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Case Report

LOW-GRADE FIBROMIXOID SARCOMA OF LOWER LEG IN YOUNG FEMALE PATIENT- REPORT OF A RARE CASE

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ABSTRACT

Low-grade fibromyxoid sarcoma (LGFMS) is a rare soft tissue neoplasm described for the first time by Evans in 1987. It may affect the subcutaneous soft tissues or subfascial space. It usually arises from deeply located soft tissue structures of extremities, head and neck, thorax, and retroperitoneum. We present a case of a female patient of age 24, admitted to the Department of "Surgical Diseases" of Medical University Hospital "D-r G. Stranski" Ltd – Pleven in July 2022, with complaints of a slowly growing non-painful soft mass, located on her right lower leg, distal 1/3 part, anteriorly initially suspected for lipoma. After wide surgical excision grossing and histological and immunohistochemical verification of the specimen, the result was LGFMS G1 pT1. We perform a literature review for another case in the world with that rare tumor. The tumor is with distinct biological behavior. Despite its low grade and benign histological appearance, it has a high potential for metastasizing, years after the primary surgical excision of the tumor, and it has a high risk for local recurrence. Because of the high risk of late metastasis, the follow-up period should be long and monitoring of the lung and chest is mandatory.

Key words: soft tissue tumors, low-grade fibromyxoid sarcoma; immunohistochemistry

INTRODUCTION

Low-grade fibromyxoid sarcoma (LGFMS) is a soft tissue neoplasm, described for the first time by Evans in 1987 as a slow-growing tumor of the scapula and chest wall in two female patients at the age of twenty and given the name of the tumor- Evans'. (1) For the next 6 years- till 1993, he described new 12 cases of that sarcoma. (2) According to the World Health Organization's classification of soft tissue sarcoma, LGFMS is a kind of malignant fibro sarcoma with a distribution of 0,6% of all soft tissue sarcomas. (3) It is an extremely rare neoplasm, and the data from the literature conclude that the exact incidence could not be estimated. Till 2000, M. Zamecnik reported 32 cases from the literature and described their experience with 8 new cases. (4) In 2005 Kim et all. reported a total of 53 cases of LGFMS in the world and made the first imaging description of that tumor upon 3 their cases. (5) Maretty- Nelsen et all. reported an incidence of 0.18 per million. (6) In Bulgaria, we found described in the medical literature only two cases of LGFMS- the first one located in the larynx in 50 years old male patient after local radiotherapy for squamous cell carcinoma. (7) The second case was in 57- years old female patient with a location of sarcoma in her left parotid gland. (8) Generally, the patients, described with LGFMS are young people in the middle age group, but a few articles reported cases in pediatrics (9). The common locations of that malignancy are the extremities and body trunk, but rare and possible locations may be the head, oral cavity and neck, chest wall and

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mediastinum, groin region, and retroperitoneum. (10-12)

We reviewed a Pub Med article focused on the topic of LGFMS of extremities and the main results were compared with our treatment results.

CLINICAL CASE

We present a case of a female patient of age 24, admitted to the Department of "Surgical diseases" of Medical University Hospital "D-r George Stranski" Ltd – Pleven in July 2022, with complaints of a slowly growing soft mass, located on her right lower leg, distal 1/3 part, anteriorly. Being a visible cosmetic defect, the patient decided to seek advice from a surgeon and undergo surgical removal of that mass. The patient has no cat scratches episodes or evidence of trauma in that region. The patient saw for the first time that mass in February 2022, as a small-sized soft nodule- like a "peanut", that grew up and reached the size of 45-50 mm in diameter for the next 4 months. The local surgical status objectively showed that the mass was not painful. It was soft in consistency and movable according to adjacent tissues. The feeling in palpation is like touching a round, smooth and soft sphere, it was not tender. The skin over the mass was of normal color, with neither swelling nor evidence of inflammation or fluctuation. The regional lymph nodules were not painful and not enlarged. The local status seems to be a lipoma formation and no macroscopic evidence that the mass is malignant. The laboratory results were in a normal range and the preoperative chest X-ray was with normal characteristics for the age of the patient. The X-ray of the lower leg was unremarkable. The preoperative CT scanning described a soft tissue, round formation, well circumscribed that did not invade the adjacent periosteum or bone substance of the right tibia. There was no evidence of distant lymph node metastases, nor metastases in liver or lungs. The surgical procedure was done with local anesthesia with Lidocaine 1%, with total extirpation of a round, soft solid formation, covered with a very thin capsule, subcutaneously located. We performed entire radical excision of the surrounding tissues, together with adjacent periosteum of the right tibia. The excision was performed at a distance with at least 30 mm safe borders out of the visible dimension of the tumor formation. The cutting surface was white and yellow stripes, with no lobulation. The wound was drained and healed by primary intention with a cosmetic intradermal suture. The surgical specimen was measured as 35x40x45 mm**. (Figure 1)**

