

# No association between herpes simplex virus 1 and cardiac myxoma

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## Summary

**PRINCIPLES:** Cardiac myxoma is the most commonly diagnosed cardiac tumour. Infection of herpes simplex virus 1 (HSV1) has been postulated to be a factor for this pathologic entity. The aim of the current study was to evaluate the association between HSV 1 and myxoma occurrence.

**METHODS:** Between 1965 and 2005, 70 patients (36 female, mean age: 52.6 years) underwent a resection of myxoma. Selected variables such as hospital mortality and morbidity were studied. A follow-up (FU; mean FU time: 138 ± 83 months) was obtained (76% complete). Immunohistological studies with monoclonal antibodies against HSV type 1 were performed on tumour biopsies of 40 patients.

**RESULTS:** The mean age was 53 ± 16 years (range 23 to 84 years, 51% female). Of the investigated population, 31 (44%) were in New York Heart Association (NYHA) class III-IV. Mitral valve stenosis was identified in 14 patients (20%), and in 25 (36%) patients mitral valve was insufficient.

During hospitalisation 3 patients suffered from a transient neurological disorder, and in addition to myxoma resection 18 (25.7%) patients had to undergo an additional intervention. The overall survival rate was 91% at 40 years. There was no early postoperative mortality in follow-up, although 4 patients died and 2 patients had been re-operated on for recurrent myxomas after 2 and 9 years. Immunohistology revealed no positive signals for HSV-1 antigens among the 40 analysed cases.

**CONCLUSION:** Complete surgical resection, septum included, was the treatment of choice and mandatory to prevent relapse. Peri-operative morbidity and mortality over 40 years remained low, and no association between HSV infection and occurrence of cardiac myxoma was found.

**Key words:** intracardiac tumours; benign heart tumours; herpes simplex infection

## Introduction

Primary tumour of the heart is a rare entity with incidence ranging between 0.00071 and 0.0029% of unselected patient autopsies [1]. Approximately 80% of the tumours are benign and nearly half of these are myxomas [2]. It seems that intracardiac myxoma is a frequent pathology which may be found in the left atrium in 80% of cases, 7 to 20% are found in the right atrium, and the remaining 10% are diagnosed either in the left or right ventricle [3]. Currently, the broadly accepted therapy modality is surgical excision with very low overall mortality of up to 3%. Although the therapy, as well the ante mortem diagnosis, of this pathological entity seems to be very successful, the underlying cause remains unclear. Familial cardiac myxomas which represent less than 10% of all myxomas are related to the Carney complex, a multiple neoplasia and lentiginosis syndrome. The sporadic tumours which represent a majority of this pathology do not have a clearly defined pathological cause. Chronic infection related to the HSV 1 infection has been suggested to be a potential factor that may provoke generation of myxoma. It is true that inflammatory symptoms are present in about half of the patients with a diagnosis of myxoma, including fatigue, fever, weight loss and laboratory abnormalities (elevation of leukocyte count, IL6, erythrocyte sedimentation rate, and serum C-reactive protein). Further immunohistological investigations have supported this theory and it has been shown that atrial myxoma may arise via a reactive process induced by HSV 1.

Herein we evaluated immunohistological patterns of 40 consecutive patients to determine if HSV 1 infection of the extracted myxomas was present. Additionally, our experience from over 40 years of follow-ups, including treatment modalities and long-term results, in 70 cardiac myxoma patients are reported.

## Methods

### Patient characteristics

From January 1965 to January 2005, 70 consecutive patients were operated on for the removal of primary intracardiac myxoma at the University Hospital Zurich. Of these, 36 were female (51%) and 34 (49%) were male. The mean age at time of the interventions was  $53 \pm 16$  years (range 23 to 84 years). The methods used to confirm the diagnosis of a cardiac myxoma varied over the four decades. In the earlier years, 2 patients were diagnosed by cardiac catheterisation. More recently, transthoracic echocardiography (TTE) was performed on 40 patients and transesophageal echocardiography (TEE) was performed on 28 patients. The correct diagnosis was made in every case. Myxomas were identified in 62 patients in the left atrium (89%) and 8 in the right atrium (11%). Swiss Carney syndrome was identified in 4 (6%) cases (table 1).

The most frequently observed symptoms were associated with congestive cardiac heart failure symptoms, and 31 patients were in class NYHA III/IV. Congestive heart failure was associated with mitral valve obstruction in 14 (20%) and with insufficiency in 25 (36%) patients (table 2). The myxoma were the source of peripheral emboli in 6 (9%) patients and 18 (26%) patients suffered a stroke. In addition, constitutional symptoms and signs of a generalised disease with fever were reported in 16 (23%) patients.

### Operative technique

The tumour was excised under cardiopulmonary bypass using aortic and bicaval cannulation. Cardiac arrest with moderate hypothermia ( $26\text{--}28\text{ }^{\circ}\text{C}$ ) was used in 44 (63%) of the patients. Myocardial protection was achieved by retrograde blood cardioplegia. Repetitive dosage was given every 10 minutes.

