



Research article

Autopsy of 54 cases of surgically excised cardiac myxomas. Investigation of their impact on immune response

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ARTICLE INFO

Keywords:

Cardiology
Immunology
Pathology
Pathophysiology
Cardiac myxoma
Neutrophil/lymphocyte ratio
NLR
Inflammatory response
Biomarker

ABSTRACT

Introduction: The impact of cardiac myxomas on the immune response is still indefinite, although laboratory tests and histological findings suggest that there is a correlation between myxomas and inflammatory reaction.**Objectives:** Our study speculates that cardiac myxomas are associated with inflammatory response and investigates potential elements of inflammation in the histopathological examination and biomarkers from laboratory tests.**Methods:** It is a retrospective study and data were collected from a single center between May 2010 to May 2018. Autopsies and laboratory tests of 54 cases were analyzed.**Results:** In 20,4% of the autopsies, inflammatory elements were identified. The neutrophil/lymphocyte ratio (NLR) preoperatively is elevated in patients suffering from cardiac myxoma while its value is correlated to the tumor size.**Conclusions:** Cardiac myxoma is an entity that affects the immune response of patients. The biomarker NLR could be utilized as a prognostic factor regarding enlarged cardiac myxomas. Future studies still need to be conducted in order to confirm the usefulness of this biomarker on cardiac myxomas.

1. Introduction

The most frequent neoplasm of the heart is the cardiac myxoma with its incidence to range from 0,5 to 1 cases per million, while it represents the 0,25% of heart diseases [1]. Cardiac myxomas are related with intermittent hemodynamic events, such as syncope, provoked by position change [2]. Major adverse cerebral and thromboembolic events are associated with this entity with its incidence reaching 20% [3].

Throughout the literature, there are many speculations concerning the tumor's origin and its impact on immune response. It is known that cardiac myxomas are presented with high histopathologic heterogeneity and the investigation of the inflammatory infiltration may reveal some aspects of their clinical behaviour [4]. Moreover, they are related with inflammatory response and that derives from the fact that infection indicators are detected in abnormal levels in laboratory tests, such as the elevation of C-reactive protein (CRP) or erythrocyte sedimentation rate

(ESR), while sometimes there are also clinical symptoms, such as fever, fatigue or weight loss [5, 6].

In this study we have collected data of 54 consecutive patients who underwent cardiac surgical operation with cardiopulmonary bypass (CPB) for the excision of myxoma at a single center. The aim of this study is to investigate the impact of cardiac myxomas on the immune response based on clinical, histopathological and laboratory findings.

2. Materials and methods

This study is retrospective and non-experimental. The data were collected regarding the period between May 2010 and May 2018 from the Cardiothoracic Surgery Department of a tertiary hospital in Athens, Greece. We studied 54 consecutive patients who were admitted for surgical excision of cardiac myxoma. We recorded information about their sociodemographic characteristics, medical background, laboratory tests

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before and after the surgery, histopathological essays, patients' hospitalization and parameters of the procedure.

The inclusion criteria were: 1) participation of adults (age more than 18 years old) and 2) patients' informed consent. The statistical analysis was performed with SPSS version 22.0. For the comparison of proportions chi-square and Fisher's exact tests were used. All reported p values are two-tailed and the statistical significance was set at p-value ≤ 0.05 .

The study was conducted after written approval of the ethics committee of the hospital. The patients' informed consent was received after fully understanding the obligations and the purpose of the study. The researcher gathered the data and the same method was used for all cases. The whole investigating and experimenting process is in accordance to the Declaration of Helsinki and the Greek legislation on Bioethics. The personal data and rights were protected according to the law.

3. Theory/Calculation

The main goal of this study is the investigation of cardiac myxomas' characteristics and their impact on immune response based on histopathological and laboratory findings. We speculate that cardiac myxomas are associated with inflammatory response and we investigate potential elements of inflammation in the histopathological examination and biomarkers calculated from laboratory tests.

