Primary Left Atrial Leiomyosarcoma: Literature Review and Lessons of a Case

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REVIEW PAPER

Primary Left Atrial Leiomyosarcoma: Literature Review and Lessons of a Case

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ABSTRACT

Primary cardiac sarcoma is an uncommon disease. In particular, leiomyosarcoma of cardiovascular origin is extremely rare. Half of all cardiac leiomyosarcomas are located in the left atrium. Due to the extreme rarity of left atrial leiomyosarcoma, there is no great experience in its management. This review includes a report of a case of left atrial leiomyosarcoma followed up over 45 months. The literature review examines the distribution of left atrial leiomyosarcoma, the physiological reasons for the tendency of cardiac leiomyosarcoma to be localized to the left atrial cavity, the clinical and physical appearance of this disease, and the key differences between left atrial leiomyosarcoma and the most common left atrial tumor, myxoma. The morphological features, using light and electron microscopy and immunochemical staining, are discussed. Treatment modalities including adjuvant therapy and surgical resection are examined and their effectiveness compared. Opinions regarding the results and optimal treatment of leiomyosarcoma are not always in agreement. This highlights the need for inter-hospital comparison to determine the optimal treatment regimen.

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INTRODUCTION

Primary cardiac neoplasms are found in 0.001–0.28% of autopsies. Approximately 25% are malignant and are represented by sarcomas. Leiomyosarcoma constitutes only 8–9% of all cardiac sarcomas, and less than 0.25% of all primary cardiac tumors.[1] Most primary sarcomas are localized to the right heart chambers and great vessels, but half of all cases of leiomyosarcoma originate in the left atrium.[2,3] As left atrial leiomyosarcoma is extremely rare, each clinical case of this tumor requires documentation of the diagnosis, treatment efficacy, and a comparison with the literature data.

CASE REPORT

A 43-year-old woman underwent routine removal of a left atrial myxoma. There was no suspicion of malignancy and a histopathological examination confirmed the diagnosis. The patient was readmitted 20 months later with symptoms of relapse. There was no indication of pericardial effusion on her echocardiogram, perhaps due to the denseness of pericardial adhesions. The symptoms of pulmonary vein obstruction were critical, and the patient underwent urgent surgery. The tumor was approached via a right atriotomy and an atrial septal incision. A giant tumor mass occupied the whole left atrial cavity and extended into the right inferior pulmonary vein. An additional pulmonary vein incision was performed to remove the tumor with the anterior venous wall. All defects were repaired using pericardial xenograft patches. Histopathological examination revealed the spindle-shaped cells of sarcoma with moderate pleomorphism, most likely of smooth muscle differentiation. No necrosis was seen. The mitotic index was 1–2/10 high-power fields (HPF). Immunochemical and ultrastructural

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examinations were not performed. As the operation was assumed to be of a palliative nature, the patient was prescribed chemotherapy using a combination of doxorubicin and ifosfamide. After the first course of chemotherapy, there was no sign of tumor recurrence on transesophageal echocardiography (TEE), so the patient was discharged home in a satisfactory state.

She was readmitted after 15 months during which she had 6 courses of chemotherapy, but her symptoms continued to gradually return. On this admission, a deeper clinical investigation was possible. Magnetic resonance imaging and TEE showed a second tumor in the left atrium, spreading into the lumen of the right inferior branch of the pulmonary vein, to the segmental division, and up to the mitral valve (Figure 1). A 3rd operation was carried out, approaching the tumor through the atrial septum and the right contour of the left atrium. The tumor originated in the right inferior pulmonary vein, penetrated the atrial wall adjacent to the vein orifice, and was directed towards the mitral valve. The atrial portion of the tumor was resected completely with a wide margin of the left atrial wall (Figure 2). Keeping in mind that the right inferior pulmonary vein was chronically occluded by the tumor, it was decided to isolate the pulmonary vein from the left atrium without risk of blood flow obstruction from the lower lobe of the right lung. This action obviated the need for a lobectomy during cardiopulmonary bypass. The wide defect of the left atrium was repaired using a xenograft patch. A biopsy of the margin was sent for a morphological study. The patient received 2 courses of chemotherapy with cisplatin for 10 days postoperatively. Lobectomy of the right lower lobe was performed one month later. The postoperative course was uneventful. The patient was discharged home well after TEE showed no tumor recurrence.

