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Review Article

Oncology Section

Cardiac Myeloid Sarcoma: Review of Literature

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ABSTRACT

Granulocytic Sarcomas (GS) also called as Myeloid Sarcomas (MS) or chloromas are the representatives of extramedullary infiltrates of immature myeloid cells including myeloblasts, promyelocytes and myelocytes. Primary cardiac malignancies per se are rare and infiltration of cardiac muscles by secondary malignant cells is also an uncommon finding. Out of these cardiac tumors, contribution of Cardiac Myeloid Sarcoma (CMS) is even more smaller thereby limiting our knowledge about this rare entity. Because of its very lower incidence, an exact guideline for diagnosis and management is still missing and usually haematologists around the world are treating CMS based on their clinical acumen. Aim of this review is to briefly discuss the presenting clinical feature, differential diagnosis, diagnostic workup and management based on published articles related to CMS till date.

Keywords: Acute myeloid leukaemia, Chemotherapy, Granulocytic sarcoma

INTRODUCTION

GS is most commonly associated with Acute Myeloid Leukaemias (AML), but can be also seen in association with Myeloproliferative Neoplasms (MPN) or Myelodysplastic Syndromes (MDS) [1]. Very rarely, it has been reported in chronic myelogenous leukaemia presenting in blast crisis. The usual reported location of chloroma is skin, bone, periosteum, spleen and soft tissues. However, acute leukaemias especially AML can have atypical presentations and we have reported rare areas of involvement such as orbit, pleura, mediastinum and spinal cord in recent past [2-7]. Presence of CMS either as locally invasive or isolated cardiac intracavitatory mass is highly uncommon. The occurrence has been reported anytime during the entire disease course i.e., before the diagnosis, during treatment, post chemotherapy relapse or post stem cell transplant [8]. In most cases, symptoms are similar to that of classical commoner cardiac illnesses [9]. Both the diagnosis as well as management is challenging and must be tailored based on clinician's experience and patient's performance status. MS in other common locations is well known findings in AML and treatment protocols have also been laid down. In view of its rarity of occurrence, diagnostic limitations and restricted of use of conventional anti-leukaemia agents (due to the fear of cardio toxicity), the same guidelines cannot be applied to CMS. This review aims to highlight the challenges which haemato-oncologists do face while dealing with such cases.

MATERIALS AND METHODS

We did a MEDLINE/PubMed search with MeSH terms–("Heart" and "Myeloid Sarcoma") and "(Cardiac and Myeloid Sarcoma)". In total, we found 36 articles reported (From 1960 to July 2016). For a comprehensive review, we have included all the cases including both paediatric and adult population. Exclusion criteria was removal of reports from review which were written in languages other than English. Hence, six cases (written in Japanese, French, Italian, and German language) were excluded. Hence, finally a total number of 30 articles were included in this study [Table/Fig-1]. Detailed summary of all the articles included in the study is mentioned in [Table/Fig-2] [1,8-36].

DISCUSSION

Underlying Basic Disease

We found that most of the cases reported had AML as the basic disease followed by Acute Promyelocytic Leukaemia (APML), MDS, CML and angiogenic myeloid metaplasia. The average age of patients was 40 years (ranging from 1.4 months to 72 years). There were in total 26 males and five females (including three children under the age 12 years). There were also four cases of post allogeneic transplantation that developed CMS during post-transplant period follow up [8].