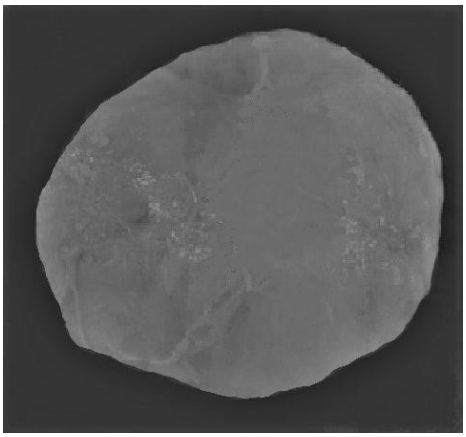

Figure 1. Macroscopic specimen.

The pathohistological verification of the form described the lesion as a well-circumscribed, partially encapsulated tumor composed of alternating areas of hypocellular, myxoid, and collagen deposition with hyalinization. In other areas, the tumor consists of fusiform cells with moderate nuclear polymorphism, and rare mitoses, with fascicular and swirling growth patterns. The vessels are of the arteriolar type, in places with perivascular hyalinization. **(Figures 2, 3, 4)**

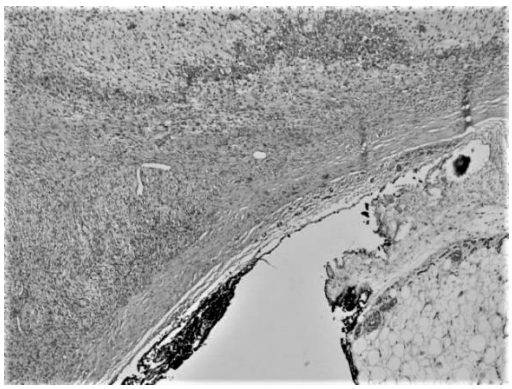

Figure 2. Well-circumscribed, fibrous lesion. Hematoxylin-Eosin staining, Magnification x 4

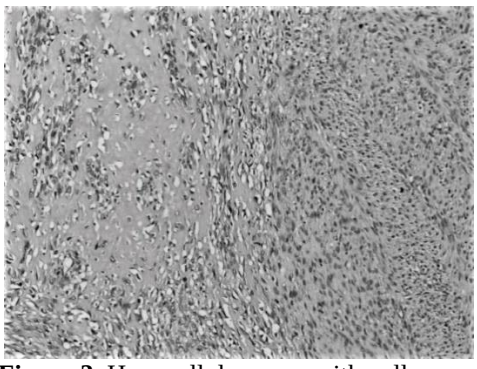

Figure 3. Hypocellular areas with collagen deposition alternating with fusiform tumor cells with diffuse growth. Hematoxylin-Eosin staining, Magnification x 10

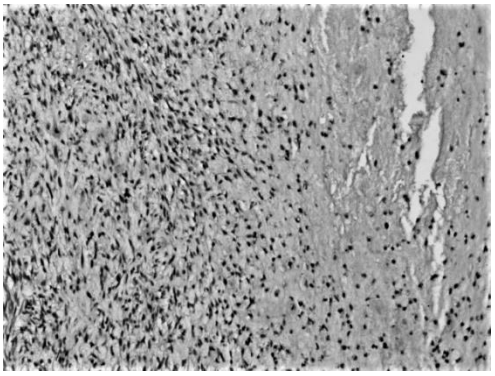

Figure 4. Areas of diffuse tumor cell growth and myxoid changes. Hematoxylin- Eosin staining. Magnification x 10

We performed additional immunohistochemical staining of other tumor markers and the morphological result corresponds with the fibroblastic nature of the tumor. According to the tumor immunophenotype, the tumor cells are negative for epithelial membrane antigen (EMA), negative for S-100 protein, either for CD68, Desmin, and alpha-smooth muscle actin (alpha- SMA), but focally positive for CD34. (**Figures 5, 6)**

