

# Cardiac myxoma as cytokine producing tumour: A review

## Abstract

Cardiac myxoma is the most common primary cardiac tumour. Many cytokines participate in the pathophysiology and growth of cardiac myxoma. Inflammatory cytokines, including interleukin-1, interleukin-4, interleukin-6, interleukin-8, interleukin-12, tissue necrosing factor- $\alpha$ , and interferon- $\gamma$ , contribute to the development of inflammation and inflammation-related symptoms and further affect tumour growth. Growth factors, including vascular endothelial growth factor, basic fibroblast growth factor, insulin-like growth factor 1, and epidermal growth factor, contribute to angiogenesis and tumour growth and interfere with the inflammatory response. Recently, we reported a cardiac myxoma whose cells were positive for interleukin-1 $\beta$  and hemopoietic factor granulocyte colony-stimulating factor in addition to interleukin-6. This review summarises the current knowledge of cardiac myxomas as cytokine-producing tumours.

**Keywords:** Cardiac myxoma • Carney complex • Cytokine

## Introduction

Cardiac myxoma is the most common primary cardiac tumour. This tumour possess a wide range of clinical presentations that may mimic a variety of neoplastic and non-neoplastic conditions [1]. The most common symptoms are systemic embolism, congestive heart failure, and nonspecific constitutional symptoms, including myalgia, muscle weakness, arthralgia, fever, weight loss, fatigue, and some skin manifestations [1,2]. Many cytokines are reported to be related to the symptoms and growth of cardiac myxoma [1,3]. Recently, we reported a cardiac myoma accompanying afebrile neutrophilic dermatosis with Granulocyte Colony Stimulating Factor (G-CSF), interleukin-1 $\beta$  (IL-1 $\beta$ ), and IL-6 positive myxoma cells [4]. This review summarises the recent knowledge regarding cytokines related to cardiac myxoma (Table 1).

## Cytokines of Myxoma

### Interleukins and myxoma

Interleukins (ILs) are a group of cytokines first to be expressed by leukocytes and were later found to be synthesised by many other cells, including monocytes, macrophages, endothelial cells, and helper CD4 T lymphocytes. ILs have paracrine and autocrine functions and exhibit multiple biological activities [5].

IL-6, the most commonly reported cytokine in cardiac myxoma [1,3,6-9], is recognised as one of the most prominent pro-inflammatory cytokines [10]. IL-6 also exerts multiple biological activities, such as regulation of immunological responses and hematopoiesis, and stimulation of some malignant and non-malignant cell growth [10-12]. Moreover, IL-6 has paracrine, endocrine, and autocrine growth functions [10,12]. IL-6 exerts its

