

## CASE REPORT

## Biphasic synovial sarcoma in a 19-year-old pregnant woman: a case report

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### Abstract

Synovial sarcoma is a rare malignant tumor of mesenchymal multipotent cells. We hereby present a case of synovial sarcoma of the upper left thigh. A 19-year-old patient was referred to our clinic by another hospital in Bucharest, Romania, for a soft tissue mass in the left upper thigh. Local examination of the left thigh revealed a 15/13 cm, ovoid, painful upon touch, soft tissue mass occupying the proximal-medial aspect of the thigh. Bilateral inguinal nodes' enlargement was noticed. Upon suspecting regional node involvement, the surgical team decided to perform left limb amputation due to tumor size and the proximity to major arterial and nervous trunks as well as the femoral shaft, making curative surgery and 'free of disease' resection margins improbable. The patient refused the operation. The surgical team (plastic surgeon, orthopedic surgeon) decided to attempt limb-sparing surgery. After tumor resection, free-of-disease surgical margins were achieved. The pathological examination as well as the immunohistochemistry (IHC) diagnosed a large biphasic synovial sarcoma warranting oncologic treatment. The association between tumor growth and pregnancy poses important therapeutic problems, such as the use of preoperative chemotherapy, potential pregnancy termination, limb amputation *versus* limb salvage intervention and types of protocols of chemotherapy or radiotherapy indicated.

**Keywords:** synovial sarcoma, pregnancy, limb-sparing surgery, radiotherapy.

### Introduction

Synovial sarcoma can occur at any age, but it is more common among teenagers and young adults [1]. It is a high-graded tumor that spreads to distant sites in up to 50% of cases [2]. There are no known risk factors for synovial sarcoma, but the disease is associated with the t(X;18)(p11;q11) chromosomal translocation [3]. Prognosis in synovial sarcoma patients is influenced by tumor size, local invasiveness, histological subtype, presence of metastases, and lymph node involvement [4]. The risk of developing distant metastases is higher in patients with tumor sizes larger than 5 cm [5].

The objectives of the current paper is to present the rare case of a biphasic synovial sarcoma, in a 19-year-old female, reviewing the most recent information on key topics in the multimodal therapy of soft tissue sarcoma. The case particularities include significant tumor growth during pregnancy, implying subsequent hormonal receptors of the tumor, the difficult therapeutic choice concerning limb-sparing surgery *versus* limb amputation, the association of adjuvant or neoadjuvant therapy, all of them guided by the pathological examination of the tumor. This particular case provides an actual guideline for the management of synovial sarcoma, covering investigations, diagnosis, surgical and oncologic therapy.

### Case report

Written informed consent was obtained from the patient for the use of any accompanying images.

A direct interview of the patient was carried out. The clinical examination noted all signs and symptoms. Radiographic and imagistic evaluations (CT-scan, MRI, angiographic studies) were performed. After surgery, the tumor was examined by a pathologist and confirmed by immunohistochemistry (IHC) studies. The patient was referred to an oncologist for adjuvant chemotherapy.

The patient, a 19-year-old woman, was admitted to the Clinic of Plastic and Reconstructive Surgery of the Emergency Hospital Bucharest, Romania, with a history of a rapidly growing soft tissue mass on the internal aspect of the upper left thigh, which resulted in pain and impairment of her ability to walk.

Her medical history described how she first noticed a 2–3 cm, tender mass on the inner aspect of the left thigh during the first trimester of pregnancy (11<sup>th</sup> week of pregnancy – w.o.p.). She asked her gynecologist for advice in her 15<sup>th</sup> w.o.p. Without any imagistic evaluation, she was advised to postpone surgery for the 'lipoma' until giving birth. The tumor grew in the second and third trimesters to an approximate size of 15/13 cm becoming painful and causing moderate functional impairment. The patient delivered a healthy baby on full-term through scheduled C-section.

One month later, during the postpartum period, she quit breast-feeding and was admitted in our clinic for further investigations and subsequent surgical therapy.

She denied any family history of soft tissue masses, local trauma, radioactive exposure or known chemical risk factors.

### Clinical findings

An ovoid soft tissue mass with a diameter of 13/15 cm could be noted on the inner aspect of the left upper thigh; it was tender, adherent to the adductor muscles and stretched the underlining skin. Bilateral inguinal nodes were enlarged. Sensory and motor examination of the lower left limb noticed no other pathological findings (Figure 1).

