Quiz

Correct answer to the quiz. Check your diagnosis

Case report

Primary cardiac atrial sarcomas. Report of two histologically different cases and review of the literature

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Primary cardiac sarcomas are extremely uncommon. We report two patients with primary cardiac atrial sarcomas: a case report of a 34-year old woman with intimal sarcoma of the left atrium and a case report of a 30-year old man with synovial sarcoma of the right atrium. Clinicopathological and differential diagnosis with a discussion regarding the role of molecular studies is presented.

Key words: heart, intimal sarcoma, synovial sarcoma, pathology.

Introduction

Primary cardiac tumors are extremely rare with an incidence of 0.001-0.03% based on the autopsy findings [1]. Metastases to the heart occur 20-40 times more frequently than primary neoplasms [2]. Approximately 75% of primary cardiac tumors are benign with 50% of those being myxomas. The remaining 25% of primary cardiac tumors are malignant with sarcomas accounting for 95% and lymphomas accounting for 5% of these tumors [1]. It was believed that angiosarcoma and undifferentiated pleomorphic sarcoma were the most frequently occurring cardiac sarcomas [3]. However, a retrospective analysis by Neuville et al, showed cardiac intimal sarcomas (InS) (42%) to be the most frequent primary cardiac sarcoma followed by angiosarcoma (26%), undifferentiated sarcoma (22%), synovial sarcomas (SS) (7%), leiomyosarcomas (2%) and peripheral neuroectodermal tumor (1%) [4].

What is more different sarcomas have predilection of developing in various parts of the heart and thus their initial manifestation can differ. In one analysis of 124 cases the most common location was right atrium (38%), and left atrium (36%), left and right ventricles (8% and 7% respectively) and pericardium (2.4%) were less common [5]. Other studies suggest left predilection [6].

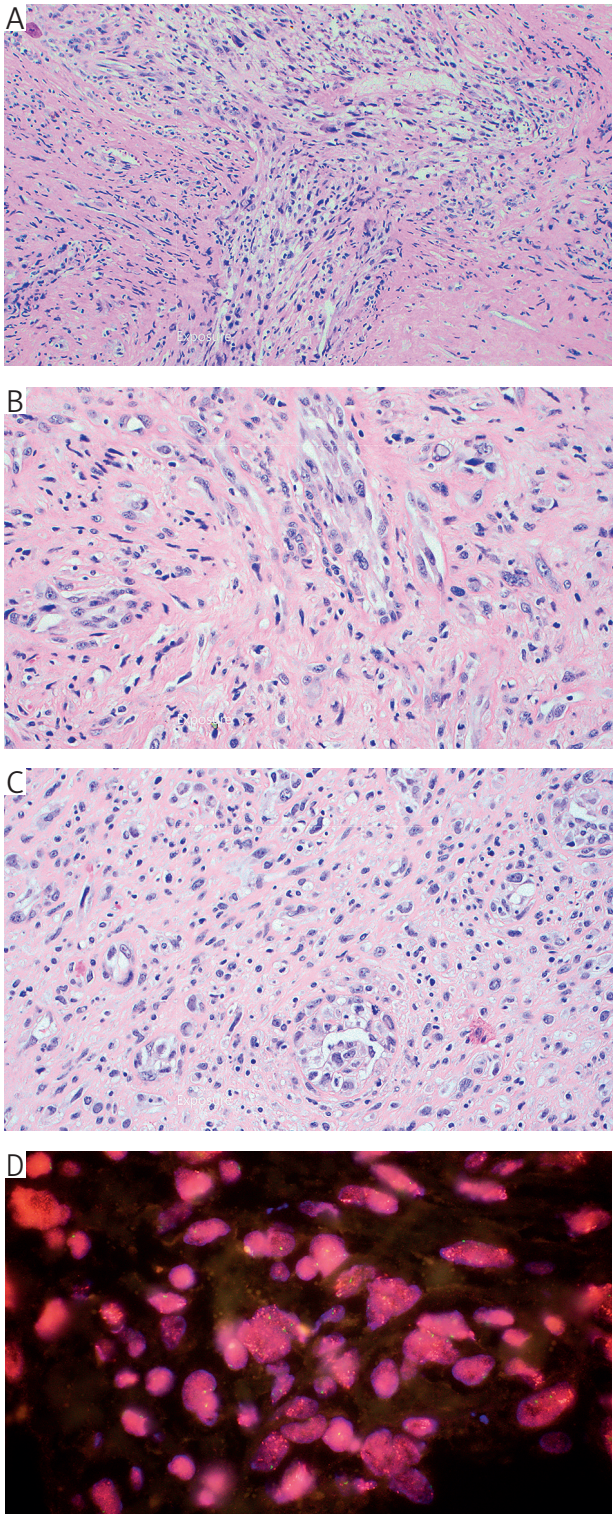

Fig. 1. Histologic and molecular features of the intimal sarcoma: areas of spindle cells with fascicular growth (A, B) and primitive epithelioid component (C). MDM2 gene amplification (D)

