

Expansive intracardiac leiomyosarcoma – a combined therapeutic approach resulting in survival with complete remission.

A literature review and case report

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Primary cardiac sarcomas are extremely rare and often with dismal prognosis. Only a few case series and retrospective studies regarding its biological characteristics, diagnostics, and treatment were reported. The multi-modality therapeutic strategy has been discussed in the published literature, but often with contradictory results. There is thus, no consensus on the optimal therapeutic approach to date. We present the case report of the 66-year old female endangered by a large primary leiomyosarcoma expanding in the right-sided heart chambers with imminent risk of acute obstruction of blood flow. The patient was managed by urgent surgical resection. After the histological confirmation of incomplete R1 resection, the treatment was supplemented by adjuvant CT-targeted radiotherapy, resulting in extraordinary survival with complete remission over a 24-month follow-up period. Our case report aims to demonstrate a favorable result of an individually suited complex surgical and oncological treatment to support the multidisciplinary therapeutic approach to these patients. The article is supplemented by a detailed literature review providing a theoretical background and an overview of the acquired knowledge and possible strategies.

Key words: leiomyosarcoma, cardiac tumour, cardiac surgery, radiotherapy

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INTRODUCTION

Primary cardiac tumours are infrequent neoplasms with a prevalence lower than 0.03% (ref.¹). The malignant group accounts for less than 1/4 and a rare subtype – leiomyosarcoma – represents only 1–9% of these^{2,3}, mostly detected in the left atrium in 76% (ref.⁴). The prognosis for heart sarcomas is poor with the mean survival interval ranging from 9.6 to 16.5 months^{5,6}. We describe a case of unusually large intracardiac leiomyosarcoma causing a hemodynamically significant obstruction of the right atrium, the tricuspid valve and the right ventricle, with progressive clinical presentation of low cardiac output syndrome.

EPIDEMIOLOGY

Of all of the primary heart tumours, only 25% are classified as malignant, mostly sarcomas, with the mean age of patients ranging from 30 to 50 years³. The primary leiomyosarcoma forms 1–9% of these. Secondary tumours are up to 20- to 40-fold more often and 15% of patients diagnosed with cancer exhibit cardiac metastases⁷.

CLINICOPATHOLOGICAL CHARACTERISTICS

Typical symptoms are dyspnea, fatigue, palpitations, chest pain, but may also include systemic neurological deficit, syncope, fevers, weight loss, or even sudden death^{2,8}. However, the disease may remain asymptomatic until later progression. Such symptomatology depends mostly on the location and size and can be summarized in 4 mechanisms: obstruction of blood flow or interference with the valve function, local invasion causing arrhythmias, pericardial effusion or ventricular dysfunction, pulmonary or systemic embolization, and constitutional symptomatology⁹. Chest pain suggests malignancy in most cases, resulting from the local invasion or a coronary embolization. Although an angiosarcoma, as the most common subtype, is mainly found in the right atrium, the other cell types are mostly detected in the left atrium as well as the primary leiomyosarcomas¹⁰, presenting as sessile structures with mucous appearance^{1,11}. At the time of diagnose, the vast majority of cardiac sarcomas are already large and invasive masses. In general, primary cardiac sarcomas most commonly establish metastases in the lungs, brain, bone, liver, bowel, spleen and lymph nodes¹².

