Histopathological findings of inflammatory activity in patients with subclinical carditis

Achados histopatológicos de atividade inflamatória em pacientes com cardite subclínica

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ABSTRACT

In patients with Chronic Rheumatic Carditis, active carditis is an often underdiagnosed condition. Rheumatic attacks promote the aggravation of existing lesions, leading to a deterioration of the patient's clinical condition. Thus, reducing the morbidity and mortality of the disease depends, in part, on controlling relapses through secondary prophylaxis. Underdiagnosis is due in part to the occurrence of subclinical rheumatic attacks. This study was carried out with data from patients who were diagnosed with Chronic Rheumatic Carditis and who underwent cardiac surgery for valve replacement or repair, without clinical or laboratory evidence of rheumatic outbreak. A fragment of myocardium was sent for histopathological analysis. Data on the frequency of histopathological alterations compatible with a rheumatic outbreak were analyzed. After analysis, 80% of patients showed changes compatible with inflammatory activity. Of these, 87.5% had lymphocytic infiltrate; 25% had Aschoff's nodules. The most frequent histopathological findings of chronic disease were myocardial hypertrophy in 56.7% of patients and fibrosis in 53.3%.

Keywords: Cardiology, Rheumatic carditis, Rheumatic fever, Subclinical carditis

RESUMO

Nos pacientes com Cardite Reumática Crônica, a cardite em atividade é uma condição frequentemente subdiagnosticada. Os surtos reumáticos promovem o agravamento das lesões já existentes, levando a uma deterioração da condição clínica do paciente. Dessa forma a redução da morbimortalidade da doença depende, em parte, do controle de recidivas a partir da profilaxia secundária. O subdiagnóstico deve-se em parte a ocorrência de surtos reumáticos subclínicos. Este estudo foi realizado com dados dos pacientes que tiveram o diagnóstico de Cardite Reumática Crônica e foram submetidos à cirurgia cardíaca para troca ou plastia valvar, sem evidência clínica ou laboratorial de surto reumático. Um fragmento de miocárdio foi enviado para análise histopatológica. Foram analisados os dados de frequência de alterações histopatológicas compatíveis com surto reumático. Após análises, 80% dos pacientes apresentaram alterações compatíveis com atividade inflamatória. Desses, 87,5% apresentavam infiltrado linfocitário; 25% apresentavam nódulos de Aschoff. Os achados histopatológicos de doença crônica mais frequentes foram hipertrofia miocárdica em 56,7% pacientes e fibrose em 53,3%.

Palavras-chave: Cardiologia, Cardite reumática, Febre reumática, Cardite subclínica

INTRODUCTION

Although there has been a decline in the incidence and prevalence of chronic rheumatic heart disease (CRHD) in countries with high levels of social and economic development, in underdeveloped countries, the disease remains an affliction[1]. Poverty, a lack of sanitation and overcrowded housing are strongly associated with persistently high prevalence rates[2,3]. This scenario facilitates the spread of infectious diseases, including beta-hemolytic group A streptococcal infection[2,3]. Although this predominantly affects underdeveloped countries, Bradley-Hewitt et al. reported the impact that this disease continues to have in the United States, where the southern states present the highest number of hospitalizations for rheumatic fever[4]. In developed countries, as a result

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of migratory movements, it is also possible to observe an increase in the prevalence of the disease[5,6]. De Maio et al. screened refugees living in Rome and reported a prevalence of 1.7%, which is similar to that of underdeveloped countries[6].

It is estimated that more than 319,000 deaths occurred in 2015 due to chronic rheumatic heart disease, primarily in underdeveloped or developing countries[7]. In Brazil, in 2017, rheumatic fever (RF) and its associated complications led to 6,648 hospitalizations and a cost of more than BRL73 million[8]. In view of this scenario, in 2018, the World Health Organization considered rheumatic fever and chronic rheumatic heart disease as being global health priorities[9]. Despite this context, there are very few studies, and little public and private investment, which thereby characterizes it as a neglected disease[10].