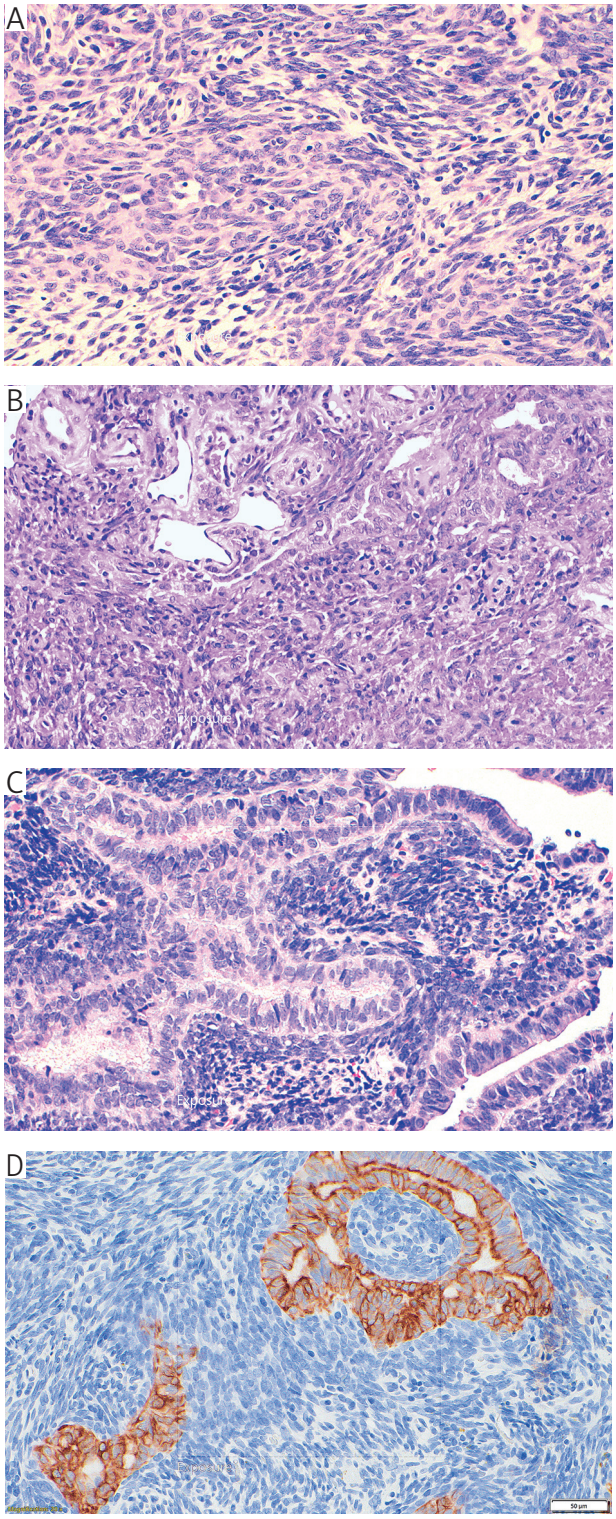

Fig 2. Synovial sarcoma: Histological texture of the tumor built of spindle cells forming herring bone fascicules (A) or haemangiopericytoma-like pattern (B). Epithelial component of the tumor with gland-like structures (C). Positive reaction for pan-cytokeratins (AE1/AE3) in epithelial cells (D)

Here, we present two histologically different cases of atrial sarcoma with particular attention to their differential diagnosis and the role of molecular studies.

Clinical data

Case 1

A 34-year-old female was admitted to the cardiac surgery clinic for an urgent procedure. Initially she presented with heart failure symptoms: New York Heart Association (NYHA) class II and weakness. An intraoperative transesophageal echocardiography (TEE) study revealed well circumscribed mass filling almost the entire left atrium of the heart. She underwent open heart surgery. Initial histopathology examination suggested high-grade sarcoma, re-consultation of the specimen in a reference center allowed to diagnose an intimal sarcoma.

Two months after the surgery she was diagnosed with malignancy localized in brainsteam and pons. At that time the patient was symptomatic with motor aphasia, dysarthria, dysphagia, left hemiparesis, asymmetric deep reflexes and positive Babinski symptom thus the biopsy of the lesion was not performed. The origin of the brain mass (sarcoma metastasis versus primary malignancy) remained unsure. Despite palliative radiochemotherapy (20 Gy in 5 fractions for pons and surrounding area and one cycle of doxorubicin) patient's condition gradually deteriorated with continuous deterioration in central nervous system (CNS) symptoms. Patient was discharged home and died soon after.

Case 2

A 30-year-old man complained of exercise dyspnea, heart arrhythmia and weakness. The diagnosis of right atrium tumor compressing right and left ventricle with pulmonary and pericardial effusion was set after obtaining magnetic resonance imaging (MRI) and positron emission tomography (PET). The patient underwent emergency surgery in December 2019, but the operation was not radical (R1). Histopathology report revealed biphasic synovial sarcoma.

The patient received 6 curses of adjuvant anthracycline monotherapy with no side effects. Three months later computed tomography (CT) revealed a mediastinal mass 82 × 39 × 25 mm invading right atrium, right ventricle and coronary sinus. The patient was offered a proton therapy, but refused. High-dose ifosfamid was administered as a first line of palliative treatment, but the progression in tumor mass with pericardial effusion after 3 cycles was noted. 4 cycles of gemcitabine with docetaxel were administered as a second line with further progression and an embolus in a heart. For the next 6 months pazopanib was continued till mildly symptomatic tamponade of the heart was seen on echocardiogram. The patient was hospitalized with surgical intervention. Additional imaging studies showed further progression. The patient started fourth line of palliative chemotherapy consisting of cisplatin and etoposide, but his performance status deteriorated soon after first cycle with clinical progression observed. He died 26 months after the heart surgery.

Histological, immunohistochemical and molecular characteristics of the atrial tumors

Case 1

Histological examination showed a tumor mostly composed of spindle cells with fascicular growth (Fig. 1AB) that were diffusely positive for vimentin and presented focal SMA reactivity. Epithelioid component (Fig. 1C) showed positive reaction to vimentin, CD31 and EMA. There was no reaction to pancytokearatins, S100 protein, melan A, desmin, miogenin, ERG, SOX10, ALK1, CD30, and PLAP. No signs of deletion in protein products of *H3K27me3* and *INI1* were noted. In situ hybridization revealed *MDM2* gene amplification in most of the cells (Fig 1D). This relatively specific finding, along with the clinicopathologic features, supported the diagnosis of a high grade intimal sarcoma.

Case 2

At the histologic level, the major part of the tumour was consisted of relatively uniform spindle-shaped cells (Fig. 2A). Furthermore, these areas showed a high mitotic rate and focal necrosis. Numerous vascular spaces resembling hemangiopericytoma-like texture were present (Fig. 2B).

Several areas, showed a biphasic pattern, the spindle cells being mixed with a prominent malignant epithelial component. The epithelial cells had large round vesicular nuclei and abundant pale-staining cytoplasm, and formed nests or gland-like spaces (Fig. 2C).

Epithelial cells were strongly positive for cytokeratin (Fig. 2D) and epithelial membrane antigen. Scattered spindle cells were also reactive for cytokeratin and, more often, epithelial membrane antigen. The spindle cells also showed reactivity for vimentin intermediate filaments. All components of the tumour were negative for S-100 protein, desmin, smooth muscle actin (SMA) and CD31.