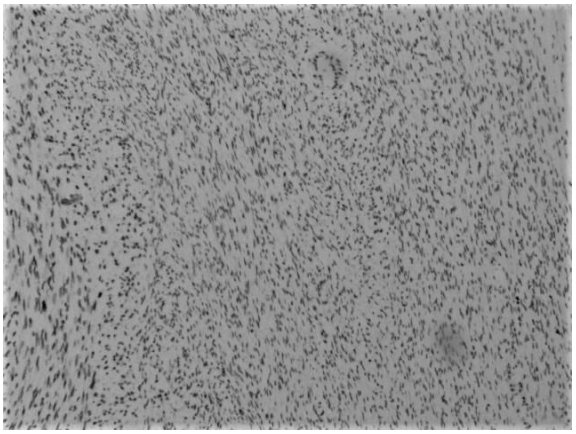

Figure 5. Negative immunohistochemical staining for desmin. Magnification x 10 Monoclonal antibody, clone D 33, Dako, Ready to use

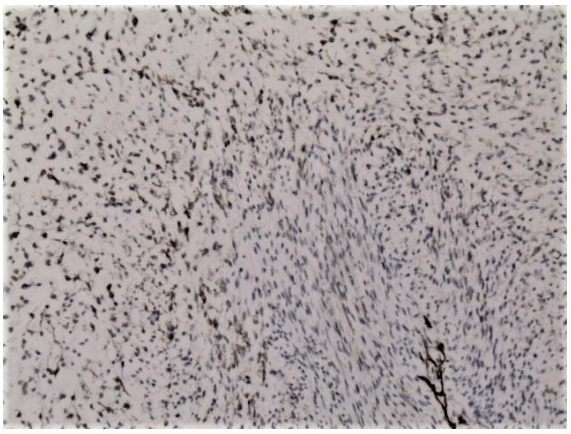

Figure 6. Focally positive immunohistochemical staining for CD 34. Magnification x 10

The highly specific and sensitive LGFMS marker- MUC 4 in our case was with negative expression. **(Figure 7)**

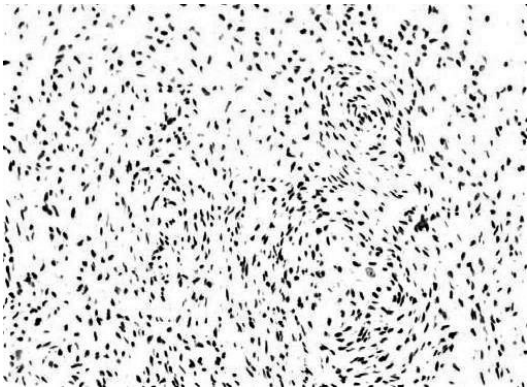

Figure 7. Muc 4 negative immunohistochemistry, Magnification x10

The tumor was resected in totally clear hystological borders and there no tumor cells in the margins of specimen. It was evaluated as pT1pN0cM0, Eastern Cooperative Oncology Group score (ECOG) Score 1-patient, restricted in physical activities and ambulatory. The clinical stage was evaluated as IIA- . Postoperatively, the wound healed primarily, without any complications. **(Figure 8)**

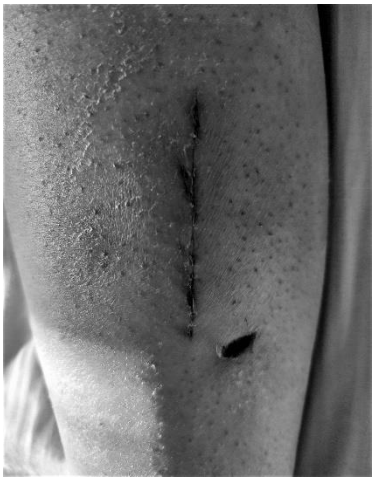

Figure 8. Primary wound healing after radical tumor excision.

