Indolent growth of low-grade myofibroblastic sarcoma of the knee with the resemblance of a benign lesion: A case report

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Abstract. Low-grade myofibroblastic sarcoma (LGMS) is a rare soft-tissue malignant neoplasm originating from the stromal cells that is predominantly comprised of atypical myofibroblasts. The present study reports the case of a patient with low-grade myofibroblastic sarcoma in the soft tissue of the knee. The patient exhibited a soft, painless mass on the medial side of the left knee. During surgery, a yellow-white mass above the posterior margin of the sartorius muscle was identified. This mass, which was irregular and adherent to surrounding tissues, had a blurry boundary, indicative of invasive growth. The morphology of the mass significantly differed from conventional lipomas and was lacking typical features. Immunohistochemical staining confirmed the diagnosis of a malignant LGMS. The patient experienced no recurrence over 1 year of follow-up and reported complete recovery of knee range of motion. The present study suggests that an incisional biopsy may be performed if LGMS is suspected based on patient symptoms and imaging results. In addition, long-term follow-up is crucial for the timely detection and management of any recurrence, playing a key role in the patient's ongoing care and treatment.

Introduction

Low-grade myofibroblastic sarcoma (LGMS) is a rare malignant neoplasm in the soft tissues that originates from the stromal cells and is characterized by atypical myofibroblasts with fibromatosis-like features (1). Predominantly affecting middle-aged men, LGMS often presents in the head and neck regions, although it could be found in other parts of the body (2). Currently, to the best of our knowledge, there is no literature reporting knee LGMS. Due to its painless nature, LGMS is frequently overlooked in clinical practice and misdiagnosed as a benign lesion or other diseases with similar symptoms or imaging findings (3). The actual incidence of LGMS may be under-reported due to unclear diagnostic criteria and a high potential for misdiagnosis. Reports about clinical details such as tumor size, method of treatment, and presence or absence of recurrence (local recurrence, regional recurrence and distant metastasis) and patient survival are sparse. Furthermore, the complete clinical picture of LGMS, including mortality rates, methods of treatment and risk factors, remains unclear (4). A population-based study in the USA reported 49 cases of LGMS with a 5-year overall survival rate of 71.6% (5). Surgery is currently the primary treatment for LGMS. Due to the rarity of reported cases, the standardization of its treatment, including surgery, chemotherapy and radiotherapy, requires further research (6). The present study details a rare instance of LGMS in the left knee.

Case report

A 75-year-old woman presented to the Department of Orthopedics at Guangzhou Red Cross Hospital (Guangzhou, China) in June 2021 with a 15-day history of a painless mass in the left knee. The patient reported no trauma, fever, joint swelling, weight loss or systemic symptoms. Physical examination revealed a soft, non-tender mass in the popliteal fossa, with normal overlying skin and no knee joint movement limitation. Ultrasound suggested a potential intramuscular hemangioma in the medial sartorius muscle layer. Magnetic resonance imaging (MRI) revealed a well-defined, heterogeneous 3.9x1.9-cm mass in the deep soft tissues of the thigh, distinct from the surrounding muscles and bone (Fig. 1). The painless nature, indolent growth and imaging reports of the mass led to the decision to perform tumor excision surgery without a pre-operative biopsy.

Intraoperatively, the tumor exhibited a unique morphology, differing from that of conventional lipomas. The well-encapsulated mass, which was adherent to the surrounding tissues, was completely excised with clear margins (Fig. 2A). For the microscopic observation, hematoxylin and eosin (H&E)