In patients with chronic rheumatic heart disease, active carditis is a frequently underdiagnosed condition, even in countries where the disease is endemic[11]. Acute rheumatic episodes tend to aggravate existing lesions, thereby leading to a deterioration of the patient's clinical condition. Therefore, reducing the morbidity and mortality of the disease depends, in part, on controlling relapses through secondary prophylaxis[12]. Underdiagnosis is due in part to the occurrence of subclinical acute episodes of rheumatic fever. On the other hand, non-specific clinical presentations, low sensitivity of Jones criteria, the absence of specific laboratory markers, and the low availability of Doppler echocardiography in underdeveloped countries, are just some of the factors that may contribute to explaining the difficulty encountered in diagnosing acute episodes of inflammatory activity[10].

In this study, we assessed the frequency of histopathological alterations compatible with inflammatory activity in a series of 30 patients with chronic rheumatic heart disease, undergoing cardiac surgery, with no clinical or laboratory evidence of rheumatic activity during the surgical period.

METHODS

This was a case series of 30 patients diagnosed with chronic rheumatic heart disease, who were monitored at an outpatient clinic at a university hospital in Northeastern Brazil. Data were obtained from notes in the medical records. Patients underwent cardiac surgery for valve replacement or repair. At the time of surgery, no patient presented signs of an acute rheumatic episode, neither in clinical nor laboratorial terms, and all patients were prescribed prophylaxis with benzathine penicillin.

All information relating to the electrocardiogram and chest X-ray performed before the surgical procedure and used in this study were noted in the medical records by the same observer.

During the surgical procedure, a fragment of the left atrium and/or right atrium and/or mitral valve and/or aortic valve was removed. This material was taken for histopathological analysis, and all biopsies were analyzed by the same pathologist.

An analysis of the fragments was performed using an optical microscope with hematoxylin-eosin and Masson's trichrome stained samples. From the results of these biopsies, data on the frequency of histopathological changes compatible with an acute episode of rheumatic fever were analyzed, using descriptive statistics tools.

RESULTS

The mean age in this study was 15.2±9.2 years (3 to 37 years), with 17 (56.7%) male patients. Most patients lived in economically and socially vulnerable conditions. Data were obtained regarding monthly family income per person of 18 patients, whose median income was 45.82 US dollars (5.63 to 348 US dollars), and 11 (61.1%) of this total earned a family income per person of less than 20 US dollars per month, classifying them in a situation of economic vulnerability. Data on the number of people living in the same household were available for 22 patients in our sample, of whom 40.9% lived in households with six or more people. All patients underwent irregular secondary prophylaxis with benzathinepenicillin.

Before surgery, all patients presented with normal laboratory evidence of inflammatory activity and none presented clinical manifestations of an acute episode of rheumatic fever according

to Jones criteria. Information on the electrocardiogram and chest X-ray are described in Table 1.

In the histopathological analysis, 24/30 (80%) patients presented alterations compatible with inflammatory activity. Of these, 21/24 (87.5%) presented lymphocytic infiltrate; and 6/24 (25%) Aschoff nodules. The most frequent histopathological findings of chronic disease were myocardial hypertrophy in 17/30 (56.7%) patients and fibrosis in 16/30 (53.3%). The detailed description of the histopathological exams are included in Table 1.

Table 1

Histopathological findings of chronic rheumatic heart disease patients undergoing cardiac surgery.