Final diagnosis was confirmed by fluorescence in situ hybridization (FISH) showing the rearrangement of *SS18* gene in the numerous tumour cells.

Table I. Cases of atrial intimal sarcoma [1, 8-43]

No	Sex	Age (years)	Location	Size (mm)	Histology	MDM2 amplification	Metastases at diagnosis)	Treatment	Survival	Reference
1	F	29	LA	50	Undifferentiated InS	Nd	No	Cardiac surgery, chemotherapy (adriamycin, ifosfamide and darcarbazine)	Died at 10 mo	Cho *et al.* 2006
2	M	57	LA	large mass	High grade spindle sarcoma	Yes	Nd	Cardiac surgery, chemotherapy	Nd	Zhang *et al.* 2007
3	M	46	LA	80	High grade spindle sarcoma	Nd	No	Cardiac surgery, chemotherapy, reoperation, chemotherapy and radiotherapy	Alive at 13 mo	Li *et al.* 2013
4	M	69	LA	45	Spindle cell InS	Nd	No	Cardiac surgery	Nd	Ibrahim *et al.* 2013
5	M	42	LA	105	High grade sarcoma	Nd	No	Cardiac surgery, pneumonectomy	Alive at 11 mo	Kuurstra *et al.* 2014
6	M	50	LA	35 and 55	Spindle cell InS	No	Nd	Cardiac surgery	Nd	Fu *et al.* 2015
7	F	70	LA	60 + additional mass	InS G3	Nd	No	Cardiac surgery, reoperation	Died at 5 mo	Holzhauser *et al.* 2015
8	M	43	LA	60	Spindle cell InS	Yes	Yes: brain	cardiac surgery, chemotherapy and radiotherapy	Died at around 2 mo	Saith *et al.* 2015
9	M	65	LA	50 and 35	InS	Nd	No	Cardiac surgery	Died after the operation	Ohnaka *et al.* 2016
10	F	70	LA	40	Hypercellular mal. spindle cell neoplasm	Yes	No	Cardiac surgery, planned chemotherapy	Nd	Valecha *et al.* 2016
11	F	43	LA	42	Hypercellular mal. spindle cell neoplasm	Nd	No	Cardiac surgery, chemotherapy (paclitaxel)	Died at 4 mo	Marques Mendes *et al.* 2017
12	F	70	LA	40	Undifferentiated InS G3	Yes	Nd	Cardac surgery	Alive at 5 mo	Fu *et al.* 2017
13	F	59	LA	52	InS	Yes	Yes: muscle	2 lines of palliative chemotherapy, pazopanib	Died at 11 mo	Crombé *et al.* 2018

Table I. Cont.

No	Sex	Age (years)	Location	Size (mm)	Histology	MDM2 amplification	Metastases at diagnosis)	Treatment	Survival	Reference
14	F	78	LA	62	InS	Nd	No	Cardiac surgery, radiotherapy to bone metastases	Died at 2 mo	Pieraets *et al.* 2018
15	F	70	LA	100	Undifferentiated InS G3	Nd	No	Cardiac surgery	Died at 7 mo	Abreu *et al.* 2018
16	F	66	LA	55	InS	Nd	Unsure	Cardiac surgery	Nd	Vinod *et al.* 2018
17	M	41	LA	75	Spindle cell InS	Yes	No	Cardiac surgery, chemotherapy (doxorubicin and ifosfamide)	Alive at 8 mo	Abid *et al.* 2019
18	M	41	LA	10	Spindle cell InS G3	Nd	Nd	Only biopsy	Died at the time if diagnosis	Edquist *et al.* 2019
19	F	Nd	LA	55	High grade InS	Yes	Yes: multiple (bone, GI)	Cardiac surgery, 2 lines of chemotherapy	Died at 8 mo	Raphael *et al.* 2019
20	M	36	LA	90	InS	Yes	Nd	Cardiac surgery	Died at the time if diagnosis	Ogechukwu *et al.* 2019
21	F	70	LA	80	InS	Yes	Nd	Cardiac surgery	Nd	Nassereddine *et al.* 2019
22	F	31	LA	48	InS	Yes	Nd	Cardiac surgery, chemoradiotherapy	Nd	Grant *et al.* 2020
23	M	34	LA	37	InS?*	Nd	Yes: brain	Cardiac surgery	Nd	Reynoso-Hermosillo *et al.* 2020
24	F	55	LA	21	High grade plemorphic InS	Yes	No	Cardiac surgery, radiotherapy, chemoimmunotherapy (doxorubicin and olaratumab)	Died at 36 mo	Alam *et al.* 2020
25	F	28	LA	45	Intimal sarcoma	Nd	Yes	Cardiac surgery, excision of metastatses chemotherapy	Alive at 12 mo	Hamre *et al.* 2020
26	M	81	RA	30	Spindle cell InS	Nd	No	Cardiac surgery	Nd	Janssen *et al.* 2020)
27	F	58	LA	nd	InS	Nd	Unsure	Cardiac surgry, radiotherapy, pazopanib	Died at 13 mo	Moeri-Schimmel *et al.* 2020
28	F	55	LA	95	InS	Yes	No	Cardiac surgery, chemotherapy (etoposide and ifosfamide)	Nd	Hwang 2020

Table I. Cont.