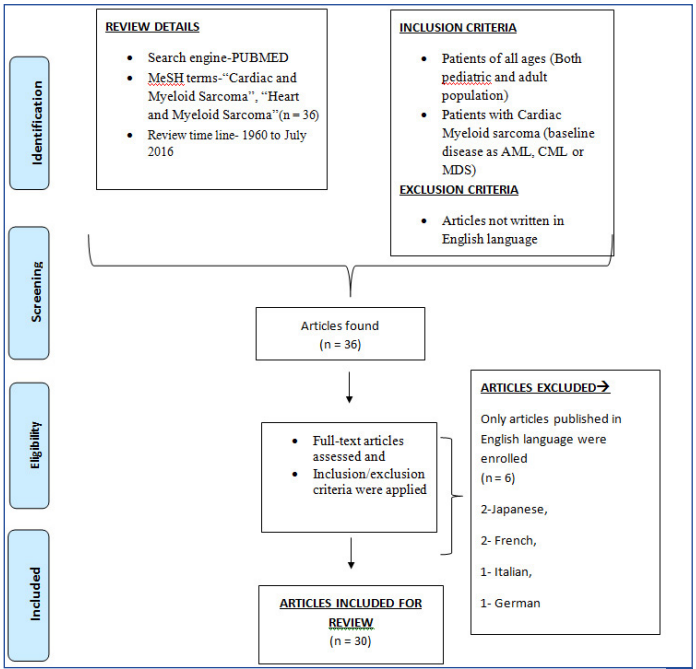
Symptomatology

Review showed that CMS can present with a wide array of symptoms. An excellent review by Lam KY et al., of over 12000 consecutive autopsies done over the span of 20 year period showed the incidence of cardiac involvement by leukaemia of just 4% [37]. A majority of these remain undiagnosed in living individuals and discovered subsequently only on autopsy. In the symptomatic individuals, pericarditis is the frequent presentation with or without leukaemic cells in pericardial fluid [25]. Other clinical findings may include tachycardia, dyspnoea on exertion, palpitations, chest pain, arrhythmias, heart block, etc. Review showed that symptomatology of CMS in general is no more different from that of classical cardiac diseases like CAD, cardiomyopathies etc. Recognition of subtle clinical signs without frank heart failure like elevated jugular venous pressure with tall "a" wave, pedal oedema and tender hepatomegaly is crucial to warrant further imaging and invasive tests.

Diagnosis and Investigative Modalities

Diagnosis of GS requires high index of suspicion and definitive diagnosis can be very laborious and unyielding. Gold standard diagnosis is histological examination of the endomyocardial biopsy specimen [26]. Yield of biopsy samples can be increased by combining with newer diagnostic tests like MRI (SSFP/FLASH MRI) and PET scan. Superiority of PET scan is due to high efficacy in finding unifocal v/s multifocal involvement, in assessing the most 18 Fludeoxyglucose (FDG) avid site for biopsy and the treatment response after chemotherapy. Various diagnostic modalities and their utilities are summarized in [Table/Fig-3] [32,33].

A detail histopathological examination including light microscopy, immunohistochemistry and Fluorescence in Situ Hybridization (FISH) should be done on biopsy samples. The common histopathological features are highly cellular, diffuse proliferation of medium-size, polygonal to rounded, polymorph, undifferentiated malignant cells, with a high nuclear-cytoplasmic ratio, high mitotic index, scattered to diffuse areas of necrosis, and irregular production of finely reticular to coarse fibrinous tissue [34]. The cytoplasm is usually eosinophilic and granular. Positivity for CD 34, 45, 17 and HLA-DR indicates tumor mass to be of myeloid origin. Combined team effort



[Table/Fig-1]: CONSORT diagram.

of radiologists, cardiologists and haematologists to diagnose and manage these challenging cases is of utmost importance.

Management Challenges

There is no consensus on the type of regimen to be used in CMS cases and haematologists worldwide have used various regimens depending on patient's tolerability and cardiac compromise. Anthracyclines are considered as backbone in the treatment therapy of AML, however the same might not be suitable in all cases due to risk of potential cardiotoxicity. Etoposide, Mitoxantrone, Cytarabine/Ara-C (EMA) based regimens have been shown to be partially efficacious in the treatment of CMS in a few case reports [35,38] Milder forms of therapy e.g., hypomethylating agents like azacytidine have also been tried which makes chemotherapy possible even in patients of older age, poor performance status and with compromised cardiac function [12,39]. A combination chemotherapy and minimal residual disease targeted therapy is needed to control the disease locally and to prevent bone marrow relapse. Newer radiotherapy protocols based on IGRT and IMRT have also broadened the treatment options where in only pathological part of heart are radiated thereby preserving the cardiac function. A total of 24 Gy in divided doses (12 fractions) was used by Yang WC et al., with successful remission achievement [12].