Age	Sex	Histological findings compatible with inflammatory activity	Histological findings compatible with chronic disease	Observations
8	F	Moderate lymphocytic infiltration in the mitral valve.	Chronic epicarditis, intense chronic valvulitis with fibrosis and capillary neoformation.	Cardiomegaly X-ray. ECG: LAO, LVO, prolonged QTc interval.
14	M	No findings of inflammatory activity.	Interstitial muscle fibrosis, myxomatous matrix degeneration, capillary neoformation, muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: LAO, LVO, prolonged QTc interval.
21	F	No findings of inflammatory activity.	Fibrohyaline sequelae of previous valvulitis and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: LAO, LVO.
11	M	Lymphocyte infiltration foci in the endocardium and epicardium.	Fibrosis, hyalinization, capillary neoformation and muscle fiber hypertrophy.	Normal X-ray CTI. ECG: RVO, LVO, biatrial overload.
23	M	Sparse foci of lymphocyte infiltration in the epicardium.	Fibroblastic proliferation area in hyaline matrix, myxomatous areas and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: LAO, LVO.
19	M	Epicarditis and myocarditis with multiple foci of lymphocyte infiltration.	Hypertrophy of muscle fibers.	Normal X-ray CTI. ECG: Sinus tachycardia, 1st degree AVB, LAO, LVO, prolonged QTc interval.
9	M	Minor foci of lymphocyte infiltration and Aschoff nodules.	Fibrosis, hyalinization, myxomatous degeneration, calcification, muscle fiber hypertrophy in the auricle, capillary neoformation and foci of chronic epicarditis.	Cardiomegaly X-ray. ECG: Junctional rhythm, LAO, LVO.
15	M	Focus of lymphocyte infiltration that penetrates the myocardium. Conclusive findings of rheumatic carditis.	Diffuse thickening of the endocardium.	Cardiomegaly X-ray. ECG: Sinus tachycardia with LAO, LVO, prolonged PR.
23	M	No findings of inflammatory activity.	Fibrosis, hyalianization with myxoid-like foci.	
19	F	Foci of lymphocyte infiltration.	Intense fibrous thickening, capillary neoformation and myxomatous degeneration.	ECG: AF, Ashman phenomenon, RVO and LVO.
9	F	Epicardium with foci of lymphocytic infiltration.	Muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: overload in the four chambers and prolonged QTc interval.
9	M	Endocarditis with multiple Aschoff nodules and epicarditis.	Muscle fiber hypertrophy..	Cardiomegaly X-ray. ECG: LAO, RVO, LAO.
3	M	Infiltration of lymphocytes in the endocardium, myocardium and some points in the epicardium.	Chronic inflammatory lesions in the endocardium, myocardium and epicardium with edema and subendocardial fibrosis.	Cardiomegaly X-ray. ECG. ECG: LAO, prolonged QTc interval.

(*Continua*)

Table 1

(Continuação)

Age	Sex	Histological findings compatible with inflammatory activity	Histological findings compatible with chronic disease	Observations
13	M	No findings of inflammatory activity.	Fibrosis and hyalinization.	Cardiomegaly X-ray. ECG: overload in the four chambers, prolonged QTc interval.
12	M	Foci of lymphocyte infiltration.	Fibrosis, capillary neoformation and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: LAO and LVO.
16	M	Lymphocyte, plasma cell and neutrophil infiltration. Interfascicular edema was also found.	Chronic epicarditis, fibrosis accompanied by myxomatous degeneration.	Cardiomegaly X-ray. ECG: overload in the four chambers, prolonged PR interval, Penaloza-Tranchesi signal.
12	M	Foci of lymphocyte infiltration.	Chronic epicarditis and muscle fiber hypertrophy.	Normal X-ray CTI. ECG: LAO, LVO, RVO.
37	F	Foci of lymphocyte infiltration.	Fibrosis, hyalinization and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: AF, LVO, RVO.
3	F	No findings of inflammatory activity.	Muscle fiber hypertrophy..	Cardiomegaly X-ray. ECG: LVO.
3	F	Foci of lymphocyte infiltration.	Chronic epicarditis and myocarditis.	Cardiomegaly X-ray. ECG: LAO, LVO.
20	F	Foci of scattered lymphocyte infiltration.	Fibrosis and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: AF, RVO, Ashman phenomenon.
24	F	Foci of lymphocyte infiltration.	Chronic epicarditis, fibrosis, endocardial hyalinization and capillary neoformation.	Cardiomegaly X-ray.
7	F	Foci of lymphocyte infiltration.	Chronic epicarditis.	Cardiomegaly X-ray. ECG: LAO, LVO.
10	F	Foci of lymphocyte infiltration.	Chronic pancarditis, with intense edema and capillary neoformation.	Cardiomegaly X-ray. ECG: LAO, LVO, signs suggestive of septal hypertrophy.
11	M	In the epicardium congestion with foci of lymphocytic infiltration; in the myocardium, edema and occasional lymphocytes in the interstitium; in the endocardium, edema, and very rare juxtamyocardial Aschoff nodules.	Mild thickening.	Cardiomegaly X-ray. ECG: overload in the four chambers.
10	M	No findings of inflammatory activity.	Muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: LAO, RAO, RVO, prolonged QTc interval.
35	F	Findings of important rheumatic activity with multiple Aschoff nodules.	No chronic disease findings.	Cardiomegaly X-ray. ECG: ventricular extrasystoles, prolonged PR interval, prolonged QTc interval.
15	M	Numerous Aschoff nodules.	Fibrosis, myxomatous degeneration, capillary neoformation and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: overload in the four chambers.
37	F	Foci of lymphocyte infiltration.	Fibrosis, muscle fiber hypertrophy.	ECG: LVO, LAO, prolonged QTc interval.
9	M	Foci of lymphocyte infiltration in the epicardium and endocardium; 3 Aschoff nodules were found.	Fibrosis, hyalinization, calcification and muscle fiber hypertrophy.	Cardiomegaly X-ray. ECG: LVO, T waves with increased amplitude, asymmetric in V5 and V6.