No	Sex	Age (years)	Location	Size (mm)	Histology	MDM2 amplification	Metastases at diagnosis	Treatment	Survival	Reference
29	M	37	LA	43	InS	Nd	No	Cardiac surgery, reoperation, chemotherapy (doxorubicin), metastasectomy (adrenal gland), chemotherapy (ifosfamide)	Alive at 18 mo	Durieux *et al.* 2021
30	M	57	LA	43	InS	Nd	No	Cardiac surgery, chemotherapy (doxorubicin and dacarbazin), reoperation, radiotherapy, metastasectomy (retroperitoneal space), chemotherapy (gemcitabine and docetaxel), pazopanib	Alive at 47 mo	Romanowska *et al.* 2021
31	F	56	LA	Nd	InS	Nd	Nd	Cardiac surgery, reoperated 2x	Died at 26 mo	Pyo and Kim 2021
32	M	58	LA	Nd	InS	Yes	No	Cardiac surgery, radiotherapy	Alive at 17 mo	Pomp *et al.* 2021
33-41	4M 5F	18-67 (38)	LA	Nd	InS	Yes*	Nd	Nd	Nd	Koelsche *et al.* 2021
42	F	51	LA	21	InS	Yes	No	Cardiac surgery, radiotherapy	Nd	Diamond *et al.* 2020
43	M	19	RA	Nd	Pleomorphic InS	Yes	No	Cardiac surgery, chemotherapy (doxorubicin and ifosfamide) and radiotherapy, reoperation, pazopanib	Alive at 24 mo	Chen *et al.* 2021
44	M	62	LA	74	InS	Yes	No	Cardiac surgery, chemotherapy (doxorubin and ifosfamide)	Alive at 9 mo	Rehman *et al.* 2021
45	M	50	LA	80	Poorly differentiated InS	Yes	Nd	Cardiac surgery, metastasectomy, radiotherapy, chemotherapy (doxorubicin and isophosphamide)	Alive at 18 mo	Chiarelli *et al.* 2021
46	F	37	LA	47	High grade InS	Yes	No	Cardiac surgery, chemotherapy (doxorubicin) and radiotherapy (brain); ref: present case	Died at 4 mo	Ho *et al.* 2021
47	F		LA	59	High grade InS	Yes	No	Radiotherapy (brain)		

InS – intimal sarcoma; LA – left atrium, RA – right atrium; mo – months; na – not applicable; MDM2 – murine double minute 2; GI – gastrointestinal tract.

** diagnosis questionable; ** including molecular changes other than MDM2 amplification.*

Studies regarding only immunohistochemical and/or molecular data of 23 InS cases {44, 45} lacking clinical patients' parameters were excluded from Table I. Studies regarding only immunohistochemical and/or molecular data of 23 InS cases {44, 45} lacking clinical patients' parameters were excluded from Table I.

Table II. Immunohistochemical and molecular characteristics of intimal sarcoma (InS) [4, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 22, 23, 25, 26, 27, 28, 30, 31, 32, 33, 36, 39, 40, 44]

	VIM	CKs	EMA	S100	CD31	CD34	ERG	DES	SMA	CALD	SOX10	MDM2	MDM2_FISH
Atrial intimal sarcomas only (data from references no [9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 22, 23, 25, 26, 27, 28, 30, 31, 32, 33, 36, 39, 40])													
No of cases studies	6	11	3	7	10	15	2	13	12	4	1	14	26
No of positive cases	6	2	0	1	2	1	0	6	4	0	0	14	26
% of positive cases	100	18	0	14	20	7	0	46	33	0	0	100	100
Atrial intimal sarcomas only* (data from references no [10, 15, 17, 19, 23, 25, 26, 27, 28, 30, 36, 40])													
No of cases studies	2	7	2	3	7	8	2	8	7	2	1	8	26
No of positive cases	2	2	0	0	1	1	0	4	4	0	0	8	26
% of positive cases	100	29	0	0	14	12.5	0	50	58	0	0	0	100
Isa from different sites (Neville *et al.* 2014) [4]													
No of cases studies	Nd	42	42	42	42	Nd	Nd	42	42	42	Nd	Nd	42
No of positive cases	Nd	6	3	3	0	Nd	Nd	14	15	0	Nd	Nd	42
% of positive cases	Nd	14	7	7	0	Nd	Nd	33	35	0	Nd	Nd	100
Arterial Isa (mainly) (Jimbo 2019) [44]													
No of cases studies	Nd	10	Nd	10	10	10	10	Nd	10	Nd	10	10	10
No of positive cases	Nd	5	Nd	0	1	2	5	Nd	9	Nd	0	10	8
% of positive cases	Nd	50	Nd	0	10	20	50	Nd	90	Nd	0	100	80

**immunofenotype of the tumours with MDM2 gene amplification*

Discussion

Depending on the location of the sarcoma: in left or right atrium the malignancy may present different initial symptoms. Generally these tumors are accompanied by a triad of symptoms: generalized /systemic symptoms; signs of embolization and heart/local symptoms [7]

Interestingly, different sarcomas are also characterized by predominance of one or the other site. Synovial sarcomas would be more commonly found in right atrium, while InS, other poorly-differentiated sarcomas and leiomyosarcomas localize in left atrium [4, 5].

Although cardiac sarcomas are rare in comparison to their soft tissue counterparts, they are the second most common type of primary cardiac neoplasm. Of the few hundred cases reported, most has been based on autopsy series. A series of 27 cardiac sarcomas removed at surgery for curative and diagnostic intent were reviewed for clinicopathologic features with correlation to available postoperative follow-up data in 17 patients [6]. There were 6 angiosarcomas, 6 myxofibrosarcomas, 3 malignant peripheral nerve sheath tumors (MPNST), 3 leiomyosarcomas, 2 synovial sarcomas, 1 epithelioid hemangioendothelioma, 1 chondrosarcoma, 1 osteosarcoma, and 4 poorly differentiated sarcomas [6]. More recent analysis of 100 cases indicated InS as the most frequent primary cardiac sarcoma followed by angiosarcoma and undifferentiated sarcoma [4]. A retrospective study of 124 cases performed by French Sarcoma Group did not provide detailed data regarding histology showing all group of poorly differentiated sarcomas counting for 36.%; angiosarcoma 32.%, leiomyosarcoma 13% and all other histologies 18.6% [5]. As suggested by Koelsche and colleagues poorly differentiated sarcomas and InS can be interpreted as the same diagnosis [8], which would show consistency of the French Sarcoma Group results with Neuville et al data [4].

Intimal sarcoma

Clinical characteristics of disease based on 46 cases collected from the literature are depicted in Table I [1, 8-43].

InS is a mesenchymal tumor arising from intimal subendothelial cells and composed of poorly differentiated spindle, pleomorphic and epithelioid cells [8, 28, 32]. It localizes in the large blood vessels and in the left atrium [5, 28, 31, 32]. By definition, InS lack specific lineage differentiation, although myofibroblastic and smooth muscle differentiation may occur [8, 31].