Author and year of publication	Age / sex	Disease /FAB Subtype	Molecular Marker/ FISH/ Cytogenetics	Cardiac chloroma at diagnosis or relapse	BM involvement	Diagnostic modality used	Pathological areas involved	Outcome
Wang Y et al., [10]	66/M	AML	NA	At diagnosis	+	PET scan 2D Echo	Ascending aorta, Pulmonary artery, pericardial effusion, B/L atrial enlargement	NA
Niu N et al., [11]	66/M	AML	NA	At diagnosis	+	PET scan 2D Echo	Both ventricles and atria, pericardium	NA
Yang WC et al., [12]	19/M	AML(Post allo-HSCT) in CR	Normal Karotype, NPM-ve)	At relapse	NA	CT scan PET scan	Soft tissue mass along the interatrial groove with an encasement of the pulmonary vein causing SVC syndrome	IMRT (24 Gy in 12 fractions) and Azycytidine following which achieved complete remission. Died soon due to sepsis.
Dorfel D et al., [13]	69/M	AML	FLT3 + ve NPM1+ve	At relapse	-	2D Echo CEMRI VPCT	Epicardial mass infiltrating right ventricular wall. Another mass at coronary sulcus	Died due to sigmoid diverticulitis and MODS
Schaffer LR et al., [14]	7/M	AML-M 5	Not mentioned	At diagnosis	+	CXR 2D Echo	Subtotal replacement of the myocardium, sinoatrial and atrioventricular (AV) nodes	Died
Kim JG et al., [15]	41/M	CML (Post MUD-HSCT) in CR	BCR-ABL 1 status not mentioned	At relapse	+	2D Echo CEMRI	Irregular shaped mass in the right atrium	Size of cholorma increased after 17 months. Dose of Dasatinib was increased to 140 mg/day
Mawad R et al., [16]	42/M	Not applicable	t(8;21) 46XY	At diagnosis	-	2D Echo PET scan	Bilateral atrial walls, intra –atrial septum	Complete remission Non FDG avid residual mass
Cash T et al., [17]	24/F	AML /M5	46,del(x) Trisomy 21	At relapse	-	2D Echo CECT chest CEMRI	Mass adhering to right ventricle with RVOT obstruction pericardial effusion	Died within four months of achieving CR1 due to relapse of choloroma at the same time
Dl Valentino M et al., [18]	38/F	AML	Not available	At relapse	-	2D Echo CEMRI	Infiltration of right free wall with RVOT obstruction	Complete remission
Makis W et al., [19]	42/M	AML	Not available	At diagnosis	NA	CT scan PET	Mediastinal mass with invasion of the parietal pericardium	Pericardial therapeutic drainage and HiDAC therapy- Did not achieved remission. Post two months PET showed disease progression.
Tirado CA et al., [20]	30/M	APML	+7p22, t(15;17)	At relapse	NA		Multiple sites- (left scapula, thoracic vertebra, right atrium, and supraclavicular mass	NA
Atallah A et al., [21]	56/M	AML	Not available	At diagnosis	+	2D Echo CEMRI	Focal, patchy, epicardial infiltrative process affecting mid-inferior wall	Died due to chemoresistant leukaemia

