Title: Multiple myeloma with cardiac involvement accompanied by partial superior vena cava obstruction: a case report and literature review

Running title: Multiple myeloma with cardiac involvement

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Abstract

Extramedullary involvement of the endocardium is rare in multiple myeloma. Here we describe a case of multiple myeloma (plasma cell) with extramedullary plasmablastic transformation and endocardial involvement, which resulted in partial superior vena cava obstruction. We also conducted a literature review and summary analysis of space-occupying lesions in the heart in 12 patients with multiple myeloma (including the current case) in the last 10 years. Echocardiography

is the preferred radiologic examination method for diagnosis and follow-up in multiple myeloma, and surgical resection is effective for alleviating symptoms.

Keywords Multiple Myeloma, Cardiac involvement, Right atrial occupation, Obstruction, Echocardiography

Introduction

Multiple myeloma (MM) is a malignant proliferative disorder of plasma cells that can cause clinical symptoms during the invasion of extramedullary soft tissues, either at initial diagnosis or during disease progression. Extramedullary MM has a cumulative incidence of approximately 9% among all patients with MM and can occur in any soft tissue, although cardiac involvement is the most serious and is intimately associated with prognosis [1]. Cardiac involvement in MM mostly presents as pericardial effusion, and endocardial involvement is rare, with very few reported cases. Plasmablastic transformation is also rare in cases with plasmacytoma extramedullary involvement, and no cases of plasmablastic transformation and endocardial involvement caused by extramedullary plasmacytoma have been reported. Here, we describe a case of MM (plasma cell) with extramedullary plasmablastic transformation and endocardial involvement. This case presented as multiple solid space-occupying lesions in the right atrium encasing the interatrial septum, and extended to the superior vena cava, leading to partial superior vena cava obstruction.

Keywords: Multiple myeloma, cardiac involvement, right atrial space-occupying lesion, obstruction, echocardiography

Case presentation

The patient was a 57-year-old male who was admitted to hospital due to progressive dyspnea, facial and bilateral upper limb swelling for more than 2 months, and exacerbation for more than 10 days. The patient underwent pacemaker implantation due to sick sinus syndrome more than 3 years prior. More than 1 year ago, he was diagnosed with MM (non-secretory type with 1q21) due to fatigue and chest tightness for more than 2 weeks. He received three cycles of “bortezomib + cyclophosphamide + dexamethasone” chemotherapy before a normal myelogram was achieved and chemotherapy was discontinued. Echocardiography was performed during the current admission, and showed multiple solid masses with medium echoes in the right atrium. These masses had an

area of 7.9 × 3.8 cm, irregular morphology, did not show significant mobility, invaded the interatrial septum, had no clear borders with the interatrial septum, and extended upwards into the proximal superior vena cava, resulting in significant thinning of the blood flow in the superior vena cava. Mild-moderate tricuspid regurgitation was present, the left ventricular ejection fraction was normal, and the left atrial masses were considered to be possible malignant lesions. The patient underwent further computed tomography (CT) scan, which demonstrated that multiple solid space-occupying lesions were present in the right atrium, together with a filling defect in the superior vena cava. To relieve symptoms caused by superior vena cava obstruction, the patient underwent superior vena cava venoplasty + partial resection of the space-occupying lesions in the right atrium under extracorporeal circulation. During surgery, a thickened right atrial wall, interatrial septum, and superior vena cava tissues were observed and the surfaces were stiff; multiple spherical space-occupying lesions were observed in the right atrium, with sizes ranging from 5 × 4 cm to 3 × 3 cm. The pathological diagnosis of the resected right atrial space-occupying lesion was MM. Microscopy showed diffuse tumor cells, consisting mainly of medium-size immature plasma cells. Immunohistochemical testing demonstrated that the tumor cells were positive for CD138, CD38, CyclinD-1, and mum-1, and were negative for CD20, Kappa, and Epstein–Barr virus-encoded small RNA (EBER).

The patient returned to the hospital 3 months later for follow-up consultation, at which point, facial and upper limb swelling had completely disappeared but chest tightness during exertion remained. Transesophageal echocardiography showed local thickening at the interatrial septum of the superior vena cava inlet but the superior vena cava blood flow was smooth.