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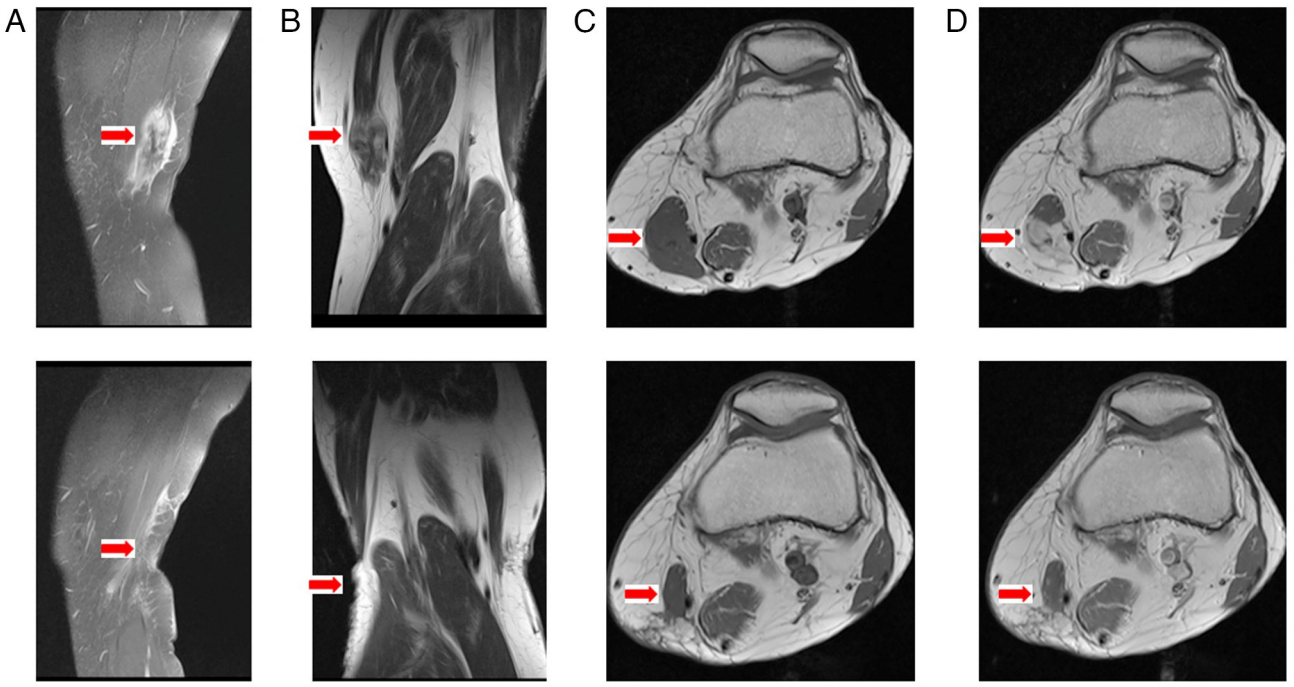

Figure 1. Magnetic resonance imaging analysis of the mass in different planes before and after surgery on both plain and enhanced scans. (A) Pre-operative and postoperative plain scans in the sagittal plane. (B) Pre-operative and postoperative enhanced scans in the coronal plane. (C) Pre-operative and postoperative plain scans in a cross-sectional plane. (D) Pre-operative and postoperative enhanced scans in a cross-sectional plane. Red arrows indicate the mass.