Immunohistochemically, almost all intimal atrial sarcomas express vimentin and MDM2. 35-50% ex-

Table III. Cases of atrial synovial sarcoma [2, 3, 6, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71]

No	Sex	Age	Location	Size (mm)	Histologic subtype	Molecular confirmation	Grade	Treatment	Survival (months)	Reference
1	M	53	RA	Nd	BF	Nd	Nd	Cardiac surgery	Died at 6 mo	Sheffield *et al.* 1988
2	F	31	RA	Nd	BF	Nd	Nd	Heart surgery, heart transplantation	Died at 3 mo	Siebenmann *et al.* 1990
3	ND	ND	RA	Nd	Nd	Nd	Nd	Nd	Nd	Sütsch *et al.* 1991
4	ND	ND	RA	Nd	ND	Nd	Nd	Nd	Nd	Sütsch *et al.* 1991
5	F	46	LA	Nd	ND	Nd	Nd	Nd	Nd	Burke *et al.* 1992
6	M	13	RA	50	BF	Unclear	Nd	Cardiac surgery 6 cycles of CTH (ifosphamide, vincristine, actinomycin)	Alive at 10mo	Nicholson *et al.* 1997
7	M	29	LA	50	BF	Nd	Nd	Heart surgery, second heart surgery	Died at 8 mo	Fujioka *et al.* 1998
8	M	34	RA	ND	MF	Nd	G2	Nd	Nd	Donsbeck *et al.* 1999
9	M	42	RA	44	Nd	Yes	G2	Cardiac surgery Palliative chmotherapy and metastasectomy (lungs)	Alive at 15 mo	Bean *et al.* 1999
10	F	24	LA	51	MF	Nd	High	Cardiac surgery	Alive at 4 mo	Casselman *et al.* 1999
11	M	47	RA	45	BF	Nd	ND	Cardiac surgery, planned CTH	Nd	Bittira *et al.* 2000
12	M	45	RA	Nd	Nd	Nd	Nd	Cardiac surgery	Alive at 60 mo	Hannachi Sassi *et al.* 2004
13	M	42	LA	Nd	MP	Yes	Nd	Cardiac surgery	Died at 1 mo	Hazelbag *et al.* 2004
14	M	53	RA	120	Nd	Yes	G3	Nd	Nd	Kim *et al.* 2008
15	F	29	RA	75	Nd	Yes	G3	Nd	Nd	Kim *et al.* 2008
16	M	66	RA	Nd	MF	Present	High	Nd	Nd	Zhang *et al.* 2008
17	M	20	RA	110	MF	Nd	Nd	Nd	Nd	Yu, Shi, and Gu 2011

Table III. Cont.

No	Sex	Age	Location	Size (mm)	Histologic subtype	Molecular confirmation	Grade	Treatment	Survival (months)	Reference
18	M	36	RA	55	MF	Nd	High	Cardiac surgery, 4 cycles of CTH (ifosfamide and doxorubicin), reoperation	Died at 12 mo	Nazli *et al.* 2011
19	F	51	RA	83	BF	Yes	G2	Cardiac surgery	Nd	Huo *et al.* 2015
20	M	35	RA	63	MF	Yes	G3	Cardiac surgery, chemotherapy (ifosfamide and doxorubicin) and radiotherapy	Alive at 24 mo	Eswaran *et al.* 2015
21	M	39	LA	70	Nd	Nd	Nd	Cardiac surgery, chemoradiation	Alive at 12 mo	King *et al.* 2016
22	F	21	RA	75	Nd	Nd	Nd	Cardiac surgery, chemotherapy	Alive at 15 mo	Maleki *et al.* 2017
23	M	46	RA	55	BF	Yes	Nd	Cardiac surgery, adjuvant cth (gemcitabine and docetaxel)	Alive at 13 mo	Osada *et al.* 2018
24	M	52	LA	50	BF	Yes	Nd	Cardiac surgery	Died at 6 mo	Zhang *et al.* 2019
25	M	Nd	RA	45	Nd	Nd	Nd	Died before treatment was started	Died at diagnosis	Thatipelli *et al.* 2021
26	M	27	RA	80	BF	Nd	Nd	Cardiac surgery	Alive at 3 mo	Shah *et al.* 2021
27	M	47	LA	Nd	Nd	Nd	Nd	Cardiac surgery, chemotherapy	Alive at 24 mo	Martinez *et al.* 2021
28	M	30	RA	Nd	BF	Yes	G3	Cardiac surgery; few lines of chemotherapy	Died at 26 mo	Present case

NA – not applicable; Nd – no data; RA – right atrium; LA – left atrium; M – male; F – female; CTH – chemotherapy; mo – months, MF – monophasic; BF – biphasic; SS18 – SSX-SYT

Piazza et al. Can J Cardiol 2004; 20: 1443-1448; not included

press SMA and/or desmin, while cytokeratins, EMA, S100, and CD117 are usually negative or only weak or focal and vary depending on tumor differentiation (Table II) [4, 44]. The reactions to CD31, CD34 and Factor VIII are also negative, but can be positive in areas with angiosarcomatous differentiation [9, 46]. All reported cardiac intimal sarcomas have been H-caldesmon negative (Table II) [4, 44].

As the InS immunophenotype is non-specific, the final diagnosis of this entity should be based on molecular studies. InS is strongly associated with *MDM2* amplification, however, this genetic alteration can be also diagnosed in case of other sarcomas including: well differentiated and dedifferentiated liposarcoma (in up to 95% of cases), angiosarcoma (in one third of all cases) and other sarcomas (in 18% of all cases) like low-grade central osteosarcoma or parosteal osteosarcoma [8, 28, 44, 47]. In case of InS FISH can show a typical pattern of small grouping of signals not characteristic for dedifferentiated liposarcomas [28]. For diagnosis of *MDM2* amplification both: FISH and dual in situ hybridization (DISH) can be used [44].

As shown by our case InS has been commonly diagnosed as undifferentiated sarcoma or high-grade sarcoma. Performing FISH with the assessment of *MDM2* amplification is an important step in assessing the final diagnosis [8].

Molecular studies are of particular importance in the differential diagnosis between InS and undifferentiated pleomorphic sarcoma (UPS), however UPS of the heart have recently been suggested to represent the cardiac analog of InS due to morphological overlap and high prevalence of *MDM2* amplifications in both neoplasms. What is more, DNA methylation profiling (t-SNE) revealed an overlap of InS and cardiac UPS, too. This InS methylation signature was distinct from potential histologic and molecular mimics, especially in cases lacking *MDM2*, *MDM4* or *CDK6* amplifications [8].