The patient was registered in the Regional Oncological Center and the decision of the oncological committee was the patient is indicated only for dispensary monitoring with regular follow-up visits in every 3 months with a focus on evidence for liver metastases with ultrasonography and lungs with chest X–ray. Body CT- scan with contrast enhancement was scheduled in every 6 months. The patient had her first follow-up visit in October 2022 and she has no evidence of distant lung metastases and no local recurrence of the malignancy. **(Figure 9)**

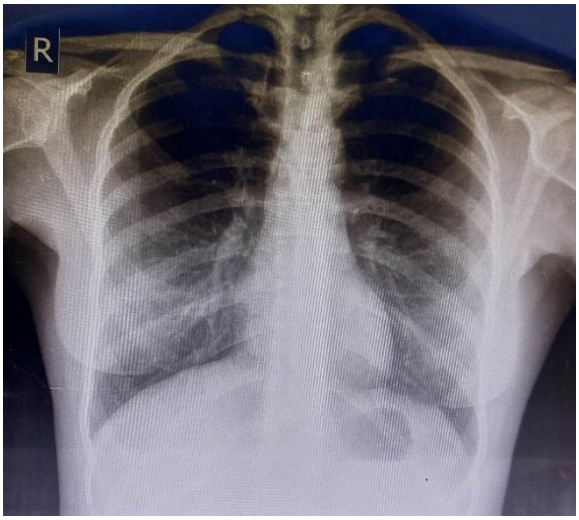

Figure 9. Follow-up chest X-ray shows no metastases.

The last follow- up visit was in April 2023 and contrast enhanced body CT scan was negative for local recidive of tumor in right lower leg and there were no imaging data for distant metastases**. (Figures 10, 11)**

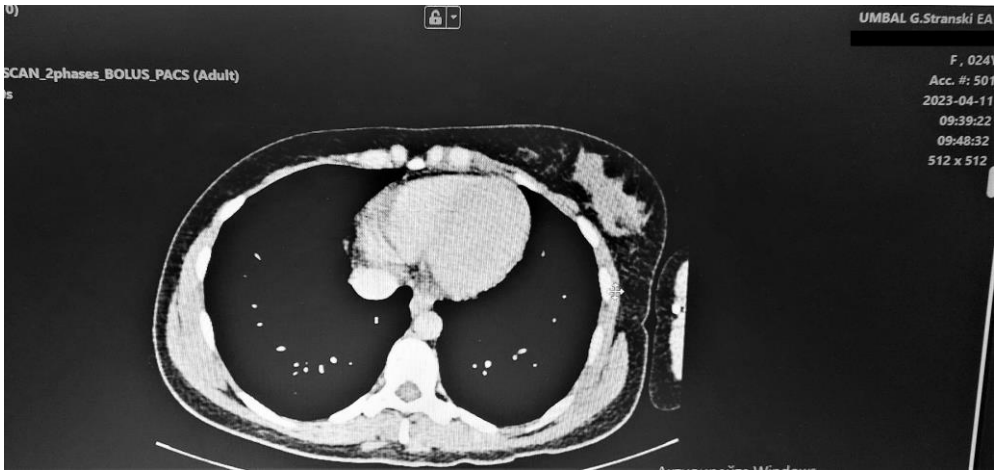

Figure 10. Follow –up chest CT with contrast shows no metastases.

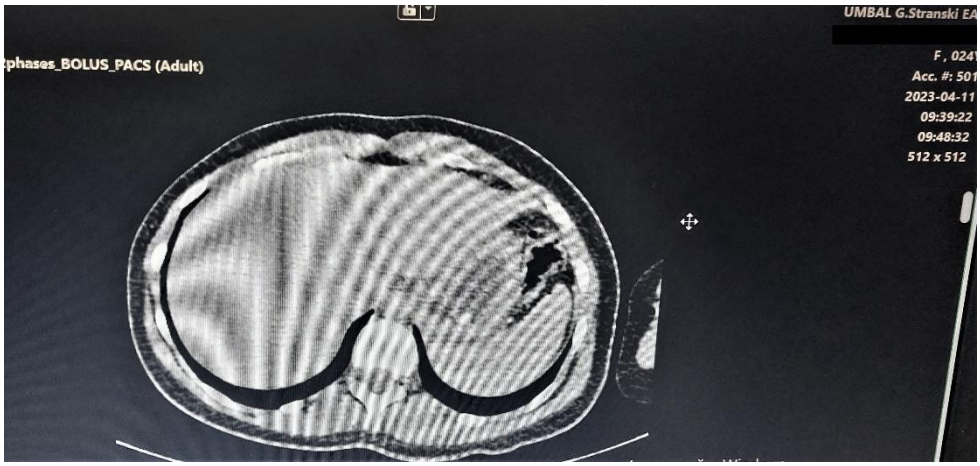

Figure 11. Follow –up Abdominal CT with contrast shows no liver metastases.