Histopathologically, both portions of the tumor in the left atrial and pulmonary vein consisted of areas of densely packed fusiform cells with atypical blunt-ended nuclei, which alternated with others much less cellular and richer in interstitial myxoid matrix. Elsewhere in the tumor section, the cells were epithelioid with marked pleomorphism. Epithelioid cells were arranged around the vessels in a stroma (Figure 3). There were a few necrotic foci in the central part of the tumor. Spindle and epithelioid cells demonstrated apparent pleomorphism, and mitotic figures were atypical. The index of mitotic activity was 5–7/10 HPF. The cytoplasm was eosinophilic and contained abundant thin filaments and focal densities along the course of the filaments. Immunohistochemically, the tumor cells showed focal or diffuse cytoplasmic immunoreactivity to monoclonal vimentin antibody, a weak focal reaction to desmin, and a positive diffuse reaction to smooth muscle actin (Figure 4). There was no

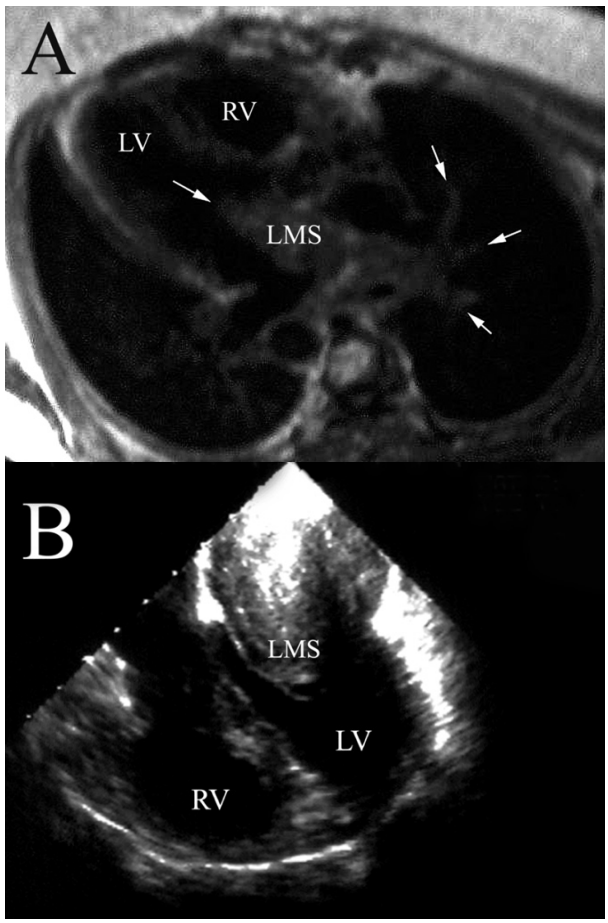

Figure 1. (A) Magnetic resonance image of relapse 2: horizontal plan shows the tumor in the left atrium diffusing into the branches of the pulmonary veins (arrows). LA = left atrium, LMS = leiomyosarcoma, LV = left ventricle, RV = right ventricle. **(B)** Transesophageal view of relapse 2.

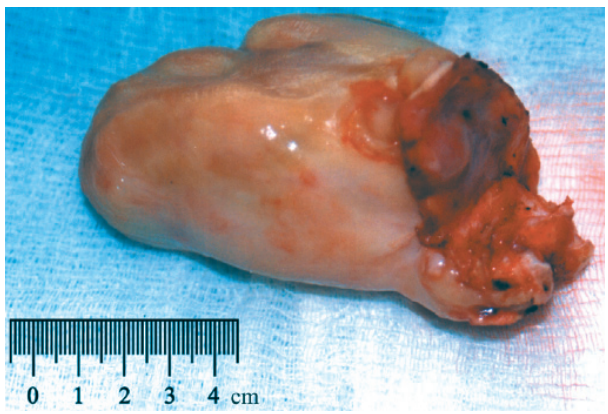

Figure 2. View of the removed tumor recurrence. One can see the reflective surface of the confluence of the pulmonary vein and the left atrium and the copy of the pulmonary vein dividing into three branches.

immunoreactivity to factor VIII, cytokeratin, myoglobin, or CD 34. These morphological features were consistent with a diagnosis of low-grade (GII) leiomyosarcoma with an epithelioid component. Biopsy of the marginal