Currently, due to uncommon diagnosis there is no standard of care (SoC) for InS treatment. Histologically clear margins (R0) achieved during radical surgery followed by adjuvant radiotherapy and chemotherapy seem to prolong the survival with surgery being pointed out as the mainstay of treatment [17, 18, 28]. In case of palliative treatment the options are surgery that can alleviate the symptoms and chemotherapy [18]. The chemotherapy regiments used in case of heart InS does not differ to these applied for other sarcomas [17]. New options that are investigated in clinical trials are MDM2 inhibitor milademetan, PDGFR inhibitor e.g. dasatinib and CDK4/6 inhibitors [28, 48, 49].

It seems that sarcomas of the left atrium carry poor, but slightly better prognosis to their counterparts localized in the right atrium [28]. Nevertheless, the survival in case of InS of the heart is usually few months with frequent recurrences within first year of radical treatment. Metastatic disease is reported in lungs, lymph nodes, brain and other sites [28]. Histological factors that indicate worse prognosis are high mitotic rate and necrosis [17].

Synovial sarcoma

Cardiac SS is an extremely rare and aggressive malignancy accounting for 3-5% of heart tumors with a significant male predominance and right heart location [2, 50, 51, 52]. The most common cardiac location is pericardium with atrium being the second one [52]. Only 27 cases of atrial synovial sarcomas have been reported previously (Table III). Twenty eight cases reported in the literature including our case are consisted of 19 men, and 6 female (2 unknown sex) with a median age of 40.5 years (13 to 66 years). Most of the tumors occur in the right atrium (in 20 cases).

In case of SS, the differential diagnosis includes mesothelioma, fibrosarcoma, MPNST and myxoid sarcoma/myxoma [50, 72]. For biphasic SS it is challenging to differentiate with mesothelioma with histology and immunohistochemistry with the support of molecular testing might be necessary [50]. For SS monophasic variant differential diagnosis with fibrosarcoma should be considered [50].

The role of immunohistochemical studies in the differential diagnosis of synovial sarcoma is limited, so the detection of t(X;18)(p11.2;q11.2) translocation resulting in fusion of *SYT* with *SSX1*, *2* or *4* present in 90% of SS cases is a hallmark in diagnosis of this malignancy [50, 73]. The diagnosis is based on FISH, but this genetic abnormality can also be detected with reverse transcription polymerase chain reaction (RT-PCT) next generation sequencing (NGS) [20, 72].

Treatment options consist of surgery – a gold standard rarely possible as a radical treatment with adjuvant chemo- or/and radiotherapy [74]. Traditionally, the first line of treatment for SS composes of high-dose ifosfamide, but other regiments are also applied [75]. As per the results of PALETTE trial the therapy with a multikinase inhibitor pazopanib in patients progressing after chemotherapy can be an option [76].

The prognosis of SS is extremely unfavorable with majority of patients dying shortly after diagnosis and only few patients with an observation time close to a year [50]. That makes our case special among only few others as current observation since the initial surgery is more than two years [62]. The reason of such poor survival can also be assigned to low radical surgery frequency resulting from tumour location [50]. It is suggested that age < 30 years at diagnosis can result in better prognosis [52].