DIAGNOSTICS

An X-ray may be the first examination to arouse suspicion when a cardiomegaly¹³, a change of shape of the heart, pleural effusions or metastatic loci are found. Echocardiography is the first-choice method to perform as it immediately provides a diagnose with generally no harm to the patient. Several features may be useful for differentiation between benign lesions and malignant tumours. Signs of malignancy include immobility, pericardial effusion, broad attachment, particularly when not attached to the interatrial septum. A contrast echocardiography may also reveal the greater vascularity of malignant lesions or assess the invasion based on the contrast enhancement of the tumour tissue compared to the myocardium¹⁴. The tissue of leiomyosarcoma may however resemble myxoma due to its soft, friable, and mobile features¹⁵. As follows from the mentioned above, the echocardiography should be interpreted not only by the detection of a mass, but also by its localization, mobility, consistency, base of the tumour, and hemodynamic consequences¹⁶. While echocardiography enables us to diagnose tumours as small as 3 mm, the CT and MRI are superior in the visualization of the complete extent of the tumour¹⁷. Both contrast CT and contrast MRI increase the accuracy of the malignant diagnosis, provide clear information about the anatomical relationship of the tumour and the surrounding tissues, or reveal possible pulmonary metastases. CT scan can be safely performed on patients with a pacemaker and can also reveal calcifications, yet the cardiac MRI is superior in the soft tissue contrast, allowing more precise assessment of the tumour matrix and its extent¹³ with its better contrast enhancement. The leiomyosarcoma appearance on CT and MRI is often lobulated, irregular, low-attenuation masses similar to myxoma, but usually arising from the posterior left atrial wall¹⁸, while the myxoma typically originates on the interatrial septum. Histological characteristics of the leiomyosarcoma are the malignant spindle cells organized in loose interweaving bundles with pleomorphic and occasionally prominent nuclei and isles of necrosis. Mitotic figures with epithelioid regions may often be present¹. Tumour cells are positive for SMA (smooth muscle actin) and – in contrast to other heart sarcomas – also strongly positive for desmin^{19,20}. The immunohistochemical positivity for Caldesmon can be used as a specific smooth muscle marker. Except for those mentioned above, there are other markers suggested for immunohistochemical identification of leiomyosarcoma such as the Calponin, HHF-35, SMMS-1 (ref.²¹). Furthermore, up to 40% of cardiac leiomyosarcomas show a positive reaction to cytokeratin, thus making it difficult to distinguish between its primary or secondary origin²². Staging diagnostics such as a whole-body PET-CT scan and a brain MRI to evaluate the presence of secondaries further determine the clinical course and decision-making process regarding the indication and selection of adequate therapy.

TREATMENT

The first choice modality is surgery aiming for the R0 resection. However, in most cases, at the time of diagnosis, the mass size and myocardial involvement often precludes the possibility of the complete excision^{23,24}. This fact is reflected in mostly suboptimal surgical results such as R1-R2 resections in the majority of published case series. Still, the surgery provides better short and mid-term outcomes compared with chemotherapy or radiotherapy alone²⁵. Many patients diagnosed with cardiac malignancy are not resectable due to extensive local progression of the disease. The role of orthotopic heart transplantation remains unclear²³, but may offer an ultimate option in younger and perspective patients without generalization of the disease. Neoadjuvant chemotherapy increases the rate of R0 resections and may double the survival interval²⁶. The benefits of adjuvant oncological therapy remain unclear and there is no consensus among the scientific community as contradictory results have been reported. A local recurrence is the most frequent cause of the first relapse in the group of non-vascular primary cardiac sarcomas such as the leiomyosarcoma. For this reason, adjuvant radiotherapy seems to be mandatory to preclude this course of the progression²⁵. A favourable response to adjuvant chemotherapy may be expected namely for the high-grade tumours of this sort. Recent work suggests the mean survival after multi-modality treatment in primary cardiac sarcomas is 36.5 months compared to 14.1 months using only surgery, chemotherapy, or radiotherapy alone²⁷. In conclusion, a multidisciplinary approach with complex evaluation of a patient is essential for the selection of the optimal therapeutic strategy that is still being based on non-cardiac sarcoma treatment principles and the results of retrospective studies²⁸.

PROGNOSIS

The achievement of a complete R0 resection belongs to the most significant prognostic factors among primary cardiac sarcomas. Signs associated with worse prognosis are an incomplete resection, a size of >5 cm, distant metastases, histological presence of necrosis in the tumour, high-grade differentiation related to faster distant metastatic spread, a high mitotic activity (greater than 5/10 HPF), and a right-sided localization, that is typical for bulky and exophytic, but also more invasive growth with earlier metastatic dissemination²⁶. The right-sided localization is also associated with a delayed diagnosis due to its longer asymptomatic course until the later stages of the disease²⁹. Utilization of mitotic activity as a prognostic factor is burdened by the fact that mitotic activity may be focally variable throughout the tumour³⁰. Even though the final prognosis does not differ among various histological subtypes of primary heart sarcomas, leiomyosarcoma is classified as a high-risk sarcoma with a high rate of local and distant recurrence³¹. 5-year survival after the treatment of the cardiac leiomyosarcoma is reported as 25.4%

(ref.³²) and the mean survival interval ranges from 9.6 to 16.5 months.