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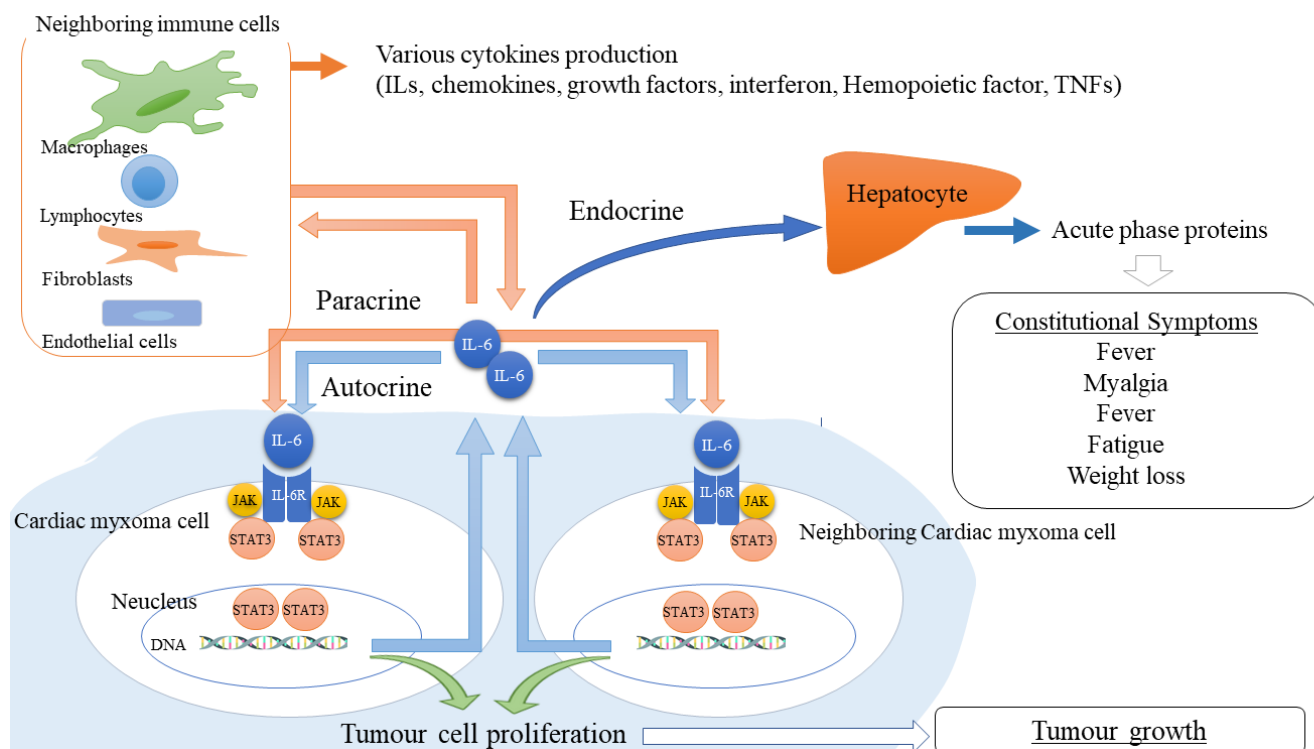
effects through (1) the IL-6 receptor (IL-6R), (2) IL-6 and IL-6R complex associates with a second receptor protein, glycoprotein 130 kDa (gp130), and (3) gp130 dimerises and initiates multiple intracellular signalling pathways, such as the Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway, rat sarcoma proto oncogene (ras)/Mitogen-Activated Protein Kinase (MAPK) pathway, and phosphatidylinositol-3 kinase (PI3K)/Akt pathway [10] (Figure 1).

**Table 1: Literature regarding cytokines in cardiac myxoma.**

Reference	Study type	Cytokines
Ajiro Y 2020 [4]	Case report (sporadic)	IL-6, IL-1 $\beta$ , G-CSF
Parissis JT 1996 [7]	Clinical study	IL-6
Lin JN 2011 [8]	Case report (sporadic)	IL-6, TNF $\alpha$ , IL-4, IL-12 interferon- $\gamma$ ,
Mendoza CE 2001 [9]	Clinical study	IL-6
Jourdan M 1990 [11]	Clinical stud	IL-6
Endo A 2002 [13]	Clinical study	IL-6
Visoiu IS 2018 [14]	Case report (Carney)	IL-6 (comments in Discussion)
Nishio Y 2005 [15]	Case report (sporadic)	IL-6
Bushnell JR 2011 [16]	Case report (sporadic)	IL-6

Salobir B 2001 [17]	Case report (sporadic)	IL-6 (comments in Discussion)
Sumino H 1997 [18]	Case report (sporadic)	IL-6
Soeparwata R [19]	Clinical study	IL-6, TNF $\alpha$ , IL-1 $\beta$ , GM-CSF
Aguilar C 2021 [20]	Case report (sporadic)	IL-6
Ezerioha N 2015 [21]	Case report (sporadic)	IL-6
Zhang T 2003 [22]	Clinical study	MCP1(CCL2)
Shi P 2015 [23]	Basic research	CCL3
Sakamoto H 2004 [24]	Basic research	IL-8(CXCL8), CXCL1, VEGF growth-related oncogene- $\alpha$
Burns ER 1982 [25]	Case report (sporadic)	erythropoietin
Liu CC 2010 [28]	Basic research	TNF $\alpha$
Kono T 2000 [29]	Clinical study	VEGF
Fujisawa H 2002 [30]	Clinical study	bFGF
Wu XL 2013 [31]	Basic research	IGF1
Huo Y 2016 [32]	Basic research	IGF1