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References

1. Vinod P, Jabri A, Hegde V, et al. Functional Mitral Stenosis: Imposture of Primary Cardiac Intimal Sarcoma. Cardiol Res 2018; 9: 307-313.
2. Donsbeck A V, Ranchere D, Coindre JM, et al. Primary cardiac sarcomas: an immunohistochemical and grading study with long-term follow-up of 24 cases. Histopathology 1999; 34: 295-304.
3. Burke AP, Cowan D, Virmani R. Primary sarcomas of the heart. Cancer 1992; 69: 387-395.
4. Neuville A, Collin F, Bruneval P, et al. Intimal sarcoma is the most frequent primary cardiac sarcoma: clinicopathologic and molecular retrospective analysis of 100 primary cardiac sarcomas. Am J Surg Pathol 2014; 38: 461-469.
5. Isambert N, Ray-Coquard I, Italiano A, et al. Primary cardiac sarcomas: a retrospective study of the French Sarcoma Group. Eur J Cancer 2014; 50: 128-136.
6. Zhang PJ, Brooks JS, Goldblum JR, et al. Primary cardiac sarcomas: a clinicopathologic analysis of a series with follow-up information in 17 patients and emphasis on long-term survival. Hum Pathol 2008; 39: 1385-1395.
7. Hudzik B, Miszalski-Jamka K, Glowacki J, et al. Malignant tumors of the heart. Cancer Epidemiol 2015; 39: 665-672.
8. Koelsche C, Benhamida JK, Kommoss FKF, et al. Intimal sarcomas and undifferentiated cardiac sarcomas carry mutually exclusive MDM2, MDM4, and CDK6 amplifications and share a common DNA methylation signature. Mod Pathol 2021; 34: 2122-2129.
9. Ibrahim A, Luk A, Singhal P, et al. Primary intimal (spindle cell) sarcoma of the heart: a case report and review of the literature. Case Rep Med 2013; 2013: 461815.
10. Zhang H, MacDonald WD, Erickson-Johnson M, et al. Cytogenetic and molecular cytogenetic findings of intimal sarcoma. Cancer Genet Cytogenet 2007; 179: 146-149.
11. Li Z, Hsieh T, Salehi A. Recurrent cardiac intimal (Spindle Cell) sarcoma of the left atrium. J Cardiothorac Vasc Anesth 2013; 27: 103-107.
12. Kuurstra EJ, Mullen JC, MacArthur RG. Massive left atrial sarcoma presenting with severe congestive heart failure. Can J Cardiol 2014; 30: 1250.e13-1250.e15.
13. Fu B, Yu H, Yang J. Primary intimal (spindle cell) sarcoma of the left atrium. Echocardiography 2015; 32: 192-194.
14. Holzhauser L, Heymer J, Kasner M, et al. Rare case of a multilocular primary cardiac intimal sarcoma presenting as left atrial mass with new onset atrial fibrillation. Eur Heart J 2015; 36: 2402.
15. Saith SE, Duzenli A, Zavaro D, Apergis G. Intimal (spindle cell) sarcoma of the left atrium presenting with abnormal neurological examination. BMJ Case Rep 2015; 2015: bcr2015209493.
16. Ohnaka M, Kyogoku M, Nakajima H, et al. Surgical resection of two independent primary intimal sarcomas in the left atrium. Cardiovasc Pathol 2016; 25: 399-404.
17. Valecha G, Pau D, Nalluri N, et al. Primary Intimal Sarcoma of the Left Atrium: An Incidental Finding on Routine Echocardiography. Rare Tumors 2016; 8: 6389.
18. Marques Mendes E, Ferreira A, Felgueiras P, et al. Primary intimal sarcoma of the left atrium presenting with constitutional symptoms. Oxford Med case reports 2017; 2017: omx031.
19. Fu X, Niu W, Li J, et al. Activating mutation of PDGFRB gene in a rare cardiac undifferentiated intimal sarcoma of the left atrium: A case report. Oncotarget 2017; 8: 81709-81716.
20. Crombé A, Lintingre PF, Le Loarer F, et al. Multiple skeletal muscle metastases revealing a cardiac intimal sarcoma. Skeletal Radiol 2018; 47: 125-130.
21. Pieraets MW, Hamad Soliman MA, van Straten BHM. Intimal sarcoma of the left atrium. J Card Surg 2018; 33: 179-180.
22. Abreu G, Salgado A, Bettencourt N, et al. Intimal sarcoma of the left atrium – A rare form of mitral valve obstruction. Rev Port Cardiol 2018; 37: 543-544.
23. Abid N, Ltaief R, Sassi A, et al. Left atrial intimal sarcoma: A rare cause of acute heart failure. Ann Cardiol Angeiol (Paris) 2019; 68: 232-235.
24. Edquist M, Lui C, Kilimnik G, Karp H. Computed tomography imaging characteristics of primary atrial intimal sarcoma. Clin Imaging 2019; 54: 112-115.
25. Raphael KL, Martinez AP, Clements SD, Isiadinso I. Role of Multimodal Cardiac Imaging in Diagnosing a Primary Intimal Sarcoma of the Left Atrial Appendage. Texas Hear Inst J 2019; 46: 28-31.
26. Ogechukwu C-N, Christopher N, Christoph S, et al. The Insidious Cardiac Tumor: A Primary Left Atrium Intimal Cardiac Sarcoma in a Young Patient. Case Reports Cardiol 2019; 2019: 1-4.
27. Nassereddine H, Sciot R, Debiec-Rychter M, et al. Cardiac intimal sarcoma: A case report of a rare tumor with peculiar histopathological findings. Ann Pathol 2019; 39: 440-443.
28. Grant L, Morgan I, Sumathi V, Salmons N. Intimal sarcoma of the left atrium presenting with transient ischaemic attack – A case report and review of the literature. J Cardiol Cases 2020; 21: 89-92.
29. Reynoso-Hermosillo M, Sandoval-Garciá J, López-Rosales B, et al. Malignant primary tumor in left atrium with mitral valve invasion, pulmonary veins and cerebral metastasis. A case report. Cir y Cir (English Ed) 2020; 88: 91-94.
30. Alam L, Agrawal K, Kankanala V, et al. Primary Cardiac Undifferentiated High-Grade Intimal Pleomorphic Sarcoma: A Case Series Report. Cardiol Res 2020; 11: 129-133.
31. Ho K, Yatham K, Seno R, Sultan O. A case report of primary cardiac intimal sarcoma presenting with atrial fibrillation and a left atrial mass. Eur Hear journal Case reports 2021; 5: ytab410.
32. Chiarelli M, Zago M, Tagliabue F, et al. Small Bowel Intussusception Due to Rare Cardiac Intimal Sarcoma Metastasis: A Case Report. Front Surg 2021; 8: 743858.
33. Rehman M, El-Dabh A, Mandal S, Sattur S. A case report of a massive cardiac intimal sarcoma manifesting as syncope during a stress test. Eur Hear J Case Reports 2021; 5: 1-7.
34. Chen Y-A, Li Y, Lee J-C, Chen J-W. Staged surgery for advanced cardiac intimal sarcoma involving the right atrium and the inferior vena cava. J Card Surg 2021; 36: 3973-3975.
35. Diamond JE, Mi MY, VanderLaan PA, et al. An Unusual Cause of Functional Mitral Stenosis: A Left Atrial Intimal Sarcoma. JACC Case reports 2021; 3: 829-833.
36. Pomp J, van Asselen B, Tersteeg RHA, et al. Sarcoma of the Heart Treated with Stereotactic MR-Guided Online Adaptive Radiation Therapy. Case Rep Oncol 2021; 14: 453-458.
37. Pyo WK, Kim JB. Sarcoma Resection With Complete Removal of Left Atrial Posterior Wall. Ann Thorac Surg 2021; 112: e439-441.
38. Romanowska A, Lewicka E, Sławiński G, et al. Case Report: Adjuvant Radiotherapy Can Be an Effective Treatment for Intimal Sarcoma of the Heart. Front Oncol 2021; 11: 1-7.
39. Durieux R, Tchana-Sato V, Lavigne JP, et al. Recurrent cardiac intimal sarcoma misdiagnosed as a myxoma or malignant transformation of a cardiac myxoma? J Card Surg 2021; 36: 357-362.
40. Hwang J-W. A rare disease of primary cardiac intimal sarcoma at the left atrium presented with mimicking mitral stenosis in a patient with polycystic kidney disease. J Cardiol cases 2020; 22: 5-10.
41. Moeri-Schimmel R, Pras E, Desar I, et al. Primary sarcoma of the heart: case report and literature review. J Cardiothorac Surg 2020; 15: 104.