CASE REPORT

A 66-year old female with no previous medical history, with a 17-day history of progressive fatigue and dyspnea, in the NYHA functional class III, was referred to our institute with a CT-angiography showing an extensive tu-

mour filling the majority of the right atrium and ventricle (Fig. 1a). The tumour origin was localized in the free wall of the right atrium near the opening of the superior vena cava as a 3 cm wide broad attachment. Furthermore, a transthoracic echocardiography revealed a dilatation and near-to-obstruction of the right chambers and the tricuspid valve caused by a tumorous mass, together with decreased filling of left chambers. The tricuspid valve annulus was dilated to 53 mm, however any evaluation of the regurgitation or stenosis was impossible due to its massive

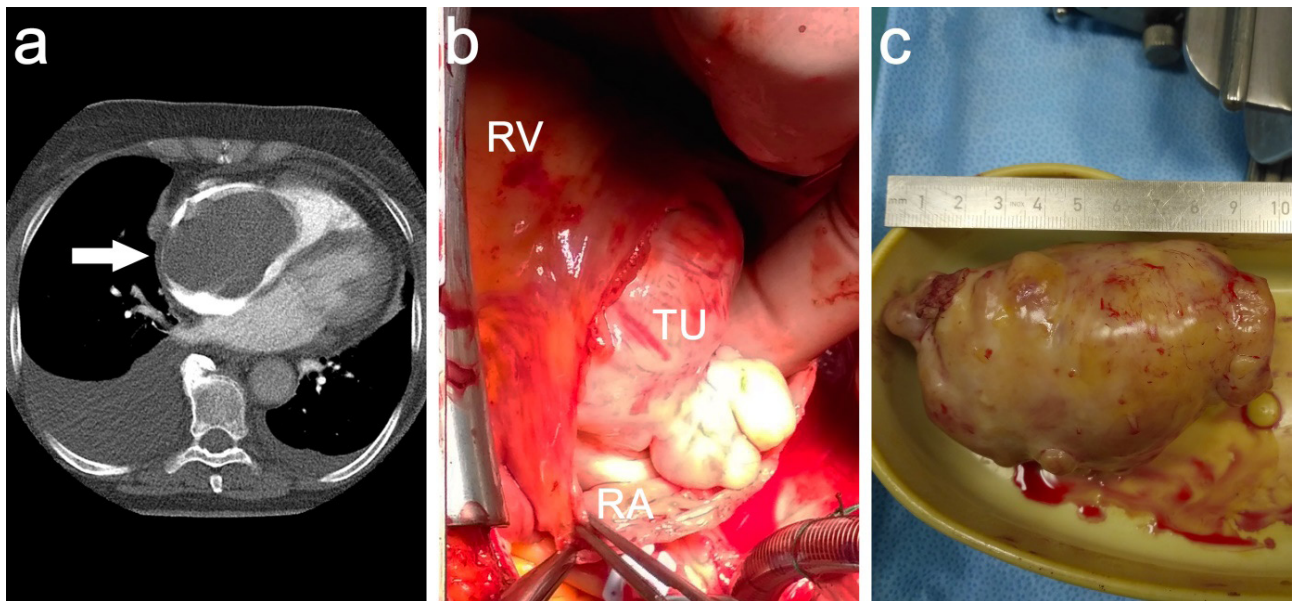


Fig. 1. **a.** Chest computed tomography scan, arrow indicates the contrast solution floating over a tumorous obstruction of a 90HU density in right chambers in the transverse plane. **b.** Intraoperative findings revealed a solid tumor (TU) with an irregular stalk originating near the superior vena cava in the right atrium (RA), prolapsing into the right ventricle (RV). **c.** Main portion of the tumor, measuring 10 cm in its longest axis, was separated from the stalk and both parts were extracted individually.