Biochemical blood investigations showed mild anemia, hemoglobin (Hb) 10.2 mg/dL, hematocrit (Ht) 32.1%. No clotting disorders were observed.

### Imagistic evaluation

The preoperative investigation protocol included chest X-ray (Figure 2), pelvis and abdomen ultrasound, a left lower limb angiogram, cerebral CT scan and several MRI examinations using gadolinium enhancement.

After chest X-ray, showing no signs of distant spread and a negative CT scan of the thorax and brain, PET-CT was recommended to confirm lack of metastasis, but could not be performed because of device failure.

The ultrasound evaluation of the abdomen and pelvis revealed no abnormal masses. Uterus and ovaries showed no pathological changes.

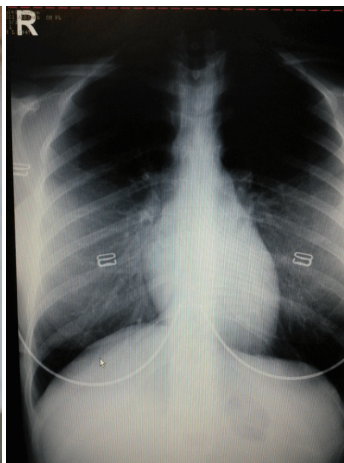
The preoperative lower limb angiogram showed a rich blood supply to the tumor; three large vessels derived from the deep femoral artery entered the tumor through its dorsal aspect (Figure 3).

MRI investigations of the lower left limb with gadolinium enhancement (Figure 4) revealed tumor of the deep posterior/inner muscle plane of the left thigh with subsequent invasion of the adductor magnus and adductor brevis muscles and of the deep femoral artery and vein; compression of the sciatic nerve; compression of the femoral shaft without a visible separation plane; numerous areas of hemorrhage, necrosis and cystic images with an increased intake of paramagnetic contrast, showing increased blood flow. The mass measured 13.6/8.7/8.4 cm in its greatest axis. Bilateral inguinal nodes' enlargement to a maximum of 3.5 cm in the longest axis was also noted.

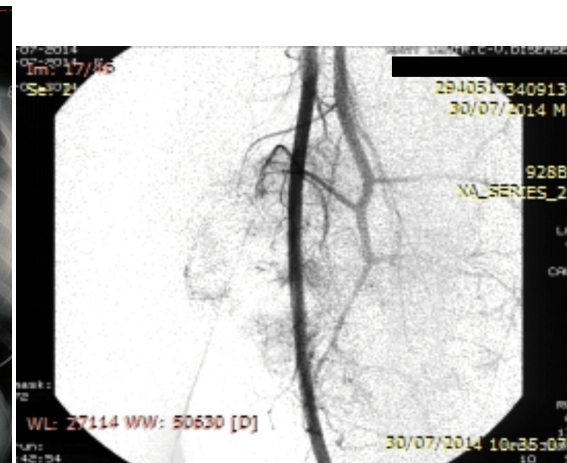
The imagistic aspect suggested a malignant tumor (suspected rhabdomyosarcoma) of the left thigh and warranted an angio-MRI scan for a more specific description of the vascular pedicles of the mass.



**Figure 1** – Soft tissue mass upper left thigh, skin distension.



**Figure 2** – Chest X-ray, excluded metastasis to lung and/or pleura.



**Figure 3** – Angiogram showing the rich blood supply of the soft tissue mass.

### Amputations versus limb sparing surgery

After completion of the investigations, the patient was staged according to FNLCC staging system with T2bN1M0, stage III disease.

The surgical team unanimously agreed to perform left lower limb amputation because of the suspicion of regional node involvement, tumor size, proximity to major arterial and nervous trunks as well as the femoral shaft, making curative surgery and free-of-disease resection margins improbable. The patient refused the operation. The surgical team (plastic surgeon, orthopedic surgeon) decided to attempt limb-sparing surgery.

After the “S”-shaped incision of the medial aspect of the thigh, the tumor was entirely excised along with the adductor magnus and brevis muscles, ensuring an envelope of 3 cm of healthy soft tissue. Dissection of the tumor from the periostum of the femoral shaft, the deep femoral artery and the sciatic nerve followed.