In 26 (37%) patients, the operation was performed in normothermia ( $36\text{ }^{\circ}\text{C}$ ) without cardiac arrest in ventricular fibrillation. In both surgical modalities, the left ventricle was vented via the left superior pulmonary vein.

### Immunohistological studies

Myxoma samples were fixed in 10% neutral formalin and embedded in paraffin for histological examination. The presence of both myxoid stroma and myxoma cells in tissue sections stained with haematoxylin and eosin (H&E) was diagnostic of atrial myxoma. A monoclonal antibody (Mab) prepared using HSV 1 strain Stoker as an antigen was supplied by Vector Lab Ltd (Newcastle, UK). This technique has been published previously [4], and for details see also Li et al. (*Am J Pathol* 2003, 163:2407–2412).

### Follow-up

All patients had follow ups at regular intervals. They underwent clinical examination, roentgenography, electrocardiography and echocardiography. Transthoracic echocardiography was performed routinely prior to discharge and then subsequently every year. Follow-up of the survivors was accomplished by means of questionnaires and telephone calls.

## Results

Complete excision of the tumour with a cuff of atrial tissue was the basic principle of excision and was successful in all patients. The surgically created atrial septal defect was either closed directly for 59 (84%) patients or repaired in 11 (16%) patients by using an autologous pericard patch or Dacron patch (C.R. Bard, Inc., Haverhill, MA). Coronary bypass was performed in 12 (17%) patients, the mitral valve was reconstructed with annuloplasty and quadrangular resection in 3 (4%) patients, and the tricuspid valve was reconstructed in 2 (3%) patients (De Vega reconstruction). Implantation of the aortic and of the pulmonary valve was performed in 1 (1.5%) patient. The mean time of extracorporeal circulation was  $71 \pm 38$  minutes. Surgical revision in the first 48 hours was performed in 3 (4%) patients, which was because of acute haemorrhage and pericardial tamponad. Surgical revision after 48 hours was performed in 2 patients; in one because of insufficient mitral valve reconstruction, and in the second patient because of late reactive pericardial tamponad. The mean intensive care unit (ICU) stay was  $32 \pm 17$  hours, patients were extubated after  $9 \pm 5$  hours (range between 3 and 24 hours), and mean hospital stay was  $10 \pm 3$  days (range 4 to 17 days) (table 3). There was no in-hospital mortality. During hospitalisation, 2 (3%) cases of pneumonia and one case of superficial wound infections were diagnosed. In all cases, therapy was conservative. One patient developed embolism of the femoral artery. The source of the embolism was a thrombus in the left ventricle, which was ascertained by histological examination. Three cases (7%) had transient neurological events (table 3).

The follow-up period after resection of a myxoma ranged between 46 and 340 months (mean  $138 \pm 83$  months). From the follow-up, 6 patients were excluded as at the time of the study they had no residency address in Switzerland. Of 64 questionnaires, 46 (72%) were returned and evaluated. The mean age at the time of evaluation was  $70 \pm 16$  years. The overall survival rate was 91% at 40 years, and 4 (9%)

**Table 1:** Preoperative characteristics of the patients.

Patients profile	No of patients (N = 70)
Male gender	34 (49%)
Female gender	36 (51%)
Mean age $\pm$ SD (years)	$53 \pm 16$
Myxoma in right atrium	8 (11%)
Myxoma in left atrium	62 (89%)
Swiss Carney syndrome	4 (6%)

**Table 2:** Clinical symptoms in 70 patients with intracardiac myxoma.

Symptoms	No. of patients
Cardiac	
Dyspnea (NYHA III or IV)	31 (44%)
Mitral regurgitation	25 (36%)
Mitral stenose	14 (20%)
Palpitation	11 (16%)
Embolic	
Central nervous system	18 (26%)
Peripheral	6 (9%)
Constitutional	
Fever	16 (23%)

patients died where the cause of death was not of cardiac origin.

One sporadic myxoma recurred, which was related to insufficient excision. Additionally, 1 of the 4 patients with familial myxoma had a recurrence. This patient was re-operated on three times in a period between 1986 and 1995.

In the long-term follow-up, 43 patients (95%) were subjectively asymptomatic and had no postoperative complications. Two patients (4%) reported cardiac symptoms. In the early postoperative period, 10 patients developed atrial fibrillation, however at discharge all were converted into sinus rhythm. In the long-term follow-up, two patients developed chronic atrial fibrillations and were treated with warfarine. No thrombo-embolic event or stroke was observed following discharge (table 4).

### Pathology results

In all 70 specimens, the diagnosis of myxoma was verified by histological examination. After the tumours were resected, the tissue was fixed in 10% formaldehyde. The histological specimens were stained with haematoxylin and eosin. Additionally, immunohistology of HSV 1 and 2 was performed on 40 specimens. The material for this investigation was gathered retrospectively from a pathology tissue bank. Tumours extracted between 1965 and 1982 were not stored, so only 40 cases were evaluated for HSV 1 presence. In all 40 cases there was no validation of HSV 1 infection.