4. Results

Data were collected for a total number of 54 patients who underwent cardiac surgical operation with cardiopulmonary bypass for the excision of cardiac myxomas. There was a predominance of the female gender (63%) and the mean age was 62,4 years old. In all cases typical median sternotomy was performed. Regarding tumors of the left atrium, 11 patients out of 54 had a biatrial-transeptal surgical approach, while 34 patients had the tumor excised through left atrial incision. The mean cross-clamp time was 43,3 (+/- 16,8) minutes and the mean circulatory bypass time was 70,6 (+/- 21,3) minutes. The mean length of stay in intensive care unit (ICU) was 3,3 days (1-11,5) and the average in-hospital length of stay were 5,1 days (+/-1,5). One patient died during the postoperative period.

Euroscore and Logistic Euroscore in all patients were calculated and all the comorbidities were recorded. The patients' characteristics based on their medical history are presented in Table 1. The percentage of asymptomatic patients was 35,1%, while the incidence of pericardial

effusion reached 38,9% (21/54 patients). About 6 out of 10 patients mentioned symptoms of dyspnea, in 21,4 % of cases an arrhythmia was present and in 16,1 % pulmonary hypertension was detected.

In the following Table, the characteristics of the excised myxoma are presented (Table 2). The most frequent location of the tumor was the left atrium (45/54 cases), followed by the right ventricle in 11,1% of the patients. The mean tumor size was 4,5 (+/-1,8) cm. The histopathological examination identified hemorrhagic elements in 62,3% of the patients while identification of inflammatory elements was possible in 20,4% of them (Table 2). At this point we should mention that viral infectious agents were absent of all cases studied. The immunohistochemical staining used in all cases were CD31, CD34 and calretinin.

Data collection and analysis of the laboratory tests revealed statistically significant decrease of red blood cell (RBC) count and hemoglobin, while white blood cell (WBC) count, glucose levels and the neutrophil/lymphocyte ratio (NLR) were elevated (Table 3). Although the RBC count, hemoglobin, levels of glucose and WBC count were found as expected due to the impact of the surgery, the NLR was affected significantly. More specifically, the preoperative average value was 2,94 and after surgery it ended up to be 13,54 respectively. Moreover, this differentiation is not derived only from the increase of WBC count but also from a remarkable decrease of the absolute number of lymphocytes.

In further analysis, we found a statistically significant correlation between the size of the tumor and higher measurements of NLR preoperatively. The change in NLR after surgery was similar regardless of the tumor size. In addition to this, we investigated whether there is any correlation between the presence of inflammatory elements in the specimens and NLR. No difference was detected between tumors with inflammatory elements and tumors without (Table 4).

5. Discussion

In our study, the percentage of asymptomatic patients, in which the tumor was a random finding, was 35,1%. On the other hand, the majority of the symptomatic patients mentioned dyspnea (57,4%) which is strongly correlated with the increased incidence of pericardial effusion (38,9%) and pleural effusion (16,6%)(Table 1). Throughout the literature, the incidence of dyspnea preoperatively ranges between 50% to 66%, which is in accordance with our study [7, 8].

Although the origin of cardiac myxoma is not definite, most of the times its structure resembles to mesenchymal tissue [9]. In our research hemorrhagic elements were identified in 62,4% of the tumors and this is related to increased angiogenesis of the tumor, which is a common

Table 1. The patients' characteristics based on their medical history. The average for Euroscore, LogisticEuroscore and the most frequent comorbidities are presented.

Medical history	N	%
Euroscore, average (SD)	4,9 (2,6)	
Logistic Euroscore, average (SD)	5,13 (5,15)	
Valvular disease	14	25,9
Coronary artery disease	12	22,2
Asymptomatic (random finding)	19	35,1
Pericardial effusion	21	38,9
Pleural effusion	9	16,6
Arrhythmias	12	21,4
Dyspnea	31	57,4
Pulmonary hypertension	9	16,6
Hypertension	15	27,7
Diabetes Mellitus	4	7,4
Smoking	17	31,4
Obesity	9	5,5
Dyslipidemia	10	18,5

Table 2. The characteristics of the excised cardiac myxomas reported from the immune-histochemical analysis.