The excised tumor as well as a fragment of periostum, were sent for pathological examination. The preliminary result was undifferentiated small cell sarcoma. The drainage tube was suppressed 48 hours later. The wound dressing was changed every 2–3 days. Postoperative evolution was favorable, without local and systemic adverse events. The patient was discharged after seven days.

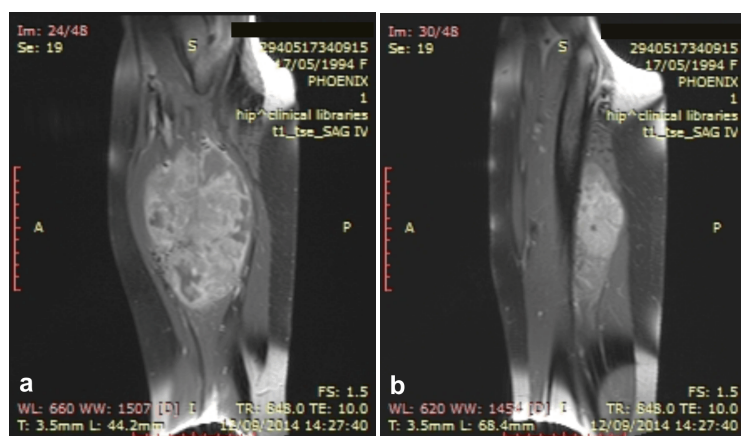
### Pathological examination

The pathological examination showed a large biphasic synovial sarcoma that invaded the surrounding fatty tissue as well as the fascia and tendons, with extensive areas of hemorrhage and calcification.

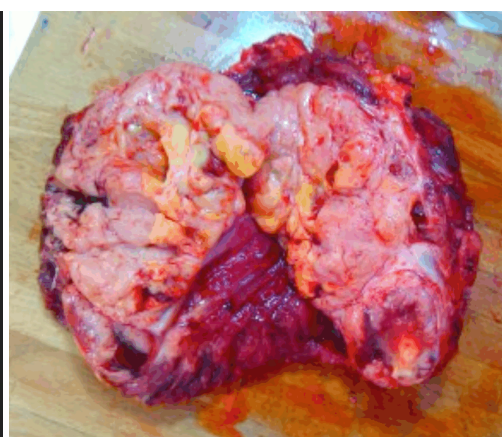
Free of disease resection margins were achieved. Lower limb function showed a decreased adduction without a significant functional impairment.

The lesion is sharply circumscribed, round, multinodular, with compression of adjacent muscle tissue, fascia and tendons. On section, the tumor appearance is nodular, yellow to gray-white, soft on palpation, friable or shaggy in areas of hemorrhage and necrosis. Other noticeable findings: cyst formation, edema, myxoid areas, calcifications (Figure 5).