**Abbreviations:** IL: Interleukin; G-CSG: Granulocyte Colony Stimulating Factor; TNF: Tumour Necrosis Factor; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; MCP-1: Monocyte Chemoattractant Protein-1; CCL: C-C motif chemokine; CXCL: C-X-C motif chemokine; VEGF: Vascular Endothelial Growth Factor; bFGF: basic Fibroblast Growth Factor; IGF-1: Insulin-like Growth Factor.



**Figure 1:** Schema of representative interleukin-6 pathophysiology of cardiac myxoma. Abbreviations: IL: interleukin; IL-6R: Interleukin-6 receptor; TNF: Tumour Necrosis Factor.

Cardiac myxoma produces IL-6, and IL-6 is expressed in neoplasms [1,3,7]. IL-6 production and many definitive and possible pathophysiology in cardiac myxoma has been reported: constitutional symptoms and elevated C-reactive protein [8,9,13,14], autoimmune diseases [11,15-17], lymphadenopathy [6], hypothyroidism [18], hypertrophy [6], endothelial dysfunction and atherosclerosis with intercellular adhesion molecule 1 expression [14], tumour growth [6,9,19], recurrence [9], remote metastasis [6], embolization [6,20], cerebral embolization relevant to IL-6 and matrix metalloproteinase-2 (MMP-2) [20], and cerebral aneurysmal [21].

Other inflammatory cytokines, such as tissue necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1, IL-8, IL-12, and interferon- $\gamma$ , have also been reported with regard to cardiac myxoma. Lin et al. reported elevated levels of both serum inflammatory and anti-inflammatory cytokines in a large cardiac myxoma with leucocytosis [8]. Soeparwata et al. reported elevated TNF- $\alpha$  and/or IL-1 $\beta$  levels in addition to IL-6 in a large myxoma [19]. Serologically elevated serum IL-1 $\beta$  levels and histologically IL-1 $\beta$ -positive cardiac myxoma cells have been reported [4,19].

### **Chemokines and cardiac myxoma**

Chemokines are a family of small cytokines that have chemotaxis and play various roles, including inflammation, tumour growth, and regulation of basal leukocyte migration. In cardiac myxoma, the monocyte chemoattractant protein-1 (MCP-1), also known as CC chemokine ligand 2 (CCL2) by structural chemokine nomenclature, was reported to be involved in tumour growth and angiogenesis [3]. Zhang et al. reported that MCP-1 is expressed together with thymidine phosphorylase in cardiac myxoma cells. MCP-1 is known to contribute to angiogenesis in many tumour types. Their study demonstrated a similar function of MCP-1 in cardiac myxoma, as understood from the correlation between high microvessel and macrophage counts, with high MCP-1 and thymidine phosphorylase expression [22]. Shi et al. reported that CC Chemokine Receptor 5 (CCR5) and Astrocyte Elevated Gene-1 (AEG-1) proteins were highly expressed in cardiac myxoma tissue and closely correlated with tumour size, which would be mediated through CCL3/CCR5-induced epithelial-to-mesenchymal transition [23]. Production of IL-8, CXC chemokine ligand 8 (CXCL8), and growth-related oncogene- $\alpha$ , and CXCL1, in cultured myxoma cells has been reported [24].