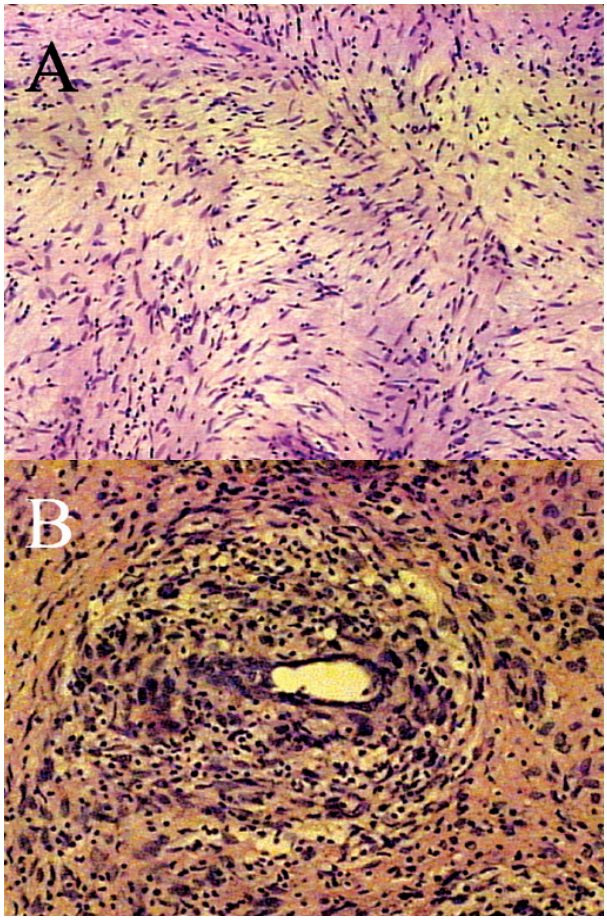

Figure 3. (A) Photomicrograph of the tumor section, showing the bundles of fusiform cells in relapse 2 (hematoxylin and eosin stain, original magnification × 100). **(B)** Photomicrograph of the tumor section showing the epithelioid cells around vessels in relapse 2 (hematoxylin and eosin stain, original magnification × 200).

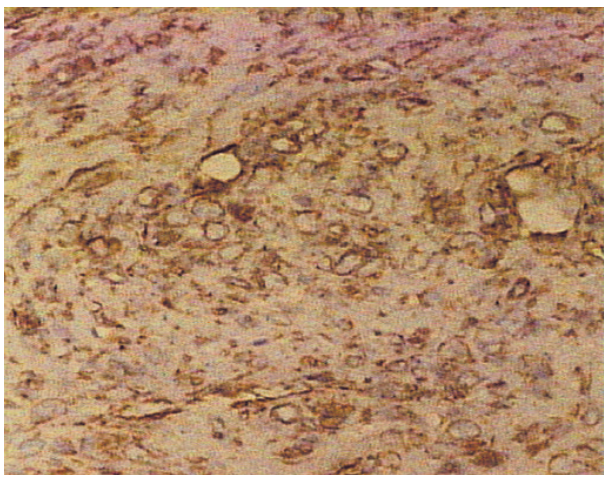

Figure 4. Photomicrograph of alpha-smooth-muscle actin immunohistochemical stain (original magnification × 200).

zones was negative for tumor cells. With every reason to consider this operation radical, the patient did not receive chemotherapy.

A 3rd relapse occurred within 6 months. The condition of the patient was critical because of obstruction of the pulmonary veins by a tumor mass in the left atrium. Transesophageal echocardiography showed growth of the tumor along the right contour of the left atrium, without diffusion into the lumen of the right upper pulmonary vein. The tumor was directed towards the left pulmonary veins and the mitral valve, and had progressive growth through the wall of the left atrium to the epicardial surface at the site of the pericardial xenograft patch. A 4th operation was undertaken after harvesting a fresh allograft of the left atrium. In the course of this operation, it was seen that the origin of the tumor was the atrial wall included in the suture line of the pericardial xenograft patch. The tumor almost completely blocked the single right, and all the left pulmonary veins, but did not diffuse into the lumens. At the same time, the tumor infiltrated the atrial wall around the pulmonary veins. During total resection of the left atrium, it was necessary to separate the pulmonary veins proximal to their confluence with the left atrium, because of tumor infiltration of the atrial wall. The atrial septum was resected partially as well as the anterior, posterior, and lateral atrial wall. The left atrial appendix and the margin along the mitral orifice were not resected. Multiple margin biopsies were performed. The resected left atrium was replaced with an allograft orthotopically. The pulmonary veins were joined to the allograft with circular running sutures. After removing the aortic clamp, sinus rhythm was restored by electrical defibrillation. The patient was weaned from cardiopulmonary bypass easily. Massive bleeding caused postoperative multi-organ failure, and she died 8 days after the 4th operation. Histopathological studies showed the same pattern of tumor as in the 2nd relapse. There were many malignant atypical cells in the margin biopsies. There were no systemic metastatic lesions at autopsy.