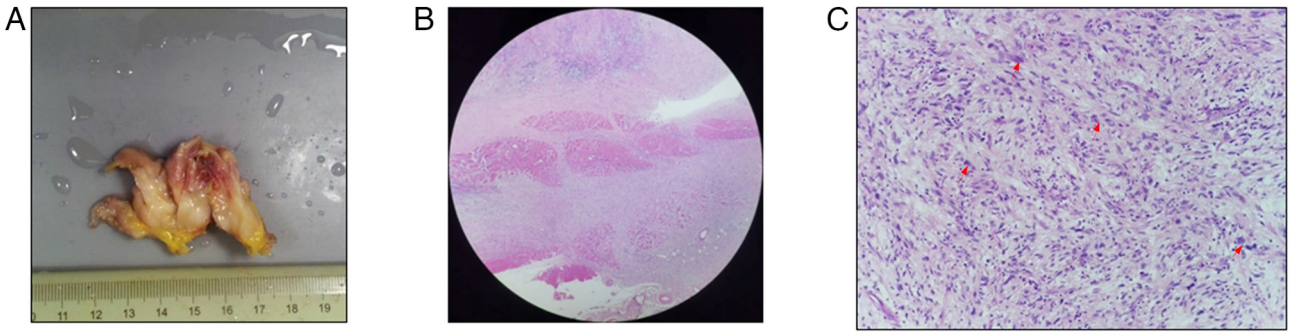

Figure 2. Macrograph and cytomorphological analysis of tissues. (A) A 7x4x1.5-cm mass of irregular gray-white-yellow tissue. (B) Histological examination of the specimen using hematoxylin and eosin staining at x40 magnification. (C) The proliferating tumor cells in a bundle-like pattern with varying amounts of collagen fibers, local patchy collagenization, and the presence of giant tumor cells and bizarre nuclear cells (arrows) at x100 magnification.

staining and immunohistochemical (IHC) staining results were examined using a Nikon Eclipse CI light microscope (Nikon Corporation). Tumor specimens were fixed in 10% neutral formalin at room temperature for ~48 h, embedded in paraffin and then cut into 4-μm thick sections for H&E staining. The sections were stained with hematoxylin for 3 min and eosin for 2 min at room temperature. At low magnification (magnification, x40; Fig. 2B), H&E staining showed infiltrative growth into the striated muscle and adipose tissue of the knee. At higher magnification (magnification, x100; Fig. 2C), Tumor cells, arranged in bundle-like patterns with varying collagen fibers and patchy collagenization, were fusiform, oval or irregularly shaped, with lightly eosinophilic cytoplasm. In total, <5/10 high-power fields contained giant tumor cells and bizarre giant cells. Chronic inflammatory cell infiltration was observed in the stroma, with no evident tumor necrosis. IHC was performed overnight at 4˚C using the following primary antibodies (prediluted by the manufacturer; Guangzhou Aisha Biotechnology Co., Ltd.): Vimentin (cat. no. IR630), smooth muscle actin (cat. no. IR611), CD99 (cat. no. IR057), β-catenin (cat. no. IR702), Desmin (cat. no. IR606), Ki67 (cat. no. IR626), anaplastic lymphoma kinase (ALK; cat. no. IR641) and S100 (cat. no. IR504). For IHC, the tissues were fixed in 4% formalin at room temperature for 48 h and subsequently embedded in paraffin. The tissue was sectioned into 4-μm thick sections. The sections were incubated at 100˚C for 20 min in a fully automatic immunohistochemistry instrument for antigen repair (Roche CC1 immunohistochemistry antigen repair buffer, High pH; cat. no. 5279801001; Guangzhou Aisha Biotechnology Co., Ltd.). Endogenous peroxidase activity was quenched with 3% hydrogen peroxide in methanol before incubation with primary antibodies. The secondary antibody, obtained from EnVision FLEX/HRP (prediluted by the manufacturer; cat.