### **Interleukins and myxoma**

Interferons were initially identified as factors that suppress viral infections. It has been shown to exhibit growth inhibitory, immunomodulatory, and many other activities, in addition

to antiviral properties. Lin et al. demonstrated elevated serum interferon- $\gamma$  in a large cardiac myxoma patient with leucocytosis [8].

### **Hemopoietic factor and cardiac myxoma**

Hemopoietic factors are cytokines that promote blood cell differentiation and proliferation. Regarding cardiac myxoma, Burns et al. showed elevated serum erythropoietin levels in a cardiac myxoma with erythrocytosis [25]. Moreover, Soeparwata et al. reported an elevated serum granulocyte macrophage colony stimulating factor (GM-CSF) in a large cardiac myxoma [19]. We demonstrated G-CSF-positive myxoma cells in a cardiac myxoma with leucocytosis and afebrile neutrophilic dermatosis [4]. The elevated IL-4, Th2 cytokine, is also reported in cardiac myxoma [8]. Although there is no direct description of hemopoietic cytokines, thrombocytosis and leucocytosis in an atrial myxoma with a PRKAR1A gene mutation and hypereosinophilia in an atrial myxoma have been reported [26,27], suggesting the involvement of GM-CSF, IL-3, IL-5, IL-11, or thrombopoietin.

### **TNF Family**

The TNF family is known to be a cytotoxic or lymphotoxin factor that induces apoptosis in cells. Elevated serum TNF- $\alpha$ , which is also known as an inflammatory cytokine, has been reported in large cardiac myxoma with leukocytosis [8,19]. Liu et al. also reported Fas-mediated apoptosis in connection with TNF- $\alpha$  in cardiac myxoma [28].

### **Growth Factor**

Growth factor is a general term for endogenous proteins to promote the proliferation and differentiation of specific cells. Among various growth factors, Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), Insulin-like Growth Factor 1 (IGF-1), and Epidermal Growth Factor (EGF) have been reported to be involved in angiogenesis and tumour growth in cardiac myxoma [3]. Kono et al. showed the expression of VEGF and VEGF messenger RNA in cardiac myxoma tissue and showed a correlation with tumour size and microvessel density, suggesting the induction of angiogenesis for tumour growth [3,29]. Sakamoto et al. demonstrated the presence of VEGF and its receptors, VEGF receptor-1 and -2, in the cytoplasm of myxoma cells, and that myxoma cells secrete large amounts of VEGF. They also demonstrated that myxoma cell proliferation was enhanced by VEGF in a dose-dependent manner, and cell proliferation was inhibited in a dose-dependent manner by a neutralising VEGF antibody. They concluded that cardiac myxoma cells possess a VEGF-autocrine system that could contribute to the malignant potential of myxomas through direct stimulation of tumour cell growth as well as through induction of

angiogenesis [24]. Fujisawa et al. revealed bFGF and its receptor expression, particularly around microvessels, appearing as a ring structure of cardiac myxoma, suggesting a possible role for tumour angiogenesis and proliferative activity [3,30]. Wu et al. demonstrated the proliferative effect of IGF-1 on cardiac myxoma cells by negatively regulating the protein/lipid phosphatase and tensin homolog deleted on chromosome ten (PTEN)/pleckstrin homology domain leucine-rich repeat phosphatase 2 (PHLPP2) signalling pathway [31]. In addition, Huo et al. also demonstrated the proliferative effect of IGF-1 on cardiac myxoma cells and further enhanced the expression of EGF receptor and MMP-9 by regulating Myocyte Enhancer Factor 2D (MEF2D) [32].

### **Cytokine-Relevant Clinical Manifestations of Cardiac Myoma**

The pathophysiology of clinical manifestations in cardiac myxoma is explained, at least in part, by the cytokines by cardiac myxoma. Symptoms of cardiac myxoma, such as fever, weight loss, arthralgia, myalgia, muscle weakness, fatigue, and some skin manifestations, may be induced by many cytokines [1,2,4,8-10,13,33-36]. Moreover, cytokine storms elicited by viral infections, such as COVID-19, resemble symptoms such as fever, myalgia, and arthralgia [35,37,38]. In tumour growth, including the recurrence and metastasis, hematopoietic and growth factors and inflammatory cytokines are reported to be involved [1,3,6,9,19, 22,23,29].