Discussion and Literature Review

Leiomyosarcomas account for between 5% and 10% of soft tissue sarcomas. Although all leiomyosarcomas of soft tissue are histologically similar, they are divided into 3 groups: leiomyosarcoma of the deep soft tissues, leiomyosarcoma of cutaneous and subcutaneous tissues, and leiomyosarcoma of vascular origin.[4] The latter is rare; 300–400 cases have been reported in the literature, with predominant localization in the inferior vena cava and right heart chambers, and less frequently in the pulmonary artery.[3–4] An extremely rare type of this tumor is leiomyosarcoma of the pulmonary veins or left atrium. Only 17 cases of leiomyosarcoma of the pulmonary veins and 20 cases of leiomyosarcoma of the left atrium have been reported.[2] The previous cases of pulmonary venous leiomyosarcoma were assumed to be misinterpretation of left atrial leiomyosarcoma with tumor growth into the pulmonary vein lumen.[5]

This may be true due to the difficulty of determining the site of tumor origin intraoperatively.[6] In addition, diffusion of the tumor into the pulmonary vein lumen is a specific feature of left atrial leiomyosarcoma.[7] In our case, we had every reason to believe that the 2nd relapse was leiomyosarcoma of the pulmonary vein. However, the 3rd relapse showed that this was not the case. On the other hand, there are reported cases of pulmonary venous leiomyosarcoma without diffusion into the left atrium, which were closely related histologically to those of the venous wall.[4,8–9] We suggest that leiomyosarcoma of the pulmonary veins, the pulmonary vein-left atrial junction, and the left atrium are a uniform disease with the origin of the tumor in the smooth muscle cells located in the subendocardial/subendothelial layer of the left atrium and pulmonary veins.[2,5,10]

The prevalence of leiomyosarcomas in veins is based on different arterial and venous wall physiology. In arteries, elastic and collagenous fibers are essential for maintaining adequate blood pressure; it is well known that in the face of hemodynamic stress, smooth muscle cells migrate from the tunica media to subendothelial layers, undergoing some degree of dedifferentiation, losing contractility, and turning into a "synthesizing" element.[11] In the great veins, smooth muscle cells are more abundant and present in the subendothelial layer as well as in the tunica media and adventitia. The dedifferentiation of smooth muscle cells in the arterial wall results in the prevalence of intimal sarcomas of low differentiation.[11–12] Leiomyosarcoma is twice as common in females.[2,13] In the Mayo Clinic experience, there was positive cytoplasmic immunoreactivity of the tumor tissue to estrogen and progesterone receptor proteins.[13] This may indicate tumor dependence at a hormonal level.[13]

The symptoms of leiomyosarcoma of the left atrium have no specific features and are similar to those of myxoma.[14] The main feature of the clinical picture is blocked outflow from the pulmonary veins with congestion of the lungs.[3,10] The echocardiographic distinction between leiomyosarcoma and myxoma is also difficult.[6] The affinity of myxoma with the midportion of the left atrial septum in the fossa ovalis is not a sufficient differentiating feature.[3] Pericardial effusion may be prevented by dense pericardial adhesions in tumor relapses. As a result, in most reported cases, as in our case, preoperative diagnosis has been impossible.[6] In this case, the diagnosis of left atrial myxoma was confirmed by histopathological examination. Histopathological misinterpretation of the tumor is common because the morphological differentiation of cardiac myxomas and sarcomas may sometimes be difficult.[14–15] Some cardiac sarcomas, including leiomyosarcoma, can be extensively myxoid; so-called myxoid imitators.[14] The presence of hypocellular or acellular areas in the tumor section may be the cause of the misinterpretation. The histopathological mistakes were the basis of the suggestion that myxomas are able to transform from benign to malignant.[14–15] However, reassessment of the initial morphology after tumor relapse has resulted in the interpretation of the primary tumor as originally malignant.[3,7] Comparative histopathological evaluation of the original leiomyosarcoma and relapses may demonstrate some differences in their morphology. Areas of malignant cartilage and osteoid deposition in the relapse of leiomyosarcoma, with increasing reaction to vimentin, have been found.[10] An increase of cellularity and mitotic activity with a decrease in the myxoid area was evident in our case.