RAO: right atrial overload; LAO: left atrial overload; RVO: right ventricular overload; LVO: left ventricular overload; AF: atrial fibrillation; CTI: cardio-thoracic index; AVB: atrioventricular block; ECG: electrocardiogram.

DISCUSSION

In our study, 80% of patients presented inflammatory activity in some of the layers of the heart, and of these, 25% presented Aschoff nodules, histological findings compatible with acute rheumatic fever. Since, at the time of surgery, we were aware that no patients presented any clinical or laboratory alterations compatible with acute rheumatic fever, this indicated a high percentage of subclinical rheumatic activity.

In a histopathological analysis of valves and auricles of 133 patients with chronic rheumatic heart disease, undergoing valve replacement and with no clinical manifestations of acute rheumatic fever, Arenales et al.[13] reported the presence of Aschoff nodules in 18%, thus demonstrating that the patients were presenting subclinical rheumatic activity. Chopra et al.[14] analyzed biopsies from 100 patients with chronic rheumatic heart disease undergoing mitral valve replacement and observed a higher percentage (35%) of Aschoff nodules compared to our study and to that of Arenales et al.[13].

Thomas et al. compared a group of 40 patients presenting no evidence of active rheumatic fever, and who had undergone biopsies of the left atrium during mitral commissurotomy, with 40 individuals who had died as a result of fulminant cases of rheumatic fever[15]. In the latter group, Aschoff nodules were observed in 72% of the cases in the endocardium and 5% in the myocardium of the patients' atria, while, in the group that underwent the surgical procedure, 55% had Aschoff nodules in the endocardium and 5% in the myocardium, thus demonstrating that more than half of the operated patients presented with subclinical active rheumatic fever[15]. Analyzing the clinical history of 45 patients whose cardiac biopsies demonstrated Aschoff nodules, Virmani et al. reported that only one presented clinical or laboratory alterations compatible with active rheumatic fever[16].

More recent histopathological studies have continued to report a high percentage of Aschoff nodules in patients undergoing surgery with no clinical signs of acute rheumatic fever. Bladenier et al. analyzed 20 biopsies of patients aged 20 years or under who had undergone mitral and/or aortic valve replacement surgery and reported a percentage of 35% of Aschoff nodules[17]. A study conducted by Nader et al. investigated the frequency of Aschoff nodules in 72 patients with chronic rheumatic heart disease undergoing surgery, and reported a percentage of 10%, lower than the previously mentioned studies[18]. This study also reported that Aschoff nodules were observed more frequently in younger individuals, with no difference between gender and location in the layers of the heart[18]. In an analysis of 40 biopsies of patients with chronic rheumatic heart disease, whose mean age was 53±13 years, reported by Gomes et al., no Aschoff nodules were observed in the analyzed samples. However, histopathological findings compatible with an active inflammatory process in the heart valves was detected, even in delayed disease[19].

A study with biopsies of the left atrium performed by Bernal et al. reported findings compatible with active rheumatic fever in 31 patients, although only eight presented clinical and/or laboratory manifestations of an acute episode of rheumatic fever, based on the Jones criteria, thus demonstrating the low correlation of these criteria with the histopathological findings[20]. It has been reported that 95% of patients with rheumatic sequelae do not present classic acute episodes[21], thus corroborating the low sensitivity of the Jones criteria and the constant need to consider the diagnosis of active carditis in clinical practice. Most patients with severe rheumatic sequelae are only diagnosed when the disease has advanced, when seeking care for symptoms of heart failure resulting from chronic valvulopathy[21,22].