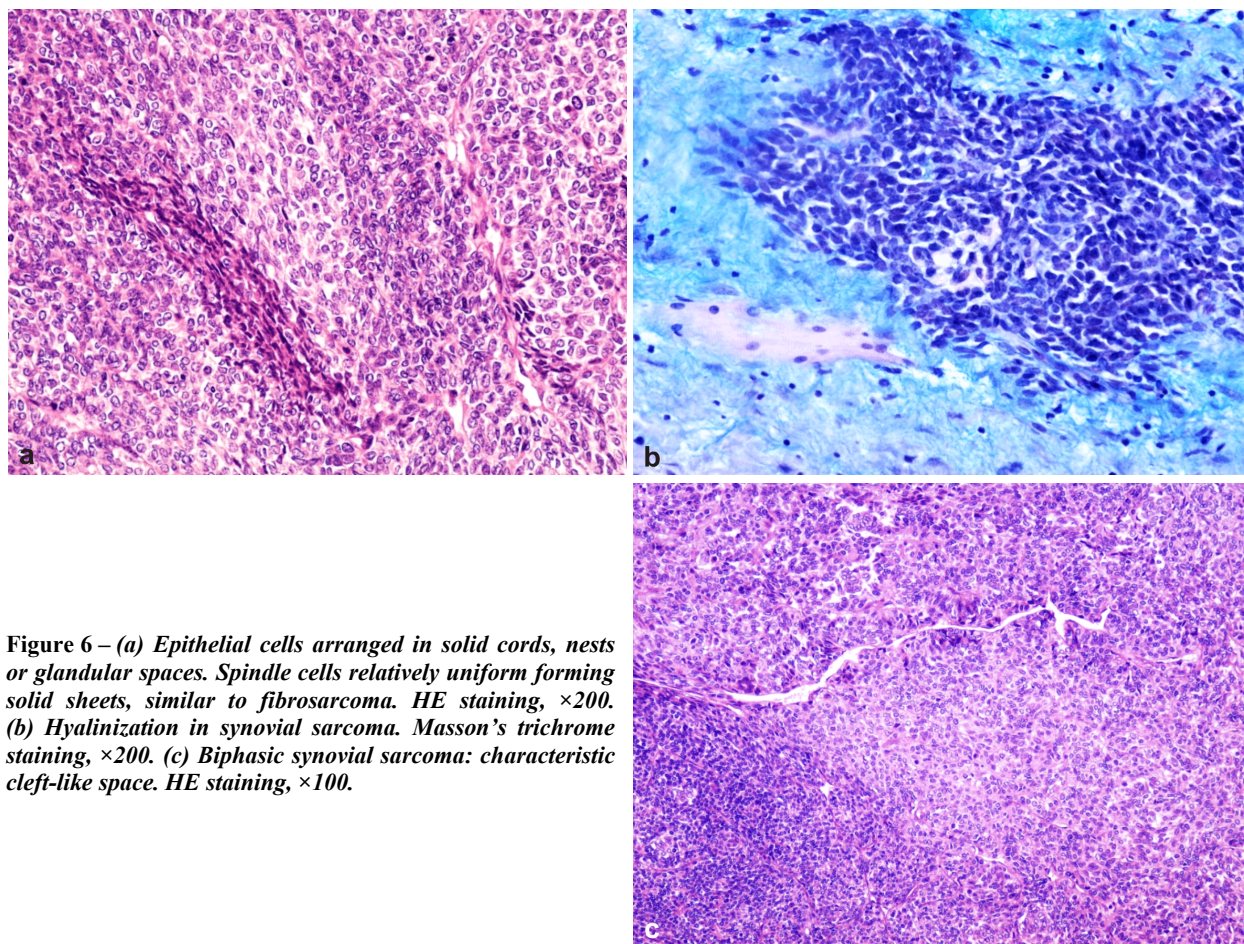
**Figure 4 – MRI showing soft tissue mass in left thigh: (a) Two coronal views; (b) Sagittal view.**



**Figure 5 – Tumor cross section showing multiple areas of hemorrhage, necrosis, and cyst formation.**

Microscopic findings show a large biphasic synovial sarcoma, composed of spindle-shaped and epithelial cell elements, with extensive areas of hemorrhage, calcification that infiltrated the surrounding fatty tissue, as well as the fascia and tendons. The biphasic type of synovial

sarcoma consists in the coexistence of morphologically different but histologically related epithelial cells and fibroblast-like spindle cells. The tumor presented areas of hyalinization, numerous cleft like spaces as well as glandular spaces and ossification (Figure 6).



**Figure 6 – (a) Epithelial cells arranged in solid cords, nests or glandular spaces. Spindle cells relatively uniform forming solid sheets, similar to fibrosarcoma. HE staining, ×200. (b) Hyalinization in synovial sarcoma. Masson's trichrome staining, ×200. (c) Biphasic synovial sarcoma: characteristic cleft-like space. HE staining, ×100.**

Resection margins were free of disease. The tumor was staged as pT2bNx G3. IHC stains of the tumor were recommended for correct diagnosis of tumor subtype.

#### Immunohistochemical findings

IHC examination confirms the initial diagnosis of biphasic synovial sarcoma: the tumor is vimetin+, B-cell lymphoma (bcl)+, epithelial membrane antigen (EMA)+,

MIC occasionally+, Ki67 20%+, and surrounding blood vessels tested positive for hematopoietic progenitor cell antigen CD34.

Genetic analysis using FISH or RT-PCR for detection of the specific t(X;18)(p11;q11) translocation would have been useful but could not be performed ahead of surgery.

The SYT-SSX fusion can be detected by real-time reverse transcriptase-polymerase chain reaction (RT-

PCR) or fluorescent *in situ* hybridization (FISH) using ice or paraffin-embedded tissue.

