Why our heart is not prone to cancer?

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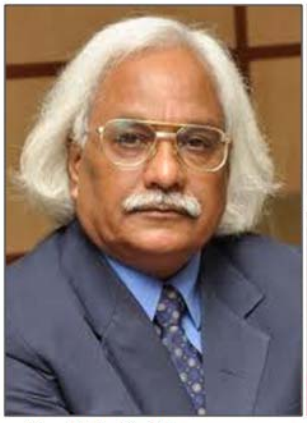

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Abstract

A rare possibility of occurring tumors in the heart is classified under two headings: primary cardiac tumors (that is originated in the heart tissues) and secondary cardiac tumors (which is metastasized to the heart). These tumors are mainly angiomas, sarcomas, myxomas, fibromas, lipomas and rhabdomyomas. Cardiac tumors are very rare with the incidence of about 0.0017 to 0.28%[1,2]. The main reason that can be attributed to such less susceptibility of heart for cancer is the less dividing nature of the cardiac myocytes. Any cell that is actively dividing is more likely to develop cancer which can be seen from the organs that are more prone to cancer for instance, skin, gastrointestinal tract, breast, cervices and many more.
Cancer occurs when the cells start to disobey the laws of cell cycle progression. Thus, the cells divide rapidly surpassing the checkpoints which results in DNA damage or deleterious mutation. The more the cells divide, the higher the chances of mutation. Further, mutations occur more if the cells are dividing and replicating their DNAs abruptly. These mutations then pass on to the daughter cells and hence cause the cancer.
In case of heart, the myocytes do not undergo cell division unless there is an injury and therefore very less cell division, the chances of mutation and cancer are less frequent. Moreover, our heart is also not directly exposed to carcinogens except for those in the circulating blood. This also leads to the decreased risk of mutations in the cardiac cells. Thus, owing to less cell division of cardiac cells, heart is at a less risk of developing cancer. In current review, we focused on different types of tumors in the heart and the cause of their rarity. Although less common, cardiac tumors affect a vital organ and hence the therapeutic perspectives should also be discussed.

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Introduction to cardiac tumors

Cardiac tumors are occurred in the inner lining of heart, muscle layer and in the pericardium. There is not a clear classification of cardiac tumors but like any other organ or tissue, cardiac tumors can be divided as primary and secondary tumors. In case of children, 90% of the primary cardiac neoplasms are benign whereas the remaining is malignant. In adults, the frequency is different with 75% being benign and 25% are malignant. Secondary or malignant tumors are 20-30 times more prominent than the primary tumors. Rhabdomyoma is the most common benign tumor in children[2] while myxoma is most common in adults[3]. Sarcoma is the most common primary malignant tumor[1,4,5]. Among the secondary tumors, melanoma is the most common.

Benign primary cardiac tumors

The occurrence of the primary cardiac tumors in children and adults is depicted in the **Table 1**[1,6,7]**.**

Table 1. Distribution of cardiac tumor in human

Type of tumor	Incidence (%)	
	In children	In adults
Rhabdomyoma	45-60	1-2
Fibroma	12-16	3
Angioma	5	10-12
Lipoma	-	20
Myxoma	5-7	45-50
Papillary fibroelastoma	-	12-15
Teratoma	14-18	<1

Myxoma

Myxomas are the most common primary tumors in adults that occur in the left atrium (about 80%) in the *fossa ovalis* region[3]. Right atrial myxomas comprise about 15-20% and ventricular occur in 3-4% of the cases. 90% of the myxomas are solitary and have property to grow very rapidly[8]. The myxomas are originated from sub-endocardial primitive mesenchymal cells that persist as embryonic residues during the septation of the heart. These are usually diagnosed at the age of 50 years but sometimes familial myxomas can be seen at younger age[9]. Facial freckling and endocrine neoplasams are common in patients with atrial myxomas where endocrine syndromes include LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, and blue naevi) and NAME (naevi, atrial myxomas, myxoid neurofibromata, and ephelides)[7]. The "*Carney complex*" is a common term used for these syndromes and studies show that gene deletion at chromosome 17q2 locus is responsible for this. Macroscopically, they appear irregular, shiny and multicoloured and are pedunculated and attached to the atrial wall[5,7,10-13].

Rhabdomyoma

Another common form of primary cardiac neoplasm that occur in infants and children. They are mainly present in the ventricular myocardium and therefore, it affects the ventricular inflow and outflow. Children with this tumor also have associated tuberous sclerosis in about one third of the cases. Macroscopically, rhabdomyomas appear round, solid, uniform and are brighter than the neighboring healthy myocardium. They also show spontaneous tumor regression[1,11,12,14].

Angioma

Hemangiomas are highly vascular tumors that occur in the interventricular septum. Macroscopically, they are identified as sub-endocardial nodules measuring 2-4 cm in diameter. Coronary angiography yields a characteristic '*tumor blush*' and undergoes spontaneous regression[7,10,15].