Author and year of publication	Age / sex	Disease /FAB Subtype	Molecular Marker/ FISH/ Cytogenetics	Cardiac chloroma at diagnosis or relapse	BM involvement	Diagnostic modality used	Pathological areas involved	Outcome
Tsai J et al., [22]	20/M	AML	Not available	At relapse	-	2D Echo MDCT	Well marginated, lobulated mass involving the intra-axial septum and both atria. Another mass located near the posterior aspect of tricuspid valve	Complete remission
Matkowskyj KA et al., [23]	59/M	T-MDS – RAEB type (treated 3 years back for Anaplastic oligodendroglioma)	Abnormal mosaic male karyotype (46,XYand 45,XY,-7)	At diagnosis	-	2D Echo	Left ventricle, septum, and right ventricle	Died before treatment could be started
Mignano JE [24]	20/M	AML, FAB M-2	Not mentioned	Relapse	-	CT	Right and left atria, intra-atrial septum, and apparent extension into the right pulmonary veins	Resolution
Tsai MH [25]	1.4 mon/F	AML	51,XX,add(1)(p32),del(4)(q31),+del(6)(q23),add(7)(q11.2),+8,+8,der(11)t(7;11)(q11.2;q23),+13, add(16)(q24), +19.	At diagnosis	+	CXR, ECG	Pericardium invasion	Died secondary to sepsis
Rigamonti F et al., [27]	52/M	AML	47,X,add(Y)(q12)	At diagnosis	-	Cardiac Ultrasound	Infiltration of the infero-lateral cardiac wall, right auricle and aortic arch	3+7 Regimen/ Patient died despite achieving remission due to fungal sepsis
Kozelj M [26]	52/M	AML	t(8;21),	At diagnosis	+	2D Echo, TTE, MRI	Right atrium, right pulmonary hilum	Remission
Antic D et al., [28]	37/M	AML	NA	At diagnosis	-	CT Chest	Large mass in right atrium extending into SVC causing SVC syndrome	Surgical excision of the mass followed by 3+7 regimen
Diab M et al., [29]	27/M	AML	NA	At diagnosis	-	CT Chest	Leukemia cutis, Pericardial effusion, mediastinal mass	Pericardiocentesis, Cytrabine, Daunorubicin and etoposide based regimen. Refractory to chemotherapy due to which patient soon.
Nasilowska AB et al., [30]	34/M	APML in CR (Post allo-HSCT)	t(15;17)	At Relapse	-	CT Chest	Multiple sites of EM relapse- pleura, heart and pericardium	During salvage chemotherapy, patient died of cardiogenic shock
Mateen FJ et al., [1]	64/W	MDS, RAEB	Not mentioned	At diagnosis	+	CXR, 2D echo	Myocardium infiltration	Died
Antón E et al., [31]	45/F	Not applicable	+4, -9, -17, add(17)(p13), -18, +21, +22	At diagnosis	-	CXR, ECG	Myocardial infiltration	Died due to multi organ failure
Kara IO et al., [8]	28/M	AML, FAB-M2 in CR 2 (Post allo-HSCT)	Not mentioned	At relapse	+	2D Echo	Nasopharynx nodular masses, right atrium, right ventricle	Etoposide, mitoxantrone, ara-C (EMA) chemotherapy regimen-achieved CR
Marcos AP et al., [32]	39/M	AML, FAB-M1	Not mentioned	At relapse	-	TEE	Right atrium	Complete remission
Markaryus AN et al., [33]	34/M	AML, FAB-M1	Not mentioned	At relapse	+	TTE, 2D echo, TEE, MRI	All chambers	Died
Erdol C et al., [34]	48/M	AML, FAB-M4	Not mentioned	At diagnosis	+	TTE, TEE, Echocardiography	Right atrium	Complete regression post chemotherapy
Tillawi IS et al., [35]	72/M	Angiogenic myeloid metaplasia			NA		Encasement of the heart and great vessels	
Jankovic M et al., [9]	12/F	APML	Not done	At relapse	-	CXR, Echocardiography	Right-sided intracardiac mass, pericardial effusion	Died due to progressive heart failure
Foucar K et al., [36]	22/M	Not applicable	Not done	At diagnosis	-	CXR, Echocardiography	Encasement of the SVC, PA, and aorta	Died due to ventricular arrhythmia

[Table/Fig-2]: Review of published cases of cardiac chloromas in literature from 1960 till July 2016, their baseline disease characters, molecular characteristics, diagnostic modality used, areas of cardiac tissue involved with outcome [1,8-36].

CONCLUSION

Despite various chemotherapeutic and radiation based treatment protocols, CMS carries a dismal prognosis. High mortality and morbidity is associated with this rare disease. Major limitation is that anthracycline based regimens cannot be used due to their own cardiotoxicity. Further research is warranted to identify newer molecular markers for diagnosis, standardize diagnostic tests and formulate efficacious chemotherapy and radiation protocols.

ECG, Chest X Ray	Non-specific test, cheap, beneficial to give quick idea about arrhythmia, effusion and cardiac borders and mediastinal involvement.
2D - Echocardiography and TEE	Fast and dynamic, TEE can be used to take biopsy.
CT Scan	Quick, easily available. To analyze intra-cardiac invasion and involvement of pulmonary vasculature. Volume perfusion scan (VPCT) to assess viable myocardium.
MRI	Steady state free procession imaging (SSFP MRI) and fast low angle short magnetic resonance imaging (FLASH MRI) can acquire dynamic images synchronised with ECG.
PET Scan [40]	Best to assess the site for biopsy and the treatment response.

[Table/Fig-3]: Diagnostic modalities and their efficacy in diagnosing.

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