A local region of the vasculature exhibited both dilated and stenotic lumens, resembling a capillary hemangioma. Histologically, the epithelial components of the breast remained between the tumor nodules. Some of the vasculature was surrounded by flattened endothelial cells characterized by small, homogeneous nuclei with the absence of cellular atypia. In other regions of the tumor, the vascular endothelial cells exhibited notably large nuclei with a hobnail appearance. In addition, pathologic mitotic figures were found in this tumor, especially in regions characterized by large nuclei (Fig. 2E-F).

Immunohistochemical staining revealed that the tumor cells were positive for ERG (Fig. 3A), CD34 (Fig. 3B), FLI-1 (Fig. 3C), CD31 (Fig. 3D), and smooth muscle actin (SMA) (Fig. 3E-F), but negative for D2–40 (Fig. 3G), Desmin, E-cadherin, and GATA3. The Ki-67 index in the hot pot was 15–20% (Fig. 3H) (Table 1).

Follow-up

The patient was followed at the primary hospital from July 2020 (the time of operation) to the present with 51 months. Throughout this period, the patient did not exhibit local recurrence or metastasis.

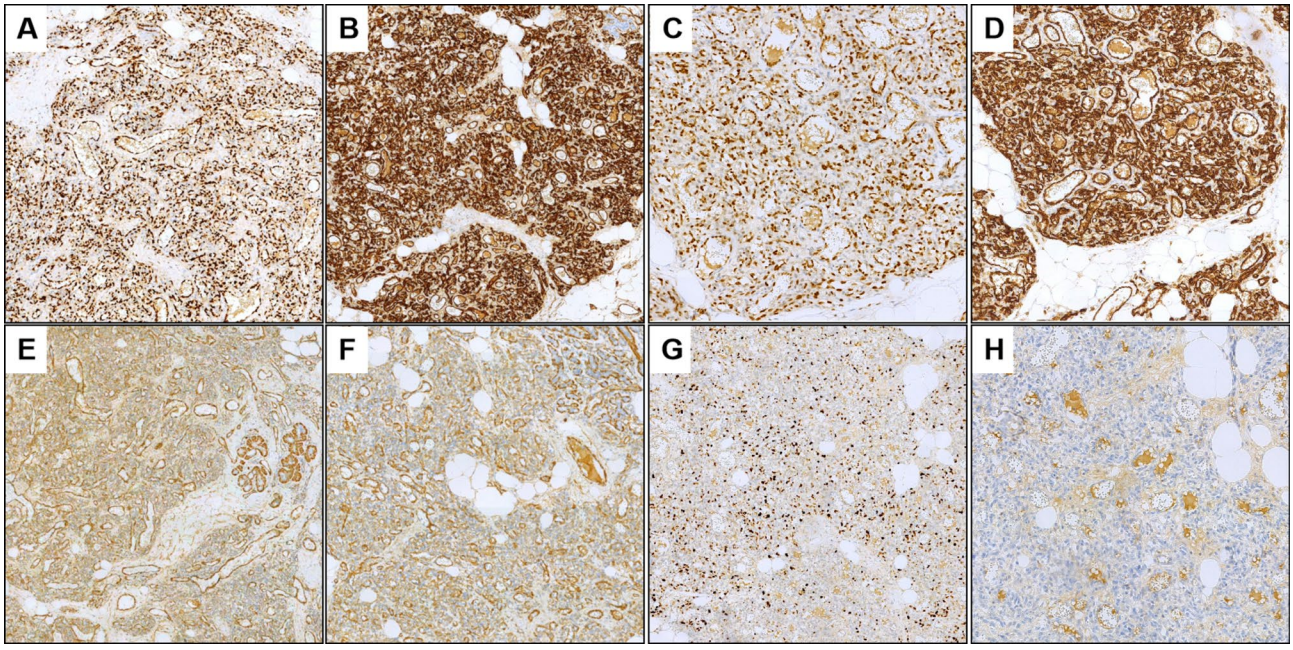

Fig. 3 The tumor cells were positive for ERG (**A**), CD34 (**B**), FLI-1 (**C**), CD31 (**D**), and SMA (**E**-**F**) and negative for D2–40 (**G**). Ki-67 expression in the hot spot (H)