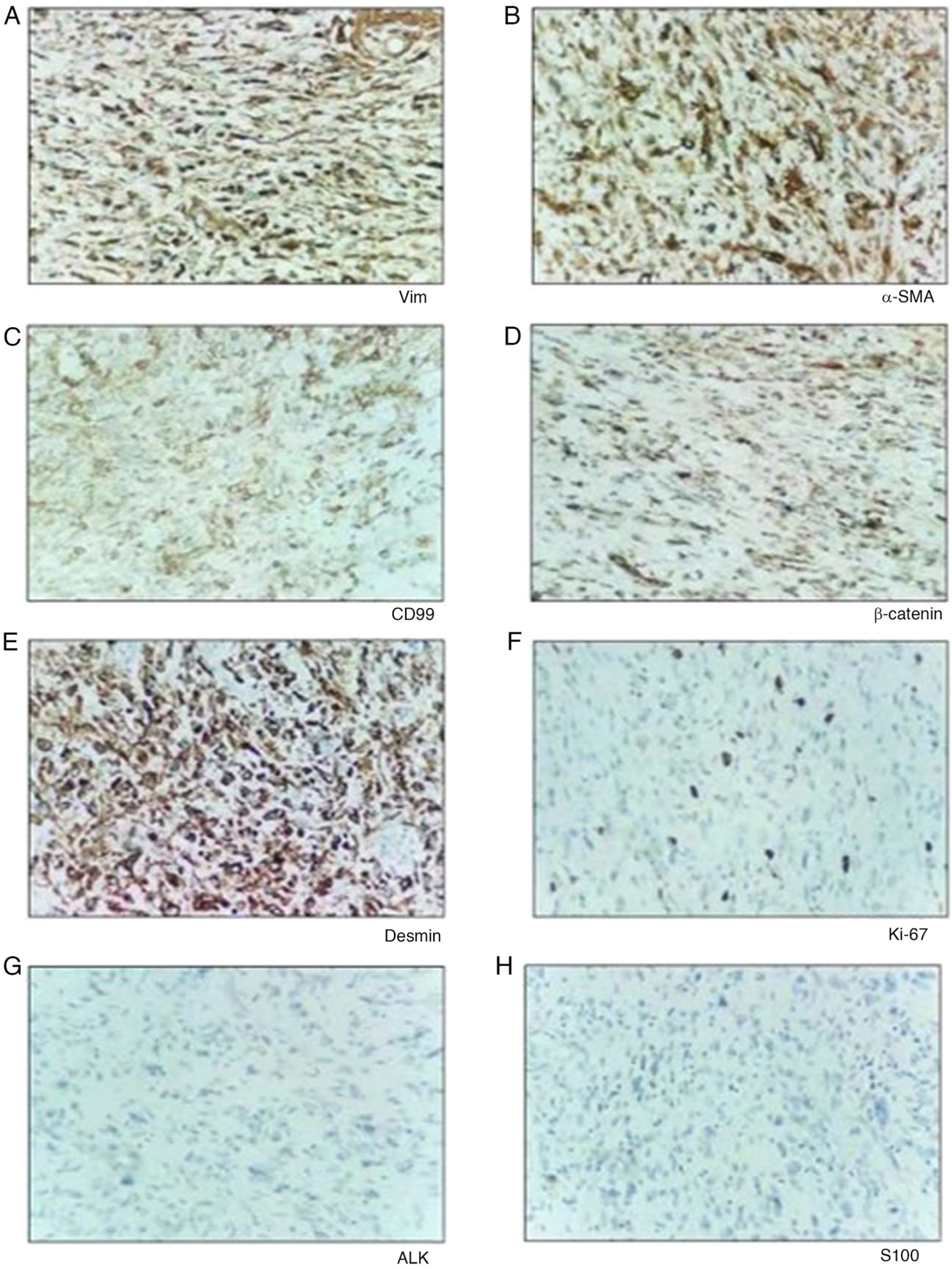

Figure 3. IHC analysis of tissues. Examination of the specimen, with IHC staining positive for (A) Vimentin, (B) α-SMA, (C) CD99, (D) β-catenin, (E) Desmin and (F) Ki-67, and negative results for (G) ALK and (H) S100, all at x100 magnification. SMA, smooth muscle actin; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry.

no. K4003; Agilent Technologies, Inc.), was used to incubate sections at room temperature for 12 min. Subsequently, an EnVision FLEX DAB+ Chromogen detection reagent was applied (cat. no. K5007; Agilent Technologies, Inc.). The IHC staining results showed positivity for Vimentin (Fig. 3A), α-smooth muscle actin (SMA) (Fig. 3B), CD99 (Fig. 3C), β-catenin (few nuclei) (Fig. 3D), Desmin (focal) (Fig. 3E) and Ki67 (15%) (Fig. 3F), but negative results for anaplastic

lymphoma kinase (Fig. 3G) and S100 (Fig. 3H). These findings led to a diagnosis of LGMS.