Characteristics of myxomas		N	%
Location	Left ventricle	2	3,7
	Left atrium	45	83,3
	Right ventricle	6	11,1
	Right atrium	1	1,8
Tumor size, average (SD)	4,5 (1,8)		
Identification of hemorrhagic elements	No	21	37,7
	Yes	33	62,3
Identification of inflammatory elements	No	43	79,6
	Yes	11	20,4

Table 3. Laboratory tests before and after surgery. Although the variation of the average levels of RBC, hemoglobin, WBC and glucose were found as expected, the neutrophil/lymphocyte ratio was differentiated in a remarkable degree.

Laboratory tests	Before surgery		After surgery		P*
	Average (SD)	Median price (Internal range)	Average (SD)	Median price (Internal range)	
Red Blood Cells (RBC)	4,59 (0,52)	4,57 (4,2–4,89)	3,98 (0,42)	3,85 (3,64–4,35)	<0,001
White Blood Cells (WBC)	8,37 (3,47)	7,56 (5,97–10,31)	14,59 (4,35)	13,92 (11,84–17,62)	<0,001**
Hemoglobin (Hgb)	12,89 (1,76)	12,65 (11,8–14)	11,24 (1,36)	10,85 (10,4–12,1)	<0,001
Glucose (Glu)	105,3 (44,76)	94 (81–111)	151,7 (36,16)	150 (121–178)	<0,001
Creatinine (Cre)	0,87 (0,23)	0,84 (0,73–1,2)	0,93 (0,36)	0,84 (0,7–1,06)	0,186
Urea (Ur)	39,81 (15,4)	36,5 (28–49)	39,24 (18,88)	36 (26–44)	0,334
Neutrophil/Lymphocyte ratio (NLR)	2,94 (2,05)	2,51 (1,66–3,25)	13,54 (7,72)	12,37 (8,82–16,4)	<0,001

* Wilcoxon test.

** Paired t-test.

Table 4. No correlation detected between the presence of inflammatory elements in the specimens and NLR.

	Presence of inflammatory elements				P Mann-Whitney test
	No		Yes		
	Average (SD)	Median price (Internal range)	Average (SD)	Median price (Internal range)	
NLR(before)	3,05 (2,15)	2,52 (1,66–3,35)	2,49 (1,64)	2,49 (1,23–3,00)	0,427
NLR(after)	13,99 (8,16)	12,39 (8,82–17,32)	11,76 (5,69)	12,20 (7,02–16,40)	0,644

finding [9]. According to some studies, cardiac myxoma is related to viral infections [10], but in this study no correlation between myxomas and viral infections was detected. Moreover, we found that in approximately 1 out of 5 myxomas inflammatory elements were identified. A study showed that increased levels of interleukin-6 found, either in the bloodstream or inside the tumor, can be used as a biomarker more efficiently than common infection markers, such as C-reactive protein [11]. Further research is indispensable in order to delineate the myxoma's biological behavior, especially in the field of inflammatory response.

Regarding the neutrophil/lymphocyte ratio, three findings are very important. The first point is the elevated mean NLR preoperatively 2,94 (+/−2,05) when studies support that the normal mean price of NLR is 1,65 (+/−1,96) [12]. Moreover, NLR was associated with the tumor size before surgery. The third point observed, is the remarkable increase of NLR after the surgery with the significant decrease in lymphocyte number. There exist studies that showed that NLR can be used as a prognostic factor in several types of cancer and in cardiovascular diseases [13, 14, 15]. These findings suggest that NLR may be used as a biomarker for the cardiac myxoma prognosis and biological behavior, although more data need to be collected and analyzed.

5.1. Study limitations

The number of cases studied was satisfactory but a larger sample would be more reliable. The financing was limited for immune-

histochemical staining. More staining could reveal more pathological characteristics of cardiac myxomas. The study was retrospective without the ability of follow-up and re-evaluation after the surgery.

6. Conclusions

Cardiac myxoma is an entity that affects the immune response in cardiac patients, although its impact still remains indefinite. The neutrophil/lymphocyte ratio was found to be associated with the presence of cardiac myxoma while its value is proportional to the tumor size preoperatively. Further research is necessary in order to evaluate the role of NLR as a biomarker for cardiac myxomas and clarify the biological behavior of this neoplasm.