Table 1 summarizes the morphological features of cardiac myxoma and leiomyosarcoma.[3,7,11,15] Other immunohistochemical features of leiomyosarcoma are negative reactions to factor VIII (inherent in intimal sarcomas), cytokeratin (inherent in carcinomas), myoglobin (inherent in rhabdomyosarcomas), general leukocytic antigen, protein S100 (inherent in liposarcomas), and CD 34 (inherent in myxomas).[3,4,10] However, it should be noted that immunohistochemical examination cannot always identify the type of sarcoma. Up to 40% of cardiac leiomyosarcomas show a positive reaction to cytokeratin.[14] Thus, it is difficult to distinguish between primary and secondary cardiac tumors. The presence of an epithelioid component in the morphology of the leiomyosarcoma was accompanied by a positive reaction to cytokeratin in the case described by Oliai and colleagues.[13] Others demonstrated the absence of an immunohistochemical reaction of leiomyosarcomas to desmin, vimentin, muscle-specific actin, and myoglobin. Only a strong positive reaction to alpha-smooth-muscle actin makes it possible to classify the tumor as a leiomyosarcoma.[6] James and Leong[16] described a case of leiomyosarcoma that did not demonstrate a positive reaction to desmin. They explained this by the loss of desmin antigen during formalin fixation of the tumor tissue. Interestingly, this case showed an epithelioid component of the leiomyosarcoma, with a prominent reaction to cytokeratin.[16] Electron microscopic studies may reveal characteristic features of leiomyosarcoma, such as signs of the smooth muscle phenotype. These features include thin filament bundles associated with cytoplasmic dense bodies and peripheral dense bands in the tumor cells.[3,11] Thus, differentiation between sarcoma and myxoma, and especially the type of sarcoma, requires a range of morphological techniques including light microscopy, immunohistochemistry, and ultrastructural microscopy. Documentation of each case is necessary for comparison of cases from different authors.

Table 1. **Features of Cardiac Myxoma and Leiomyosarcoma**

Morphologic Sign	Cardiac Myxoma	Leiomyosarcoma
Main pattern of tumor growth	Towards mitral valve	Towards pulmonary veins
Light microscopy		
Cellularity and location	Hypocellularity around vessels and tumor surface; other areas consist of stroma	Hypercellularity, minimal stromal tissue and lots of cellular fascicles
Mitotic activity	No	Yes, including atypical
Necrosis	No	Yes
Pleomorphism	Never	Often
Immunohistochemistry		
Vimentin	Strong diffuse reaction	Moderate diffuse reaction
CD 34	Strong diffuse reaction	Negative
Desmin	Negative	Strong diffuse reaction
Smooth muscle actin	Negative	Strong diffuse reaction
Ultrastructural study	Cells form vessel lumen, confirming endothelial or vascular cell origin	Cytoplasm contains thin filament bundles with dense bodies and peripheral dense bands in tumor cells

The natural course of leiomyosarcoma may be less aggressive than other sarcomas. Despite intravascular localization, this tumor tends towards regional invasive growth and relapse.[1,11] On the other hand, metastases were also described as a natural course of leiomyosarcoma as well as after radical surgical resection.[4,13] Metastases are thought to depend on the mitotic index of the tumor.[3,9,12] A statistical difference in survival has been seen between cardiac sarcomas with mitoses less than 5/10 HPF compared with those with greater than 5/10 HPF.[17] However, there are descriptions of metastatic appearance with a low mitotic index (1–4/10 HPF).[13] Other factors having a positive influence on long-term survival are localization of the leiomyosarcoma in the left side of the heart compared with the right side, absence of necrotic areas in the tumor section, and absence of distant metastases at the time of diagnosis.[9,12] Our case complied with these factors; multiple tumor relapses and corresponding surgery were not accompanied by distant metastases. The survival of our patient was prolonged to 3 years 9 months from the time of diagnosis, and there were no systemic metastases at autopsy. Leiomyosarcomas with a similar histopathological pattern were reported by James and Leong[16] and Pins and colleagues.[17]