### Discussion

Myxomas are the most frequent benign primary tumours of the heart and they represent approximately 0.3% of all open-heart surgeries reported in the literature [5, 6]. The

first case of intracavitary myxoma was described in 1854 and, until 1951, the diagnosis of cardiac tumour was deduced in post-mortem investigations. The introduction of echocardiography definitively facilitated the diagnosis, and to-date remains the most important modality for imaging of cardiac tumours. This non-invasive technique allows adequate identification of tumour size, position, mobility and location [7].

The therapy of choice, after establishing diagnosis, is surgical excision. This has to be performed as soon as possible because of the risk of valvular obstruction and/or systemic embolisation [8]. It appears that good visualisation of all four chambers is an indication of successful surgical treatment. From such visualisation, additional tumours may appear which were not identified during the preoperative work up [9]. As such, a bi-atrial approach has previously been advocated [10]. In our series, in the first two decades we also performed the proposed bilateral exposure in order to evaluate the left and right cardiac chambers. However, with the use of intraoperative transesophageal echocardiography we focused on the target chambers, with exposure of ventricular and atrial chambers on the corresponding side.

Although the diagnosis and the treatment strategies in this pathological entity seem to be well established with very low mortality (ranging between 0 and 3%), the origin of myxomas is not clearly defined. In most cases, myxomas are diagnosed as sporadic tumours, and about 10% of cases are familial and are transmitted in an autosomal dominant way [11, 12]. Familial myxomas are presented as a component of a Carney syndrome [13]. In Carney syndrome, the mutation of the *PRKAR1alpha* gene, encoding the R1alpha regulatory sub-unit of cyclic-Amp-dependent protein kinase A, is responsible for complex symptomatic and manifestation [14]. Compared to the sporadic myxomas, the familial cardiac myxomas may have multiple intracardiac locations with a recurrence rate of about 22%, whereas the recurrence rate of sporadic tumours is at 3–4% (15). In our series, 4 patients with Carney syndrome were operated on successfully and only 1 (25%) patient had recurrences, being re-operated on three times in a period of 9 years.

Although the pathogenesis of familiar myxomas is well defined, the pathogenesis of sporadic myxomas remains unknown. In the past, because of abundant expression of mucopolysaccharidic matrix in tumour stroma, extensive expression of mucin gen was suggested as a potential factor for tumour generation [16]. However, clinical implications of mucin gens in cardiac myxomas have never been assessed.

Additionally, it has been postulated that the origin of disease might be in relation to HSV 1 infection. In a series of 17 patients being operated on for myxoma resection, Li et al. were able to find the presence of the HSV 1 antigen in 12 (70%) patients, and in 8 (30%) cases the DNA of HSV 1 was identified [7]. In our series, tumour diagnosis of benign myxoma was confirmed in all 40 investigated cases. Using the immunohistology method that was described by Li et al. [7], we were unable to confirm the presence of the HSV1 antigen. Furthermore, according to the questionnaires and telephone conversations to the personal physicians, none of the 40 investigated cases had either a clinical

**Table 3:** Peri-operative evolution of the patients.

Peri-operative data	No. of patients
Successful Tumour resection	70 (100%)
Ventricular fibrillation	26 (37%)
Cardiac arrest	44 (63%)
Closure of the septum with patch	11 (16%)
Coronary bypass graft	12 (17%)
Mitral valve reconstruction	3 (4%)
Tricuspid valve reconstruction	2 (3%)
Superficial wound infection	2 (3%)
Pulmonary valve replacement	1 (1.5%)
Aortic valve replacement	1 (1.5%)
Transient neurological events	3 (7%)
Peripheral embolisation	1 (2%)
Hospitalisation time $\pm$ SD (Days)	10 $\pm$ 3
In Hospital mortality	0

**Table 4:** Follow up in 46 patients after the myxoma resection.

Follow up	No. of patients
Mean age at follow up $\pm$ SD (years)	70 $\pm$ 16
Mean time after intervention $\pm$ SD (Months)	138 $\pm$ 83
Mortality during follow-up	4 (9%)
Recurrent myxoma	2 (4%)
Chronic atrial fibrillation	2 (4%)
Diagnosed HSV (serological diagnosis)	0

or serological suspicion of HSV 1 infection. Thus our results cannot confirm that HSV 1 is responsible for myxoma generation.

We have to be aware that HSV 1 infection is very common in an adult sexually active population and that its prevalence has a growing tendency with age. The prevalence in a non-high-risk middle-age population, ranges between 40 and 60% and reaches its plateau after 30 years. On the other hand, prevalence in high-risk groups may reach up to 90% and is often combined with HIV infections [17]. This demographic data would suggest that if HSV 1 is responsible for myxoma development, the prevalence, especially in patients with a compromised immune system, would definitively be higher than the observed 0.002%. According to data presented in this retrospective study, the theory of HSV 1 infection as a factor cannot be supported from either a diagnostic or epidemiological point of view. In this context, we believe further pathological as well epidemiological investigations have to be performed.

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