Fibroma

Fibromas are solitary, low grade tumors occurring in the ventricular wall and mostly seen in childhood with the median age at 13 years. They arise from connective tissue fibroblasts. Macroscopically, they are firm, grey white masses ranging from 1 to 10 cm in diameter. Calcification occurs in the central portion of the tumor and usually dormant in nature and hence, spontaneous regression rarely occurs[1,6,7,14,16].

Lipoma

Lipomas are comparatively smaller and occur mainly in the adults. They are subepicardial encapsulated tumors and comprise a benign accumulation of adipocytes. Occasionally they become large and extend into the left atrial cavity and are commonly asymptomatic[1,10-12].

Papillary fibroelastoma

Papillary fibroelastomas are small and most common tumors of the cardiac valves[11,14,17]. They are pedunculated which gives them the 'sea anemone' like appearance. Recent studies show that these have high degree of embolisation to the cerebral and coronary arteries[10].

Teratoma

Cardiac teratomas are the second most common tumor in the infants. They are most commonly found in pericardial cavity and in the heart. Intracardiac tumors arise from atrial or ventricular walls as nodular masses and extend into cardiac chamber. Macroscopically, they have typical cystic and multilobulated appearance and range from 2-9 cm in heart and upto 15 cm in pericardium[1].

Malignant primary cardiac tumors

These are more prominent in the adults than the children. The majority of primary malignancies are sarcomas (95%) and lymphoma (5%). Sarcomas are malignant mesenchymal neoplasms confined to heart or pericardium[18]. The occurrence of major sarcomas is shown in the **Table 2**[6,18-20].

Table 2. Occurrence of major sarcomas in human

Type of sarcoma	Incidence (%)
Angiosarcoma	33-37
Rhabdomyosarcoma	9-11
Fibrosarcoma	5-7
Liposarcoma	3
Osteosarcoma	5-9
Leiomyosarcoma	9-13

Angiosarcoma

Angiosarcomas are the most common primary malignancy that occurs predominantly in male. They arise from the endothelial cells and mostly originated from the right atrium. It shows epicardial, endocardial, intracavitary extension and local spread commonly occurs to pleura and mediastinum. Systemic metastases develop in patient with lung being the most common metastatic organ followed by bone and brain. Angiosarcoma show rapid and aggressive behavior and hence surgical resection is not possible[1,10,11,19,21].

Rhabdomyosarcoma

It is the second most common primary malignancy after angiosarcoma which is originated from the striated muscle. This type of tumor occurs in males and found in any

chamber of the heart and hence obstruction may occur in more than one valve orifices. The tumor rarely infiltrates beyond the parietal pericardium unlike angiosarcoma[1,7].

Fibrosarcoma

Fibrosarcomas are mesenchymal neoplasm that stem from fibroblasts and infiltrate the heart muscle. They are found in both left and right chambers. They are found as firm grayish white small nodules at multiple intracardiac sites[1,19].

Liposarcoma

These are mesenchymal tumors containing lipoblasts. They are large multi lobulated tumors with necrosis[19].

Osteosarcoma

These arise from malignant bone producing cells. They are generally located in the left atrium and grow to large masses with variable degree of calcification. Cardiac metastases occur to distant important parts[10,19].

Leiomyasarcoma

These arise from smooth muscle and tend to mimic myxomas. They are lobulated low attenuated masses of spindle cells in left atrium and mitral valve[11,14,19].

Lymphoma

Primary cardiac lymphomas involve heart and/or pericardium. They are very rare form but their occurrence has increased owing to the rise of immunodeficiency syndrome. They arise in right atrium and ventricle and B-cells lymphomas are the major histological type[1,10].

Secondary cardiac tumors

Secondary cardiac tumors are 20-30 times more common than the primary tumors. They are usually epicardial in nature but may be myocardial or endocardial. Cardiac metastases are clinically silent in most of the cases. Macroscopically carcinomatous metastatic tumors are multiple, discrete, small and as firm nodules[1,22].

Melanoma has the highest affinity for metastasizing to the heart. They invade the walls of the heart chambers commonly in the right atrium[23,24]. Leukemia and lymphoma also commonly metastasize to the heart where leukemia infiltrates between myocardial masses and large deposits and lymphoma form discrete intra-myocardial masses[7]. Reports also suggest metastases from other common tumors such as lung, breast, colon-rectum, liver.

There are four major paths for cardiac metastases: local invasion, haematogenous spread, lymphatic spread and extension from the inferior *vena cava*[10,24]. Hematogenous spread preferentially gives rise to myocardial metastases while lymphatic spread tends to give rise to pericardial metastases[25].