Declarations

Author contribution statement

N. Michopanou: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

C. Charitos: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

N. Schizas: Analyzed and interpreted the data; Wrote the paper.

D. Rontogianni: Performed the experiments; Contributed reagents, materials, analysis tools or data.

G. Saroglou, A. Vatopoulos and I. Pavlopoulou: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

R. Eltheni: Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

- [1] I.M. Keeling, P. Oberwalder, M. Anelli-Monti, H. Schuchlenz, U. Demel, G.P. Tilz, P. Rehak, B. Rigler, Cardiac myxomas: 24 years of experience in 49 patients, *Eur. J. Cardio. Thorac. Surg.* 22 (6) (2002 Dec) 971–977.
- [2] A. Karabinis, G. Samanidis, M. Khoury, G. Stavridis, K. Perreas, Clinical presentation and treatment of cardiac myxoma in 153 patients, *Medicine* 97 (2018) 37.
- [3] H. Hirose, B. Youdelman, J.W. Entwistle, Stroke from a large left atrial myxoma, *Open Cardiovasc. Med. J.* 2 (2008) 115–117.
- [4] A. Di Vito, G. Santise, C. Mignogna, E. Chiefari, G. Cardillo, I. Presta, F. Arturi, N. Malara, F. Brunetti, A. Donato, D. Maisano, S. Leonetti, D. Maselli, T. Barni, G. Donato, Innate immunity in cardiac myxomas and its pathological and clinical correlations *Innate, Immunity* 24 (1) (2018) 47–53.
- [5] L.D. Panos, C. Brunel, S. Berezowska, R. Engisch, A. Kollar, C. Bassetti, M. Sturzenegger, H. Krestel, Early and delayed neurological manifestations of cardiac myxomas, *Clin. Neurol. Neurosurg.* 190 (2020) 105673.
- [6] J. Cho, S. Quach, J. Reed, O. Osian, Case report: left atrial Myxoma causing elevated C-reactive protein, fatigue and fever, with literature review, *BMC Cardiovasc. Disord.* 20 (2020) 119.
- [7] M. Sotoudeh Anvari, M. Ali Boroumand, A. Karimi, K. Abbasi, H. Ahmadi, M. Marzban, N. Movahedi, N. Moshtaghi, A. Salehiomran, S. Davoodi, M. Shirzad, S. Seyed Hesameddin Abbasi, Histopathologic and clinical characterization of atrial myxoma: a review of 19 cases, *LABMEDICINE* 40 (10) (2009).
- [8] A. Garatti, G. Nano, A. Canziani, P. Gagliardotto, E. Mossuto, A. Frigiola, L. Menicanti, Surgical excision of cardiac myxomas: twenty years experience at a single institution, *Ann. Thorac. Surg.* 93 (2012) 825–831.
- [9] A. Boutayeb, L. Mahfoudi, S. Moughil, Atrial myxoma: from diagnosis to management, *Clin. Surg.* 2 (2017) 1498.
- [10] Yanwen Li, Zhigang Pan, Ji Yuan, Mary Sheppard, Donald J. Jeffries, Leonard C. Archard, Hongyi Zhang Herpes simplex virus type 1 infection associated with atrial Myxoma *American, J. Pathol.* 163 (6) (December 2003).
- [11] Shi-Min Yuan, Hui-Zhen Lin, Predictors of normalization of circulating interleukin-6 after cardiac myxoma Resection *Braz. J. Cardiovasc. Surg.* 34 (1) (2019) 22–27.
- [12] P. Forget, C. Khalifa, J.P. Defour, D. Latinne, M.C. Van Pel, M. De Kock, What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res. Notes* 10 (2017) 12.
- [13] O. Haki Yuksel, A. Verit, A. Sahin, A. Urkmez, F. Uruc, White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker, *Int. Braz. J. Urol.* 42 (2016) 53–59.
- [14] R. Howard, P. Kanetsky, K. Egan, Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer, *Sci. Rep.* 9 (2019) 19673.
- [15] Li Han, Xiangxue Lu, Ruifang Xiong, Shixiang Wang high neutrophil-to-lymphocyte ratio predicts cardiovascular mortality in chronic hemodialysis patients mediators inflamm 2017 (2017) 9327136.