It is important to note the polyfunctional and multiplicity characteristics of cytokines, including its action in an autocrine, paracrine, and endocrine manner. When our myxoma case was considered, nuclear factors for the IL-6 gene function as promoters of G-CSF for IL-1 $\beta$  response [39]; IL-1 $\beta$  promotes IL-6 production and neutrophil activation via macrophage stimulation [40,41]; stimulated macrophages further produce cytokines including IL-1 $\beta$  [22,40,41]; the resultant activated cytokines would cause neutrophilic dermatosis in remote areas of the heart [4]. In addition, once neoplasms, including cardiac myxoma, produce cytokines, their effects will be enhanced and spread to the whole body owing to the cytokine characteristics of self-enhancement and a lack of inhibitory feedback due to neoplasm. The pathogenesis of cardiac myxoma has not been fully elucidated due to its complexity. Understanding the pathophysiology of cardiac myxoma will further elucidate the therapeutic target for inhibiting cardiac myxoma growth and controlling cytokine-related clinical manifestations.

### **Genetic and Tumorigenesis Consideration**

The protein kinase cAMP-dependent type 1 regulatory subunit

$\alpha$  (PRKAR1A) gene mutations are found in familial cardiac myxoma associated with Carney complex [42], whereas most non-familial cardiac myxoma do not show mutations [43]. PRKAR1A gene, acting as a tumour suppressor gene, encodes the regulatory subunit of cAMP-dependent protein kinase A. The mutations of PRKAR1A gene cause PRKAR1 $\alpha$  haplo insufficiency and reduction of protein with predisposition to tumorigenesis [1,3]. The relevancy between PRKAR1A gene disorder and cytokines has not been investigated profoundly. Barely, elevated serum IL-6 level and IGF-1 protein and mRNA in cardiac myxoma associated with Carney complex are reported [44,45]. Considering the fact that the cytokine relevancies are shown regardless of familial or sporadic cardiac myxoma, the cytokine network activation is considered to be common pathophysiology not related to genetic disposition in cardiac myxoma.

For tumorigenesis, environmental mutagens, genetic predisposition, and acquired susceptibility from life style factors should be considered [46]. As life style factors, infection may play a role in tumorigenesis [46], and nutrition has an important influence on the risk of developing cancer [47]. The inflammation due to infection increases proliferating cells which are more sensitive to the induction of DNA damage and thereby are more likely to propagate the mutagenic events into daughter cells than dormant cells [48,49]. Nutrition can also exert tumorigenesis through providing mutagens and, at least in part, through stimulating inflammation [47,50]. From this perspective, cytokines would function not only growth promoter but also tumorigenesis as acquired susceptibility factor in cardiac myxoma.

Interestingly, Puntila et al. reported a 4-year-old-boy with cardiac myxoma which was found out by close continuous observation from infancy of Carney complex family member with PRKAR1A gene mutation [51]. This report implies that the acquired factor other than ageing will contribute, at least in part, to tumorigenesis of cardiac myxoma. In addition, this report also gives an idea that the well-designed prospective observation of cytokine measurements on Carney family members would illuminate role of cytokines not only on tumour growth but also tumorigenesis of cardiac myxoma. Progress in understanding the complex pathophysiology of cardiac myxoma will serve to explore novel therapeutic approaches.

### **Conclusion**

Various cytokines, including interleukins, chemokines, interferon- $\gamma$ , TNF- $\alpha$ , growth factors, and hematopoietic factors, play an important role in the pathogenesis of cardiac myxoma. Progress in understanding the complex pathophysiology of cardiac myxoma will serve to explore novel therapeutic approaches.

### Conflict of Interest

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