Table 1 The details of the antibodies

Antibody name	Company	Clone number	Repair conditions	Dilution ratio	Species
ERG	ZSGB-BIO	UMAB78	pH 8 (EDTA)	No dilution	Rat
CD34	DAKO	IR632	pH 8 (EDTA)	No dilution	Rat
FLI-1	ZSGB-BIO	G146-22	pH 8 (EDTA)	No dilution	Rat
CD31	DAKO	IR610	pH 8 (EDTA)	No dilution	Rat
SMA	ZSGB-BIO	UMAB237	pH 8 (EDTA)	No dilution	Rat
D2-40	ZSGB-BIO	D2-40	pH 9 (EDTA)	1:50	Rat
Desmin	DAKO	IR606	pH 8 (EDTA)	No dilution	Rat
E-cadherin	ZSGB-BIO	OTI1B8	PH 9 (EDTA)	No dilution	Rat
GATA3	ZSGB-BIO	EP368	pH 8 (EDTA)	No dilution	Rabbit
Ki-67	ZSGB-BIO	UMAB107	pH 8 (EDTA)	No dilution	Rat

SMA, smooth muscle actin

Discussion

This study presents a unique case of an APH. The tumor posed diagnostic challenges as an atypical APH due to its significant size (12 mm), indistinct border in certain areas, extensive growth pattern, hobnail appearance of endothelial cells, and the noted nuclear pathologic mitotic figure. Consequently, due to the morphological characteristics and immunohistochemistry findings, the patient was not initially diagnosed with APH at either of the other two large institutions and was instead misdiagnosed with well-differentiated angiosarcoma. However, our findings indicate that the tumor does not exhibit real vascular anastomosis and displayed an infiltrative growth pattern akin to low-grade angiosarcoma. Tumor cells may be located within and outside lobules. The distribution pattern of all the tumor cells was consistent with the morphology of perilobular hemangiomas. This tumor also displayed atypical cytological and structural characteristics, including enlarged hyperchromatic nuclei and mitotic figures in certain tumor endothelial cells. These characteristics resulted in the diagnosis of APH for the tumor. The lesion was excised in accordance with current treatment guidelines [2].

At present, only 6 cases of APH have been described in the literature, including our present case (Table 2). The mean age of the APH patients was 49.5 years (range: 39–75 years). The tumors were small, typically measuring no more than 2 mm, and difficult to palpate or identify [1]. To the best of our knowledge, our case is larger than those previously reported in the breast and is more likely to be misdiagnosed as angiosarcoma. 60% (3/5) of APHs of the breast previously reported in the literature were initially thought to be angiosarcomas, and the patient in our study had already been diagnosed with malignant sarcoma in two different hospitals. This type of tumor may be more difficult to diagnose and treat because of its large size (12 mm), the existence of an unclear border in some areas, an extended growth pattern, and the mitotic

Table 2 Reported cases of primary atypical perilobular hemangioma in literature

Case	Age/Sex	Size	Site	Presentation	Border	EGP	VA	MC	EC	IHC	Treatment	Follow-up
Michael A. et al. [1]	39/F	Micro	NA	Fibrocystic mass	Well-circumscribed	Y/lobules and fatty	N	N	Atypia	NA	Simple mastectomy	NED, 120 months
Michael A. et al. [1]	36/NA	Micro	NA	Fibrocystic mass	Well-circumscribed	Y/lobules	N	NA	Atypia	NA	Excisional biopsy	NED, 77 months
Michael A. et al. [1]	46/F	2 mm	R	Fibrocystic mass	Well-circumscribed	Y/lobules	Appear to be	N	Atypia	NA	Simple mastectomy	NED, 7 months
Michael A. et al. [1]	75/NA	Micro	NA	Fibrocystic mass	NA	NA	NA	NA	NA	NA	Excisional biopsy	NED, 16 months; contralateral carcinoma 11 years before
Michael A. et al. [1]	54/NA	Micro	NA	Mammographic finding of calcification in duct hyperplasia	NA	NA	NA	NA	NA	NA	Excisional biopsy	NED, 15 months
This case	47/F	12 mm	R	Hypoechoic nodules detected by ultrasonography	Well-circumscribed; Ill-defined	Y/lobules and fatty	N	Y	Most: mild; few: atypia	CD34 (+), ERG (+), CD31 (+), FLI-1 (+), SMA (+), Ki-67 15–20% (+)	Simple mastectomy	NED, 35 months

F, female; NA, not available; IHC, Immunohistochemistry; R, right; VA, vascular anastomosis; MC, mitotic count; EC, endothelial cell; EGP, extending growth pattern; Y, YES; N, NO; NED, no evidence of disease

count figure, in addition to the enlarged hyperchromatic nuclei of endothelial cells described.