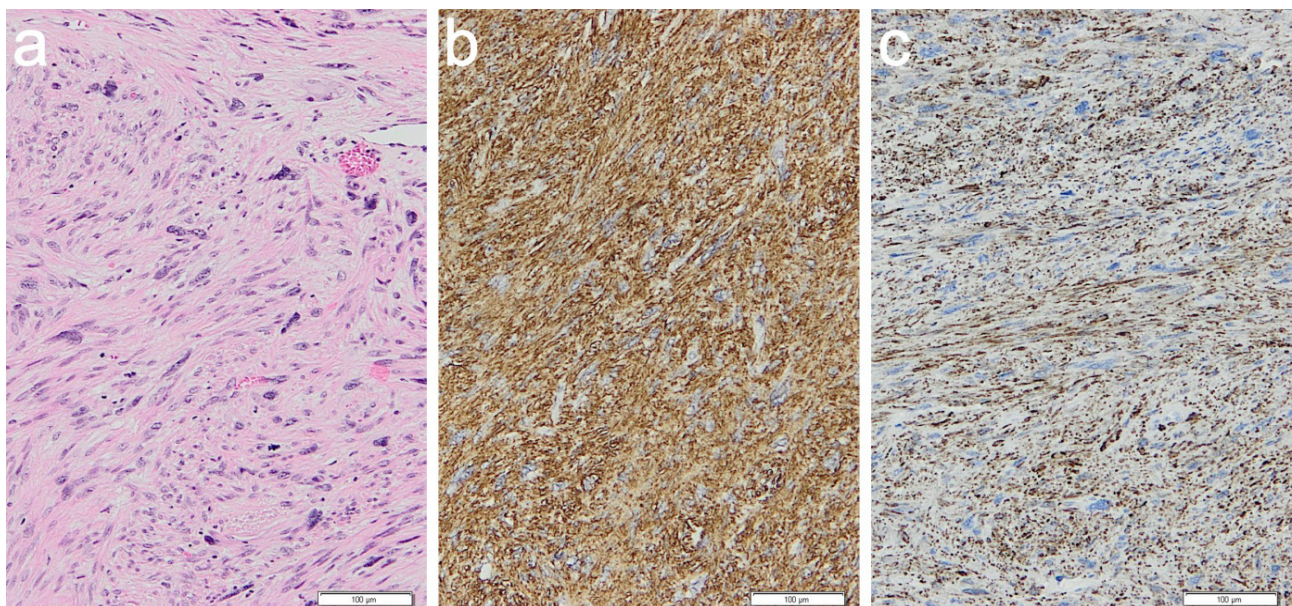


Fig. 2. Histological and immunohistochemical examination of the tumor proved the classical subtype of leiomyosarcoma formed by spindle-cells. WHO classification: Differentiation score 2–3, Mitotic score 10–19 per 10 high-power fields, Necrosis score 0, Total score 5 indicating a Grade 2. **a.** Hematoxylin-Eosin stain image. **b.** Immunohistochemical positivity for smooth muscle actin. **c.** Immunohistochemical positivity for desmin.

obstruction by the tumour. A 13 mm pericardial effusion was also present. Laboratory examination revealed only a mild liver enzyme elevation induced by a right-sided heart failure, but without accompanying clinical signs. The myxoma was very suspect, but the biological nature of the tumour remained uncertain by the time of the admission as the surgical removal of the mass was indicated urgently due to imminent risk of blood flow obstruction.

The procedure was performed on the arrested heart with aorto-bicaval cannulation via superior vena cava and the right femoral vein, cross-clamping of the aorta and also the pulmonary trunk to increase the protection against the perioperative dissemination of the tumour cells into the pulmonary circulation. After total venous occlusion, a 5cm incision was done into the appendage of the right atrium. A solid 10 cm tumour that almost completely filled the atrium (Fig. 1b) was prolapsing into the right ventricle through a severely dilated tricuspid valve orifice. The tumour was adhering by a 3 cm wide irregular stalk to the free portion of the atrial wall just anteriorly to the orifice of the superior vena cava. The main portion was separated from the stalk and extracted (Fig. 1c), followed by the excision of the stalk from the atrial wall. A perioperative cryopathology revealed that the tumour was of malignant nature with suspicion of a leiomyosarcoma. With such findings, the resection of the atrial wall was extended by 5 mm safety margins, limited by close distance to the SA node location. The atrial defect was closed using an autologous pericardial patch and the tricuspid valve was repaired with an annuloplasty ring size no. 34.