The patient was strongly recommended to perform a genetic analysis by in situ fluorescence hybridization for translocation and presentation of fusion of FUS- CREB3L2 genes. This mutation is typical for LGFMS and has only diagnostic value, in case of negative MUC 4 marker. Presence of that mutation does not change the postoperative monitoring or oncological treatment strategy, because there no specific target gene therapy for that malignancy. The information from genetic analysis is additional and only support the final diagnosis and do not affect the treatment regimens or strategies for that malignancy.

DISCUSSION

LGFMS is a malignant fibroblastic neoplasm, either infiltrative or circumscribed. All cases described with the primary location of lower extremities are with painless, soft tissue mass, very well circumscribed and no tendency for infiltrative growth pattern and have a very slow rate of gaining in size. (13,14) On a microscope, tumor "face" can be recognized by alternating collagenous and myxoid areas, that are usually found to surround the curvilinear capillaries network. (15) The cells are deceptively bland and spindle, with eosinophilic cytoplasm, and round to ovoid nuclei without nucleoli. The small vascular elements are like arcades. The rosettes of collagen are usually described. Immunohistochemically, LGFMS may be positive for CD 99, bcl-2, EMA and extremely rare may be positive for CD 32 and SMA. As a type of sarcoma, LGFMS is generally negative for S-100, desmin, cytokeratin, caldesmon, and CD 117. (16) MUC 4 is a highly specific and sensitive marker for LGFMS, and its cytoplsmatic expression is approximately 99% of cases. (16,17) In our study MUC 4 expression was negative, but morphological characteristics in hematoxylin-eosin staining focused on the typical structural characteristics for LGFMS in a differential plan with another soft tissue sarcomas. In case of negative results for MUC 4, genetic analysis is highly recommended. The expression of cell elements and matrix in LGFMS has its genetic base – it is a result of a gene mutation that leads to translocation of chromosomes 7 and 16 or translocation between 11 and 16 chromosomes and fusion of two genes- FUS and CREB3L2 or FUS gene and CREB3L1. These genetic characteristics are 100% specific for the final diagnosis of LGFMS and may help with the T-PCR test in case of collecting a little tissue specimen. They may be highly informative in cases when the typical histological markers for LGFMS like MUC 4 and CD 24 (target genes of CREB3l1) are with negative expression in immunohistochemistry. (18) Linos et al, 2014, described the first case of negative for MUC 4 case of 79 – years old female patient with LGFMS on her right femur. Despite the negative MUC 4 result, the genetic analysis concluded the presence of gene translocation between 7 and 16 chromosomes and fusion was positive for FUS- CREB3L2. The main advice was despite MUC 4 negativity; pathologists should keep the diagnostic algorithm through molecular investigations to decrease the risk of misdiagnosis. (19) Males are more often diagnosed with LGFMS than females. The local recurrence rate is reported to range between 13.6%-54% of cases. (20) Systemic chemotherapy and radiotherapy have limited efficacy in that malignancy. Surgical treatment with wide secure margins, at least 30 mm is still the procedure of choice. (14) Distant metastases occur in 6 % and usually affect the lungs and that happens in a long period ahead, after the primary surgical procedure, as the longest period described is 45 years after primary surgery. Because of the high risk of late metastasis, the follow-up period should be long and monitoring of the lungs and chest is mandatory. (20)

CONCLUSION

The LGFMS is a tumor with distinct biological behavior. Despite its low grade and apprently benign histological appearance, it has a high potential for metastasis, years after the primary surgical excision of the tumor, and it has a high risk for local recurrence. Because of its sporadic and very low incidence, there are no protocols for diagnosis and surgical and postoperative monitoring of patients with LGFMS. That's why LGFMS is a challenge for surgeons, pathologists, and radiologists because it requires a long period of follow up and that principle is mandatory for exact patient management. Surgical resection in oncological clear borders is the radical treatment of choice for cases with LGFMS because this tumor is extremely insensitive to chemo and radiotherapy. Our patient is still alive, 9 months after the diagnosis, and has no evidence of local recidive of the described malignancy. This is the first case of LGFMS located on the lower leg, described in a medical journal in Bulgaria.

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