The main differential diagnosis for APH includes angiosarcoma, specifically postradiation angiosarcoma and primary angiosarcoma of the breast. The fifth edition of the World Health Organization (WHO) classification of breast tumors outlines the diagnostic criteria for postradiation angiosarcoma, which comprises essential and desirable criteria [3]. The essential criteria include a history of previous radiation therapy and a morphologically infiltrative growth pattern. The desirable criteria include MYC overexpression by immunohistochemistry and *MYC* amplification by fluorescence in situ hybridization (FISH) [3]. The patient in our study lacked a history of breast cancer and had not received radiotherapy, thereby allowing for the initial exclusion of postradiation angiosarcoma patients.

Another differential diagnosis for APH is low-grade angiosarcoma. The immunohistochemistry markers available for differentiating the two lesions are currently limited. Research indicates the smooth muscle actin (SMA) is positive in most nonbreast benign hemangiomas [4, 5], although a small percentage could have negative results [6]. Conversely, other studies indicate the SMA is predominantly negative in angiosarcomas of nonbreast tissue [7, 8], with positivity observed in a limited number of cases [2]. A study on the utility of the SMA in differentiating benign from malignant vascular tumors of the breast revealed that SMA expression was absent in 80% (12/15) of angiosarcoma cases and present in 96% (22/23) of benign vascular lesion cases [9]. This observation is consistent with the findings of SMA expression in vascular lesions at nonbreast sites. Molecular studies concerning breast vascular tumors are scarce, and only a limited number of specific genetic alterations have been identified in atypical vascular lesions. Although *C-MYC* amplification is infrequent in primary (nonradiation-related) breast angiosarcoma, it occurs in approximately 90% of secondary angiosarcomas, some of which may additionally exhibit *FLT4* amplification [9]. Molecular testing provides limited assistance in identifying vascular tumors of breast origin, whereas morphological differences continue to serve as a crucial reference for distinguishing APH and low-grade angiosarcomas.

Our study has several limitations. First, the external consultation of the case precluded the acquisition of paraffin tissue, thus hindering the performance of molecular tests. Second, research on APH is currently limited, with only two publications including six cases. Therefore, it is crucial to collect a greater number of cases and summarize their clinicopathological and molecular features to improve the diagnosis of APH.

Conclusion

In summary, we present a patient with an APH in the breast measuring 12 mm, significantly exceeding the sizes documented in the literature. Furthermore, distinguishing breast APH from low-grade angiosarcoma presents challenges; thus, identifying low-grade angiosarcoma requires careful morphological assessment of the vessels adjacent to the lobules, adipose tissue, and the tumor cell morphology. A low-grade angiosarcoma can mimic a hemangioma or an angiolipoma when it is diagnosed using a core-needle biopsy. We present this case to further elucidate the characteristics of APHs and improve the understanding of this tumor type, particularly the distinguishing features between APH and angiosarcoma, which will help with properly diagnosing and treating these tumors.

Abbreviations

APH	Atypical perilobular hemangioma
H&E	Hematoxylin and eosin
IHC	Immunohistochemistry
WHO	World Health Organization
FISH	Fluorescence in situ hybridization
SMA	Smooth muscle actin

Acknowledgements

None.

Author contributions

HS and YW: conceived and designed the study; YW and ML acquired and interpreted the clinical data, and drafted and revised the manuscript. HL: formal analysis, writing– review & editing. AH and HS: confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. There was no need for patient consent based on our university policy because this study does not contain any identifiable information about the patient.

Consent for publication

This case report has consent from patient for publication.

Competing interests

The authors declare no competing interests.

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