

## Letter to the Editor



# Systemic Inflammation in the Setting of Cardiac Myxomas: an Overview of Clinical and Practical Considerations

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## OPEN ACCESS

**Received:** Jun 21, 2021

**Accepted:** Jul 14, 2021

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### Funding

The authors received no financial support for  
the research, authorship, and/or publication  
of this article.

### Conflict of Interest

The authors have no financial conflicts of  
interest.

► See the article “Unusually Early Recurrence of Mitral Valve Myxoma in a Child” in volume 51 on page 554.

In clinical practice, cardiac myxomas have been the most common type of benign cardiac neoplasms generally presenting with a variety of obstructive, embolic and constitutional symptoms.<sup>1-3</sup> Typically, these tumors involve the left atrium, and are mostly encountered in middle-aged females.<sup>2,3</sup> In their recently published interesting article by Eun et al.<sup>1</sup> have reported an unusual case of mitral valve myxoma involving the left ventricular outflow tract in an adolescent male. We hold the opinion that substantial systemic inflammation and potential genetic basis might have a pivotal role in the unusually early recurrence of cardiac myxoma in this case. Accordingly, we would like to comment on this interesting case along with a particular emphasis on general implications of systemic inflammation in the setting of cardiac myxomas:

First, the case seems to have a substantial inflammatory reaction as might be evidenced by a variety of unusual constitutional findings including Janeway lesions and Osler's nodes that typically arise in response to severe and relatively long-term inflammatory conditions with a high antigenic burden including infective endocarditis. Cardiac myxomas are well known to be infected by a variety of microorganisms particularly with risk factors including immunocompromised status and history of invasive procedures.<sup>4</sup> In this context, we are wondering whether these risk factors were present in the patient.

However, histopathological findings of the excised material and absence of positive blood cultures (even in the presence of fever) suggest that substantial inflammatory reaction in the patient might be regarded as an inherent feature of his cardiac myxoma. Importantly, severe systemic inflammation associated with cardiac myxomas might potentially facilitate systemic embolism as a consequence of enhanced tumoral fragility<sup>4</sup> (as evidenced by the multisystemic embolism in the patient),<sup>1</sup> and hence; mandates urgent excision. More interestingly, interleukin-6 (IL-6) has been suggested as a myxoma-related cytokine, and might play a pivotal role in myxoma recurrences.<sup>5</sup> Therefore, persistent systemic inflammation might have triggered local recurrence of cardiac myxoma in the patient. On the other hand, the issue of whether persistent systemic inflammation following myxoma resection appears to arise just as a consequence of residual tumoral burden and local aggressiveness (accounting for future recurrences after resection) or potentially exerts a direct impact on myxoma recurrences still remains to be established.<sup>5</sup> In this

**Data Sharing Statement**

The data generated in this study is available from the corresponding authors upon reasonable request.

**Author Contributions**

Conceptualization: Yalta k, Ozturk C, Yalta T, Yetkin E; Data curation: Yalta k, Yalta T; Formal analysis: Yalta k, Ozturk C, Yalta T, Yetkin E; Investigation: Yalta k, Ozturk C, Yalta T, Yetkin E; Methodology: Yalta k, Ozturk C, Yalta T, Yetkin E; Resources: Yalta k, Yetkin E; Software: Yalta k, Ozturk C, Yalta T, Yetkin E; Supervision: Yalta k, Ozturk C, Yalta T, Yetkin E; Validation: Yalta k, Ozturk C, Yalta T, Yetkin E; Visualization: Yalta k, Ozturk C, Yalta T, Yetkin E; Writing - original draft: Yalta k, Ozturk C, Yalta T, Yetkin E; Writing - review & editing: Yalta k, Ozturk C, Yalta T, Yetkin E.

context, substantial impact of systemic inflammation on stimulation of certain growth factors is a well known phenomenon.<sup>6)</sup> In particular, certain cytokines including IL-6 might be harnessed as a predictor of myxoma recurrences.<sup>5)</sup> Moreover, persistent systemic inflammation after myxoma resection might also be due to a variety of chronic inflammatory conditions (rheumatological diseases, etc.) that need to be identified and treated specifically. Accordingly, we wonder about the levels of inflammation markers after the first and second surgeries in the patient. Did these markers drop significantly or remain persistently high following the tumor resections? Did the patient also suffer a chronic inflammatory disease?

Second, systemic inflammation was previously suggested to be associated with the evolution of more insidious manifestations including 'distant tumoral seeding' in the setting of cardiac myxomas.<sup>7)8)</sup> In this context, 'distant tumoral seeding' is mostly characterized by the involvement of central nervous system (CNS), and presents with cranial aneurysm formation and solid parenchymal lesions in association with variable degrees of hemorrhagic parenchymal lesions.<sup>8)9)</sup> Mechanistically, these distant myxomatous lesions have been attributed to the transmigration of myxoma cells through the cerebrovascular endothelial cells with the particular actions of certain proinflammatory mediators including IL-6 and consequent expression of intercellular adhesion molecule-1.<sup>7-9)</sup> Of note, these distant CNS lesions might potentially arise any time in patients with cardiac myxoma (even after several years following resection [namely systemic recurrence]).<sup>8)9)</sup> In general, surgery, chemotherapy and radiotherapy constitute the fundamental management strategies for the established CNS lesions.<sup>9)</sup> Moreover, certain cytokine blockers might have a speculative role in the prevention of local and systemic myxoma recurrences particularly in those with idiopathic and persistent systemic inflammation. Accordingly, we wonder whether the patient, besides embolic findings, had signs of distant tumoral seeding on imaging. We also wonder about the authors' follow-up strategy for further local and systemic recurrences. In this context, patients with persistent systemic inflammation might need more frequent clinical and radiological follow-up for the timely diagnosis of recurrences.

Finally, a familial background also might be related in the case.<sup>1)</sup> In this context, familial cardiac myxomas might be encountered as part of certain syndromes including Carney's complex (characterized by a variety of endocrinological abnormalities and cutaneous tumors) or in a non-syndromic manner.<sup>10)</sup> Importantly, familial cardiac myxomas generally arise in atypical locations, and usually present at relatively young ages along with a higher risk of recurrence.<sup>10)</sup> Of note, these features are consistent with the characteristics of the present case. Accordingly, we wonder about family history of cardiac myxoma along with subtle extracardiac findings in the patient. Did the authors perform (or plan) a genetic analysis in the patient? Of note, familial cardiac myxomas also tend to occur at multiple locations<sup>10)</sup> potentially leading to high tumoral burden and pronounced systemic inflammation. Therefore, pathogenetic, prognostic and therapeutic implications of systemic inflammation might be even stronger in the setting of familial cardiac myxomas as compared with sporadic ones.

In conclusion, systemic inflammation most likely arises as an inherent feature of cardiac myxomas usually in correlation with constitutional and embolic findings. Importantly, persistent sytemic inflammation after myxoma resection might have a central role in local and systemic myxoma recurrences, and hence; might have prognostic and therapeutic implications in this context. Therefore, proper evaluation of systemic inflammation (as best quantified with levels of inflammation markers) might help risk stratification, and guide the

subsequent management strategies in patients with cardiac myxoma particularly following the resection of primary cardiac tumor.

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