### Current status

The patient was referred to an oncologist. Adjuvant chemotherapy was administered for six weeks using a regimen of Ifosfamide 5 g/m<sup>2</sup> and Doxorubicin 50 mg/m<sup>2</sup> once a week. After the completion of the regimen, the patient was referred to a radiotherapist.

External radiotherapy for the prevention of tumor recurrence was administered up to a total dose of 50 Gy using a 10 Gy/week regimen. At the moment, the patient continues the external beam radiotherapy. The follow-up MRI shows decreased inguinal lymph nodes and inflammatory alteration of the tumor bed with no local relapse.

### Discussion

Synovial sarcomas are rare, malignant, high graded soft tissue neoplasms. The estimated incidence of this subtype in the general population is around 2.75/100 000 [6–8]. Approximately 30% of these tumors occur in the 2<sup>nd</sup> and 3<sup>rd</sup> decades of life, with a maximal incidence in young adults between 20–40 years of age. Males are more frequently affected. No differences in ethnic groups were noted [8–10].

The most common presentation is that of a palpable, deep-seated swelling or mass associated with pain or tenderness in slightly more than half of cases. There may be minor limitation of motion, but severe functional disturbance is rarely encountered. The mechanism for the common symptoms of pain and tenderness is unknown [11].

Synovial sarcomas develop near joints, tendons or bursae, but locations elsewhere than in the proximity of joints have been reported. The most frequent location is the lower limb, the tumor being located around the knee or ankle [12].

Delay in diagnosis and treatment is frequent, because of patients' lack of medical education.

Misdiagnosis is frequent. Improper investigation of the tumor and inadvertent resection are responsible for local relapse.

This particular type of soft tissue sarcoma is known for its 55% risk of lymphatic spread, so clinical evaluation must take this into account [9].

To this day, the golden standard regarding imagistic studies is considered to be gadolinium enhanced MRI of the affected region.

Core needle biopsy of the tumor should be performed if possible. Biopsy allows pathological typing of the tumor and sheds light on its natural history [13].

The cornerstone of the multimodal treatment plan consists of surgery. The proposed operation was limb amputation at the beginning of the century. Since the application of microscopy in the operative field, complex reconstructions are possible, allowing the more modern concept of limb-sparing surgery to develop. Limb amputation has few current indications, including neurovascular invasion, bone invasion and massive soft tissue loss. The primary sarcoma should be excised with a 2–3 cm thick envelope of healthy tissue. Since fascia and the periostum

naturally fight the spread, an excision of no more than 1 mm of these structures is usually enough [14].

The pathological examination has to distinguish between the known forms of synovial sarcoma: monophasic type, consisting of spindle cells only and the biphasic type, composed of both spindle and epithelioid cells. If the tumor is poorly differentiated, additional tests are necessary for the proper diagnosis, such as IHC stains, specific stains, RT-PCR or FISH [15].

Immunohistochemically, most synovial sarcomas are positive for vimentin, cytokeratin and epithelial membrane antigen and lower reactivity for S100 and CD34 [16].

After completion of surgery, oncologic therapy is advised. Preoperative chemotherapy or radiotherapy may be effective in shrinking inoperable tumors. As a post-operative therapy, radiation therapy has proved successful, while the role of chemotherapy is still debated [17].

Most patients are young but hold a poor prognosis, because these tumors are locally aggressive and associate a high metastasis rate. According to literature, local recurrence and/or metastatic disease is found in up to 80% of patients. The 5-year survival rate is estimated between 30–55%.

The presented clinical case poses several diagnostic and therapeutic challenges:

This is a rare case of synovial sarcoma in a 19-year-old pregnant female; there is only one other case described in literature, of a 22-year-old pregnant patient with a large synovial sarcoma of the thigh, who was treated through wide excision of the tumor, but distant metastasis were diagnosed in two months after surgery [18]. The association between tumor growth and pregnancy poses important therapeutic problems: should we focus on the pregnancy or should we terminate the pregnancy and perform an early operation? The development of cancer in a pregnant woman is relatively rare and the association of sarcoma and pregnancy is exceptional. The influence of pregnancy on the initiation, promotion and development of sarcomas is still unclear. The medical approach is strongly influenced by the type and location of the primary tumor, the growth rate and associated symptoms, as well as by the need to treat the patient and minimize fetal toxicity. Pregnancy outcome is strongly influenced by the need for short-term treatment. Additional tests such as magnetic resonance imaging, ultrasound and biopsy are safe during pregnancy [19].