Factors that is responsible for the protection of heart from tumors

No post-mitotic cell division in cardiac myocytes that helps to evade incidence of primary cardiac tumors

Organs that have high rate of cell division are more prone to cancer. Decades ago, it was confirmed that adult cardiac myocytes are terminally differentiated cells and the cell division does not occur in the heart muscle[26,27]. A fetal or neonatal cardiac cell is highly proliferative but in the postnatal condition, post-mitotic cell division is arrested and therefore,

cardiac cells lose the capacity to divide. Cell proliferation and differentiation occur simultaneously in the cardiac myocytes and thus leads to the early withdrawal of these cells from the cell cycle. There are certain conditions, for instance, cardiac hypertrophy where adult heart muscle cells undergo DNA synthesis and nuclear mitosis without undergoing cytokinesis which renders majority of adult cardiac myocytes binucleated. In this situation, there is an increase in the mass of the heart due to increase in cell size but not in cell number. The cell cycle regulators also play a major role in this where; Rb has been attributed to mediate the exit and the irreversible entry of the cardiac myocytes to cell cycle[28-30]. This blockage in the cell cycle supports the observation that primary cardiac tumors are very rare. Further, cardiac myocytes are non dividing cells that render them least favorable for the development of primary tumors [31].

However, some studies have shown that few cardiac myocytes do divide after myocardial infarction or in the end stage of cardiac failure[32]. This observation also supports the rare occurrence of cardiac tumors. Moreover, due to less dividing nature of the cardiac myocytes, the rate of spontaneous mutation in these cells is also less. The cells do not replicate their DNA abruptly and as a result mutation does not occur with much high frequency. Even if the mutation occurs during replication it cannot be passed on to the daughter cells. Hence the chances of developing tumors are greatly reduced. Another observation that strengthens this point is the higher occurrence of primary benign tumors in infants which is understandable as neonatal cardiac cells undergo cell division. Thus the less dividing nature of the cardiac myocytes can be attributed as one of the reason for the rare occurrence of primary cardiac tumors.

Less frequency of DNA mutation in cardiac cells also lead to rarity of cardiac tumors.

Mutations in the genome are the basis of development for any cancer. Carcinogens also cause cancer by inducing mutation in the genes. In case of cardiac cells, cell cycle arrest occurs after few months of birth and adults' cardiac cells irreversibly withdraw from cell cycle unless there is an injury. Therefore, the rate of DNA replication is greatly reduced in the cardiac cells. As a result, the cardiac cells have very less frequency of mutation in their DNA. Moreover the heart is also not exposed with too much carcinogens except those in the blood and hence the rate of induced DNA mutation is less and incidence of cardiac tumor is highly rare[31].

Therapeutic approach to cure cardiac tumors

Four decades ago, cardiac tumors were only detected in the post-mortem analysis but advanced non-invasive techniques like echocardiography, computed tomography (CT), magnetic resonance imaging (MRI) have led to the ante-mortem diagnosis of cardiac tumors. Earlier photodynamic therapy, chemotherapy, radiotherapy were used but they did not produce satisfactory results[33]. The best possible treatment of cardiac tumor is complete surgical resection. Complete resection of benign cardiac tumors is possible and there are no signs of recurrence[34-36]. Surgical resection patients have excellent long-term survival in case of primary benign tumors[37] whereas surgical resection of malignant tumor is not completely successful. Adjuvant chemotherapy and radiotherapy are used after surgical removal of malignant tumor but it does not provide complete cure and only prolongs the survival of the patient[38]. If the resection of the cardiac tumor is not possible, then orthotopic cardiac transplantation can be considered. This treatment is only for unresectable tumors with evidence of no metastatic involvement of the heart. The delay in diagnosis and treatment also lead to less possibility of complete resection[39]. Thus, benign cardiac tumors can be completely treated but prognosis of malignant cardiac tumor is poor.

Conclusion

Cardiac tumors are lesions occurring in the heart. Benign cardiac tumors are less common as compared to malignant cardiac tumors. Myxomas, angiomas and rhabdomyomas are the most common benign tumors in heart. Angiosarcoma is the commonest primary malignant tumor while melanoma has high affinity to metastasize to the heart and give rise to secondary malignant tumors. The low incidence of cardiac tumors is attributed to the less dividing nature of the cardiac myocytes and less degree of mutation in the cardiac cells. Surgical resection serves as the best possible treatment option available but still the prognosis is poor mainly in case of malignant tumors.

Future perspectives

The incidence of different types of cardiac tumors is very rare but as they affect the vital organ, it is very important to understand the various therapeutic approaches to prevent the cardiac tumor. Present available treatment options does not provide complete cure but only prolongs the lifespan. Hence new treatment possibilities are needed to be researched. Adjuvant chemotherapy after surgical resection can provide better results if new targeted drugs is discovered. Immunotherapy promises to be a better treatment possibility but alot work is still left to be done.

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