Similar to the present study, these studies have reinforced that there is a high prevalence of subclinical rheumatic activity, which is difficult to identify in medical practice. This phase of the disease is characterized by the absence of detectable inflammatory activity and no clinical manifestation compatible with an active myocardial inflammatory process, with a retrospective diagnosis[21,22]. At this stage, low-grade inflammation occurs, with a reduced number of auto-reactive T-lymphocyte clones in the myocardium, promoting mild, persistent inflammation and, thus, slow, insidious valve damage[22]. Many of these individuals do not adhere to secondary prophylaxis and have

continued exposure to streptococcal antigens, with a chronification of the autoimmune process with sustained, low-grade inflammation[22]. At least two cases in this series revealed different histopathological findings to those described above. The eighth patient in Table 1 presented intense inflammatory findings, which led the pathologist to conclude that it was active carditis, although Aschoff nodules were not observed. On the other hand, in the histopathological examination of the antepenultimate case in the same table, numerous Aschoff nodules were observed. In both cases, no symptomatic or laboratory manifestations compatible with an acute episode were reported.

Our attention was also drawn to the similar clinical, radiological and electrocardiographic findings of two children of the same age, identified in the Table as cases 19 and 20, whose histopathological findings differ significantly. In one, no signs of inflammation were observed, while in the other, these signs were present. It should be noted that the latter abandoned outpatient follow-up two years after surgery, which highlights the importance of adequate adherence to secondary prophylaxis, which did not occur, to a greater or lesser degree, with any of the patients in our series.

When present, some signs of acute myocarditis may be confused with decompensation of heart failure resulting from chronic valvular lesions[22,23]. Thus, complementary exams that are more accurate, accessible and less invasive than a biopsy could help to identify an acute episode of rheumatic fever[11]. Hence, in recent years, there have been studies indicating the benefit of other methods, such as scintigraphy and magnetic resonance in order to facilitate the diagnosis of carditis[11,24,25]. It has been demonstrated that scintigraphy has a high sensitivity for diagnosing carditis[25], but it is costly and not always available. Xavier et al. have also reported the benefits of using magnetic resonance imaging associated with scintigraphy for diagnosing acute rheumatic fever[11].

The unfavorable socioeconomic context of these patients reinforces how the disease is underdiagnosed and aggravated, as well as the low adherence to secondary prophylaxis. Studies on the epidemiology of the disease have indicated that most patients monitored for chronic rheumatic heart disease have low socioeconomic and educational levels[26-28]. In our study, it was found that the mean monthly family income per person was below 20 US dollars for more than 60% of the patients, demonstrating that most of them live in a condition of socioeconomic vulnerability. This vulnerability may hinder the understanding of the patient, as well as that of family members, regarding the importance of adhering to outpatient monitoring and secondary prophylaxis[26], which enables us to hypothesize that subclinical episodes would be more frequent in economically disadvantaged populations, contributing perhaps for patients to deteriorate faster.

On the other hand, it has been hypothesized that therapies targeting specific points of the immune system may be more effective in preventing the progression of valve damage than current secondary prophylaxis[29]. Recent data have traced several possible pathways associated with the development of valve damage[29,30], such as the signaling pathways activin/Smad 2 and 3[30]. It is possible that, in the future, with a better understanding of the immune mechanisms involved in chronic rheumatic heart disease, it will be possible to obtain new therapies to prevent the clinical progression of the disease, and thus improve the survival and quality of life of patients.

In recent decades, there have been no significant scientific and/or technological advances applied to chronic rheumatic disease, with regard to diagnosis and treatment, which partially explains the persistence of high rates of subclinical rheumatic activity found in our study. Thus, similarly to what took place in developed countries, which experienced a significant reduction in the incidence and prevalence of chronic rheumatic disease over recent decades[31], public policies are essential for promoting significant changes in the morbidity and mortality profile due to chronic rheumatic disease in Brazil.

CONCLUSION

Our study has demonstrated a high frequency of histopathological alterations compatible with rheumatic activity in patients with no clinical or laboratory manifestations of acute rheumatic fever.

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