After researching protocols, the author believes that the proper management would have consisted in imagistic studies of the primary tumor using the MRI, termination of the pregnancy as soon as the fetus was viable and prompt treatment. The hormonal imbalance of pregnancy may have affected the tumor, causing a more rapid growth.

Why did the tumor have such a rapid growth during the second and third trimester of pregnancy? We could suspect the existence of a hormone sensitive receptor of the sarcoma that could potentially be used for detection or targeted therapy in the future. A review of the available literature discovered a case of sarcoma (extra-uterine leiomyosarcoma) testing positive for hormone receptors (both estrogen and progesterone receptors). Another study reported positive estrogen and androgen receptors in well-differentiated liposarcoma. The arising problem is

whether targeted therapy using antiandrogen and SERMs (selective estrogen receptor modulators) such as Tamoxifen might have been useful in this case [20, 21].

Would adjuvant therapy have been useful? Since the patient was referred to a surgeon after giving birth, any preoperative chemotherapy would have damaged the fetus, so the authors does not recommend it. Radiation therapy would not have been advisable.

Would limb amputation have been a better, safer surgical procedure in this selected case? The decision of proposing hip disarticulation was based on imagistic and clinical findings, suggesting a highly aggressive tumor. Hip disarticulation would have allowed curative surgery, removing the tumor, the regional lymph nodes, the neurovascular bundle and the femoral shaft, presenting a higher chance of survival. A core needle biopsy of the tumor or a fine-needle aspiration biopsy of the enlarged lymphatic nodes would have allowed a pathological examination of the tumor, completing the therapeutic plan.

The patient understood the risks of refusing the operation. Limb sparing surgery is possible in this particular case, because of the tumor location in the medial compartment of the thigh, the adductor muscles having little importance in limb function. Adductor muscle excision and limited adduction does not pose a significant functional problem. Had the femoral artery been involved microvascular reconstruction using saphenous vein graft would have been warranted. Sciatic nerve involvement would have caused significant morbidity, due to the resulting dropping-foot.

Fortunately, none of the above was necessary.

The patient was overall content with the result; mobilization using support (a cane) was possible in the 3<sup>rd</sup> day after surgery. She could perform her daily activities.

During her hospital stay, the patient complained about depression caused by the anxiety of having multiple investigations done, the indication of amputation and the overall burden of suffering from cancer. It is the authors' opinion that psychological support from a specialist is beneficial.

Other investigations that would have proven useful are RT-PCR or FISH of the excised fragment, and detection of the specific fusion gene SS18-SSX. The result however would not have changed the overall therapy.

The oncologist recommended administration of the MAID (Mesna, Doxorubicin, Ifosfamide, Dacarbazine) protocol, but clinical trials failed to prove an increase in disease free survival associated to this therapy.

External beam radiotherapy was applied after the following protocol: 2 Gy  $\times$  5 (days/week) for five weeks to a total of 50 Gy.

A close postoperative follow-up is necessary in order to insure the best vital and functional outcome in this case.

## ☐ Conclusions

We report a case of synovial sarcoma of the thigh in a 19-year-old pregnant woman presenting as a rapidly growing soft tissue mass. Lymphatic spread was suspected due to inguinal lymph node enlargement. After complex investigations (CT scan, MRI, angiogram, ultrasound, blood analysis) and interdisciplinary involvement (plastic surgeon, vascular surgeon, orthopedic surgeon) the final

treatment plan was established. After the patient's refusal of the amputation, the surgical plan was adapted to the patient's wish. Oncologic treatment was mandatory. The prognosis is uncertain, most probably the patient already having suffered from metastatic spread, even if it was not observed on the CT scans. All efforts having been undertaken, the patient's overall survival and disease free interval remain to be observed.

## Conflict of interests

The authors declare that they have no conflict of interests.

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## Author contribution

All authors contributed extensively to the work presented in this paper. AMO played a major role in writing the manuscript and analyzed the patient data. AMO also followed-up the patient, collected the medical investigations. SIT and VM aided in editing the manuscript. LI, VM, PSA and SIT reviewed the manuscript and helped analyzing the medical data. RS analyzed the microscopic specimens, interpreted them and took the photographs. All authors read and approved the final manuscript.

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