The postoperative course was uneventful. Final histological analysis proved a grade 2 classical subtype of leiomyosarcoma (Fig. 2a-c) with high mitotic activity marked as Ki67 positivity forming 5–10% of the tumour cells and a microscopic tumour-cell infiltration of resection margins, proving the R1 resection. The final staging was pT2N0M0 as the whole-body contrast CT scan and a brain MRI showed no sign of a metastatic process. Postoperative echocardiography showed only a mild residual tricuspid regurgitation and the patient was discharged on the 8th postoperative day. Adjuvant CT-targeted radiotherapy was applied on the area of the right atrium in cycles with low doses of 2 Gy and a cumulative dose of 66 Gy.

24-months after the surgery, the patient is still being examined periodically with PET-CT scans and echocardiography with no signs of a tumour recurrence so far.

DISCUSSION

Symptoms of obstruction are the most common initial clinical signs of heart tumours. In our patient, the recent onset and fast progressing dyspnea and fatigue resulted from a right-sided blood flow obstruction caused by the tumour and a pericardial effusion, leading to decreased flow through pulmonary circulation and in left sided heart chambers.

The biological nature of primary cardiac tumours is often unclear at the time of the diagnosis and an MRI study was recommended for further evaluation. In this case, we

were forced to skip these examinations and to conduct urgent surgery even though the suspicion for malignancy was high due to the presence of pericardial effusion and right-sided localisation of the tumour. We aimed for radical excision. However, infiltration of the resection margins was later confirmed, indicating only R1 resection.

Preoperatively, neoadjuvant therapy was not an option due to an acute clinical presentation. After the post-operation staging confirmed no signs of generalization, adjuvant chemotherapy was not indicated and the patient was subjected to selective irradiation of the tumour origin to eliminate any potential tumour residue after an R1 resection. To decrease the risk of a post-radiation cardiomyopathy, the complete irradiation dose was divided into multiple cycles of low dosage. Over the 24-months follow-up, the patient remains in complete remission and no complications after the treatment were observed.

CONCLUSION

This case report describes a progressive clinical presentation of a particularly aggressive subtype of primary heart sarcoma and also one of the largest intracardiac leiomyosarcomas with successful treatment reported in the literature. Despite the suboptimal surgical resection, a good therapeutic result may still be achieved by combination with well-tailored adjuvant oncological therapy, in our case the residue-targeted selective low-dose radiotherapy in patient without generalization of the disease. Such a result supports the latest theories that suggest a combined surgical and oncological approach in the management of these patients.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies on the epidemiology, clinicopathological characteristics, diagnostics, treatment and prognosis of the primary cardiac leiomyosarcomas. Scientific articles from 1962 to 2021 were searched using PubMed database. All searches were up to date as of October 2021. The search terms used included “primary cardiac leiomyosarcoma”. Only English language articles were reviewed. Search results were analysed based on the full-text content and relevant articles were included in the literature review. The aim was to identify articles referring to the clinicopathological characteristics, epidemiology, diagnostics and treatment of the primary cardiac leiomyosarcomas. The total number of articles obtained by the search was 249. Articles not adhering to the inclusion criteria were discarded. Relevant information from selected articles (n=30) was included in the review

ABBREVIATIONS

CT, Computed tomography; MeSH, Medical Subject Headings; NYHA, New York Heart Association; SA node, Sinoatrial node; SMA, smooth muscle actin; HPF, high-power fields; pTMN, Surgical specimen tumor extent,

lymph node metastasis, distant metastatic spread; MRI, Magnetic resonance imaging; PET-CT, Positron emission tomography – computed tomography; WHO, World Health Organization.

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