The patient underwent regular post-surgery evaluations every 3 months. After 1 year, no local recurrence or distant metastasis was detected. Quality of life (QOL), assessed using the EQ-5D-5L scale [EQ (visual analog scale) VAS] (7), improved over time, with scores of 80, 90, 94, 95 and 95 at the time of surgery and 3, 6, 9 and 12 months post-surgery, respectively. The patient expressed satisfaction with their post-surgery condition during the 1-year follow-up phone call.

Discussion

Vasudev and Harris (8) initially introduced the concept of LGMS in 1978, which was later verified by Mentzel *et al* in 1998 (9). In 2002, the World Health Organization recognized LGMS as a distinct entity and classified it under the fibroblast/myofibroblastic tumor category (10). Predominantly, LGMS occurs in the head, neck and oral cavity regions, with the tongue being the most commonly affected site (11). This tumor is known for its tendency to recur locally, although distant metastasis is rare. The diagnosis of LGMS in clinical practice is challenging due to its asymptomatic nature, slow growth, absence of distinctive biological features and limited diagnostic imaging options, often leading to misidentification as a benign lesion (12).

Wang *et al* (13) reported the clinical and radiographic characteristics of LGMS in bone. Radiologically, LGMS presents as extensive, infiltrative or worm-like bone destruction on X-rays and computed tomography (CT) scans, characterized by poorly defined lesion margins and cortical bone erosion. In the soft tissues, LGMS manifests as slightly irregular masses of varying densities that are poorly demarcated from adjacent tissues and lacking of specific features. MRI findings include a uniform or high signal on T1-weighted images and a uniform or uneven high signal on T2-weighted images. Enhanced scans typically show uniform or uneven signal enhancement. Pathological immunohistochemistry is crucial for LGMS diagnosis, which is often considered a diagnosis of exclusion (14). Microscopically, the tumor cells are elongated or star-shaped, with blurred cytoplasmic borders and mild acidophilia. The nuclei are elongated or wavy, containing evenly distributed chromatin. Some nuclei may appear slightly swollen, vacuolated and contain small nucleoli. LGMS is characterized by its diffuse infiltrative growth pattern. By contrast, low-grade malignant fibromyoblastoma features sparsely arranged cells with spindle-shaped cytoplasm, indistinct borders and mild acidophilia. The fusiform nuclei in these cells might display vacuolization, small nucleoli and notches, or they may be slender and wavy, resembling neural differentiation (15). Areas of collagen degeneration are also observed in LGMS. The tumor is enriched with thin-walled capillaries, and the presence of inflammatory cells such as lymphocytes and plasma cells is not significant. The immunophenotype of LGMS is varied, generally showing positivity for at least one myogenic marker, such as Desmin, α-SMA, Vimentin or Calponin (16). Usually, LGMS is an atypical tumor consisting of myofibroblasts and often expresses Vimentin. In the present case, the tumor was positive for Vimentin, Desmin and α-SMA, while Calponin expression was not evident.

The differential diagnosis of LGMS includes leiomyosarcoma, fibrosarcoma, fibromatosis and inflammatory myofibroblastic tumors (IMTs) (17). Leiomyosarcoma is a malignant spindle cell tumor that exhibits characteristics of smooth muscle; it is often identified by the presence of fusiform cells arranged in alternating fascicles. These cells have longitudinally fibrillary cytoplasm and cigar-shaped vesicular nuclei with paranuclear vacuolation. IHC tests for leiomyosarcoma usually yield positive results for α-SMA, Desmin and h-caldesmon. Fibrosarcoma is a type of neoplasm that consists of malignant spindle cells with fibroblastic differentiation; it is characterized by a herringbone fascicular architecture and spindle-shaped cells with elongated, tapered nuclei and minimal cytoplasm. Unlike myofibroblasts, fibrosarcoma cells do not show any myoid differentiation, as there is no immunohistochemical evidence of fibronectin, SMA or calponin. Fibromatosis is characterized by the presence of a prominent nodule that has a tendency to invade nearby tissue. The tumor cells in fibromatosis do not exhibit atypia or mitosis, and they only test positive for vimentin. Similar to fibrosarcoma, fibromatosis cells do not display myoid differentiation and do not express actin or SMA (2,18). IMT has a more distinct border, and under light microscopy, it exhibits a diverse cellular composition. In addition to spindle-shaped cells with fibromyoblastic characteristics, IMT may contain fibroblasts, histiocytes, plasma cells, lymphocytes and eosinophils, showing mucinous, vascular and inflammatory changes similar to nodular fasciitis. By contrast, low-grade malignant fibromyoblastoma typically exhibits infiltrative growth, predominantly consisting of fibromyoblast cells, with infrequent infiltration of inflammatory cells (19).