In spite of the fact that radical surgical resection of the tumor is the only chance of prolonging the patient's life, the results of surgical treatment are palliative in most cases because of the inevitable tumor relapses or metastases.[1,3,6,9] The average survival without operation is 6 to 12 months.[1–2] Surgery extends survival to 24 months.[2] Of the 17 published cases of leiomyosarcoma of the pulmonary veins, survival up to 3 years was recorded in only 2 patients.[4] Complete resection of the tumor is accompanied by great technical difficulties and requires numerous patches.[1] In the case of tumor diffusion into the lumens of the pulmonary veins (or in the case of a tumor originating in the pulmonary vein, with growth into the left atrium), simultaneous removal of the corresponding lung with extensive resection of the tumor and the atrial wall en bloc has been described.[8] Removal of the atrial part of the tumor in the first stage, with delayed resection of the lung or lobectomy with partial removal of the atrial wall in the second stage is more common.[4,13] In addition, extensive resection of the left atrium and replacement with an allograft and simultaneous pulmonectomy has also been reported, without a reliable result.[6,18] In our case, primary tumor resection and removal of the first relapse could be regarded as non-radical procedures. As to the second relapse, we had many reasons to consider this procedure as completely radical. We applied two-stage surgical management. In contrast to the published two-stage operation, we performed complete resection of the tumor and atrial wall, cutting off the pulmonary vein from the left atrium during the cardiac (first) stage of the operation. After complete tumor obturation of the pulmonary vein, signs of obstruction of blood outflow were absent.

The palliative nature of most operations has resulted in the use of heart transplantation to achieve a guarantee of surgical efficacy.[1,19] However, having never been evaluated in this sense, heart transplantation has many limitations for this purpose. In particular, the data from the Single National Transplant Organ Network of the United States shows that an adult of blood group O waits an average of 595 days to find an appropriate donor.[20] However, leiomyosarcoma is a fast-growing tumor with an average term of regional relapse of 6 months.[2]

As a result, there is a real chance of not receiving a donor organ at the appropriate time. In addition, our case demonstrated a reduction in the interval between tumor relapses. Furthermore, there is a danger of tumor dissemination after the use of immunosuppressive therapy in cancer patients.[1,14,18] In general, the results of heart transplantation are unclear and contradictory.[1,19] Our case demonstrated one more potential contraindication to heart transplantation. In the 3rd relapse, we observed tumor infiltration of the atrial wall located in the pulmonary vein-left atrial junction. However, there were many malignant atypical cells in the margin biopsies harvested at this point. The involvement of the pulmonary vein region in tumor development and the disposition of leiomyosarcoma to invasive growth are serious barriers to heart transplantation, due to technical problems and the inevitable appearance of tumor relapse.

The palliative character of the surgery generates hope for adjuvant therapy. Radiotherapy may help to control local tumor growth, however, leiomyosarcoma is a malignant tumor of low radiosensitivity.[6] There is a risk of the development of radiation myocarditis and pericarditis with high doses of radiation.[6] The benefits of postoperative chemotherapy are also unknown. The application of chemotherapy in combination with surgery for prolongation of survival is considered to be expedient.[2,5–6] At the same time, all described cases of supposed efficacy of chemotherapy were coupled with surgical resection. This makes it difficult to observe a real benefit of chemotherapy because there are some reports of the self-sufficient role of surgery in prolongation of survival.[8] Due to the unknown efficacy, there are no data on an optimal chemotherapy regimen. Doxorubicin has been suggested as a useful chemotherapeutic agent in view of its benefit in other soft tissue sarcomas.[1,16] On the other hand, a lack of efficacy of doxorubicin has been noted.[12] Besides doxorubicin, ifosfamide, uracil/tegafur, etoposide, vincristine, dacarbazine, mitomycin, cisplatin, cyclophosphamide, and hormone therapy have been used.[2,6,9,11,13] In most of these cases, there was no observed efficacy of chemotherapy.

It should be recognized that currently there are no effective ways to influence the development of cardiac leiomyosarcoma. The treatment is still controversial and palliative in most cases. The most effective method is surgical resection, but its potential for prolongation of survival is based rather on the natural course of the disease than on the possibility of radical tumor resection. Radiotherapy and chemotherapy are not recognized as independent treatment modalities. Attempts to use a combination of all known methods of cure are justified to prolong the patient's survival.

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