42. Janssen N, Verheyen J, Albert A. Right Atrial Intimal Sarcoma on 18F-FDG PET/CT. Clin Nucl Med 2020; 45: e307-308.
43. Hamre CFB, Kvammen EMH, Vinge LE, et al. Sarkom i hjertet. Tidsskr Den Nor legeforening 2020.
44. Jimbo N, Komatsu M, Itoh T, Hirose T. MDM2 dual-color in situ hybridization (DISH) aids the diagnosis of intimal sarcomas. Cardiovasc Pathol 2019; 43: 107142.
45. Roszik J, Khan A, Conley AP, et al. Unique aberrations in intimal sarcoma identified by next-generation sequencing as potential therapy targets. Cancers (Basel) 2019; 11: 5-7.
46. Gupta A. Primary cardiac sarcomas. Expert Rev Cardiovasc Ther 2008; 6: 1295-1297.
47. Sciot R. Mdm2 amplified sarcomas: A literature review. Diagnostics 2021; 11: 496.
48. Frezza AM, Assi T, Lo Vullo S, et al. Systemic treatments in MDM2 positive intimal sarcoma: A multicentre experience with anthracycline, gemcitabine, and pazopanib within the World Sarcoma Network. Cancer 2020; 126: 98-104.
49. Hsu JY, Seligson ND, Hays JL, et al. Clinical Utility of CDK4/6 Inhibitors in Sarcoma: Successes and Future Challenges. JCO Precis Oncol 2022; 6: e2100211.
50. Hazelbag HM, Szuhai K, Tanke HJ, et al. Primary synovial sarcoma of the heart: a cytogenetic and molecular genetic analysis combining RT-PCR and COBRA-FISH of a case with a complex karyotype. Mod Pathol 2004; 17: 1434-1439.
51. Shah D, Gupta K, Naik D, Bhavsar N. Right atrial synovial sarcoma with thrombocytopenia: A deceptive presentation. J Card Surg 2021; 36: 2992-2995.
52. Wang J-G, Li N-N. Primary cardiac synovial sarcoma. Ann Thorac Surg 2013; 95: 2202-2209.
53. Sheffield EA, Corrin B, Addis BJ. Synovial sarcoma of the heart arising from a so-called mesothelioma of the atrio-ventricular node. Histopathology 1988; 13: 478-479.
54. Siebenmann R, Jenni R, Makek M, et al. Primary synovial sarcoma of the heart treated by heart transplantation. J Thorac Cardiovasc Surg 1990; 99: 567-568.
55. Sütsch G, Jenni R, von Segesser L, Schneider J. [Heart tumors: incidence, distribution, diagnosis. Exemplified by 20,305 echocardiographies]. Schweiz Med Wochenschr 1991; 121: 621-629.
56. Nicholson AG, Rigby M, Lincoln C, et al. Synovial sarcoma of the heart. Histopathology 1997; 30: 349-352.
57. Fujioka M, Suehiro S, Shibata T, et al. Primary cardiac synovial sarcoma – A case report. Japanese J Thorac Cardiovasc Surg 1998; 46: 923-927.
58. Bean SH, Sadler DJ, Gray RR, et al. Embolization of pulmonary pseudoaneurysms secondary to metastatic synovial sarcoma of the right atrium. J Vasc Interv Radiol 1999; 10: 649-652.
59. Casselman FP, Gillinov AM, Kasirajan V, et al. Primary synovial sarcoma of the left heart. Ann Thorac Surg valejimbgupthchiar 1999; 68: 2329-2331.
60. Bittira B, Tsang J, Huynh T, et al. Primary right atrial synovial sarcoma manifesting as transient ischemic attacks. Ann Thorac Surg 2000; 69: 1949-1951.
61. Hannachi Sassi S, Zargouni N, Saadi Dakhlia M, et al. Primary synovial sarcoma of the heart. A clinicopathologic study of one case and review of the literature. Pathologica 2004; 96: 29-34.
62. Eswaran P, Devadoss P, Narasimhan LS, Kannan K. Synovial sarcoma of the heart: A case report and literature review. J Cancer Res Ther 2015; 11: 659.
63. Kim CH, Dancer JY, Coffey D, et al. Clinicopathologic study of 24 patients with primary cardiac sarcomas: a 10-year single institution experience. Hum Pathol 2008; 39: 933-938.
64. Yu L, Shi E, Gu T. A giant primary cardiac synovial sarcoma. J Card Surg 2011; 26: 74.
65. Nazli Y, Karabulut MN, Goya C, Colak N. Synovial sarcoma in the right atrium and right ventricle. Acta Cardiol 2011; 66: 271-273.
66. Huo Z, Lu H, Mao Q, et al. Primary synovial sarcoma of the right heart involving the tricuspid valve in an elderly Chinese woman: A case report. Diagn Pathol 2015; 10: 1-6.
67. King N-M, Potgieter DW, Diqer A-M. Unusual case of a synovial sarcoma mimicking a left atrial myxoma involving the right atrium and inferior vena cava. ANZ J Surg 2016; 86: 1061-1062.
68. Maleki MH, Makouei MA, Hatami F, Noghabi RZ. Primary cardiac synovial sarcoma: A case report. J Tehran Univ Hear Cent 2017; 12: 32-34.
69. Zhang G, Gao Q, Chen S, Chen Y. Primary cardiac synovial sarcoma that was continuous with the mitral valve caused severe thrombocytopenia: A case report. J Cardiothorac Surg 2019; 14: 1-6.
70. Thatipelli S, Raissi S, Akhter N. Urgent Need for Diagnosis of a Rapidly Growing Right Atrial Mass. JAMA Cardiol 2021; 6: 350-351.
71. Martinez HA, Kuijvenhoven JC, Annema JT. Intracardiac EUS-B-Guided FNA for Diagnosing Cardiac Tumors. Respiration 2021; 100: 918-922.
72. Sharma A, Dixit S, Sharma M, et al. Primary Synovial Cell Sarcoma of the Heart: A Rare Case. Heart Views 2015; 16: 62-64.
73. Okoro KU, Roby MD, Sane DC, Budin RE. Infiltrating Cardiac Synovial Sarcoma Presenting as Acute Cerebrovascular Accident. Case Rep Med. 2017; 2017: 1-4.
74. Coli A, Chiariello GA, Novello M, et al. Treatment of cardiac synovial sarcoma: experience of two cases. J Cardiothorac Surg 2018; 13: 84.
75. Zhang H, Huang W, Feng Q, et al. Clinical Significance and Risk Factors of Local Recurrence in Synovial Sarcoma: A Retrospective Analysis of 171 Cases. Front Surg 2022; 8: 708.
76. van der Graaf WTA, Blay J-Y, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England) 2012; 379: 1879-1886.

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