In vivo molecular imaging currently offers unique advantages in tumor diagnosis; it allows for high spatial resolution at reduced costs, and the capacity to detect sensitive, high-resolution light signals in deep tissues, which could aid in the diagnosis and differentiation of LGMS (20). While LGMS often presents as a slow-growing, painless mass, it is still classified as a low-grade malignancy, prone to local recurrence and distant metastasis. To the best of our knowledge, the current report presents the first case of LGMS in the knee. The standard treatment for LGMS remains as surgical resection, with some patients receiving postoperative radiotherapy and chemotherapy, although the efficacy of these treatments is debated (21). In the present case, the mass was completely and widely excised with clear margins. Patient QOL was assessed using the EQ-VAS on the day of surgery and at 3, 6, 9 and 12 months post-surgery, with scores of 80, 90, 94, 95 and 95, respectively. At the 1-year follow-up, the patient reported full recovery of the ROM, with no recurrence or metastasis observed upon regular reexamination.

Peng *et al* (22) documented a case where a patient with LGMS underwent two cycles of adjuvant chemotherapy post-surgery, resulting in no recurrence over 5 years. Conversely, Maruyama *et al* (23) observed a higher recurrence rate of LGMS following postoperative radiotherapy compared with surgery alone, suggesting radiotherapy should be avoided post-surgery. However, Mamikunian *et al* (24) suggested that radiotherapy is less likely to induce recurrence, advocating its use as adjuvant therapy, particularly for malignant tumors with or without adverse pathological

features. Chemoradiotherapy, however, is not recommended as a routine treatment for patients with margin-negative LGMS and may be considered for those with positive margins or recurrent disease (25).

In conclusion, LGMS, although relatively rare, tends to exhibit infiltrative growth and a high likelihood of local recurrence, while distant metastasis remains infrequent. The early presentation of LGMS is often atypical and easily overlooked, leading to frequent misdiagnoses in clinical settings and subsequent delays in receiving appropriate treatment. In cases where LGMS is suspected based on patient symptoms and imaging results, biopsy and surgical excision are viable approaches. A definitive diagnosis is typically established through a combination of postoperative pathology and immunohistochemical analysis. In instances where immunohistochemistry yields atypical results, molecular diagnostic methods may be employed. The decision to use adjuvant chemoradiotherapy post-surgery is influenced by several factors, including the tumor's location, the patient's overall health and the presence of metastases. Due to the risk of recurrence and potential metastases, it is crucial to maintain long-term follow-up with the patient. This vigilance helps in timely detection and management of any recurrence, thus playing a key role in the patient's ongoing care and treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WW designed and conceived the study, and revised the manuscript. TC was responsible for collecting clinical, imaging and pathological data of the patient, and was responsible for the conception, design, content and writing of the manuscript. SL operated on the patients, provided the surgical details described in the manuscript and was responsible for the conception, design, content and revision of the manuscript. JZ contributed to the writing of the manuscript, the conception of the study and the collection of pathological images. TC, SL and WW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided specific written informed consent, which included the acquirement of clinical data and pictures, in the form of an anonymous document for publication purposes.

Competing interests

The authors declare that they have no competing interests.

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