Discussion

MM is a common hematologic malignancy in which clonal proliferation of plasma cells in the bone marrow causes a series of clinical symptoms. MM accounts for 17% of hematologic

malignancies and tends to occur in middle-aged and elderly people [2]. In MM, extramedullary soft tissue involvement can occur at the initial diagnosis or during disease progression, and can occur in any system. Extramedullary cardiac involvement is rare and mainly presents as pericardial effusion, while endocardial involvement is extremely rare, with very few cases reported so far. We searched for cases of MM with cardiac solid space-occupying lesions reported in the last 10 years on PubMed and only found 11 other cases [3–11]. We used a table to list the sex, age, symptoms, disease course, imaging method used for mass diagnosis, site and size of mass, treatment method, and outcome of these patients (including the current case) (Table 1). These 12 patients comprised 8 males (67%) and 4 females (33%), with a mean age of 64.3 (45–82) years. Dyspnea was the most common clinical symptoms (n = 11, 91.6%); in addition, some patients presented with limb edema, and only a few presented with chest pain. In 10 (83%) of the 12 patients, the cardiac space-occupying lesion belonged to secondary invasion, and only 2 patients presented with primary cardiac plasmacytoma. These masses were mostly located in the right atrium (n = 10, 83%), and very few were located in other chambers (1 in the right ventricle apex, and 1 in the left ventricular lateral wall and great vessel). Solid space-occupying lesions in the right atrium are usually larger in size and spread along the endocardium to surrounding tissues; this leads to embolism or obstruction and corresponding clinical symptoms [14]. Our patient developed facial edema due to partial superior vena cava obstruction caused by a large space-occupying mass in the right atrium.

Cardiac space-occupying masses are primarily diagnosed by echocardiography, CT, and magnetic resonance imaging. However, transthoracic echocardiography (TTE) was the preferred radiologic examination method in our collected cases (100% of patients were diagnosed using TTE). TTE can show the tumor site, size, mobility, relationship with neighboring tissues, hemodynamic changes, and can be used to evaluate cardiac function. Although TTE cannot be used for histological diagnosis it can be used in dynamic follow-up to understand disease progression. Thrombosis must be suspected when short-term intracardiac solid echoes are found by

echocardiography in patients with MM due to the inherent risk of thrombosis in this patient group, as well as their increased susceptibility due to chemotherapeutic drugs. However, in the current case, TTE showed that the linear strong echoes in the normal interatrial septum basically disappeared; instead, the interatrial septum was encased by a rough solid mass that showed significant invasion, which aided in differential diagnosis. Ultrasound imaging can be used for further differential diagnosis of solid intracardiac masses with soft tissue invasion that is not substantial. Given the risk of embolism caused by intracardiac tumor detachment, CT or MRI examination should be performed in parallel in order to determine whether lesions are present in distal blood vessels, and to provide comprehensive information for formulating a treatment strategy.

Plasmablastic transformation is extremely rare in MM with extramedullary involvement. The clinical significance, disease characteristics, and molecular mechanisms of this inconsistent transformation are unclear and may be related to c-Myc and/or p53 overexpression, a high Ki-67 proliferative index, and frequent mutations in the Ras pathway [15]. Treatments of MM with extramedullary involvement include chemotherapy, radiotherapy, and stem cell transplantation, although there is currently no unified standard. This may be because there is a possibility of recurrence, which may be caused by local growth factors, and adhesion molecules on malignant plasma cells and their ligands on endothelial surfaces [16]. There is no clear consensus on the optimal treatment strategy for MM presenting with intracardiac space-occupying lesions; however, several studies have reported a number of successful treatments (Table 1), including surgical resection [9]. In our patient, surgical resection was used to remove a large part of the space-occupying mass, and superior vena cava venoplasty was performed. Short-term follow-up showed that the symptoms of obstruction completely disappeared and Transesophageal echocardiography(TEE) showed no signs of recurrence. Thus, at present, the treatment can be considered effective.

Endocardial involvement is extremely rare in MM and mostly presents as right atrial solid space-occupying lesions. Echocardiography is the preferred radiologic examination method for lesion diagnosis and follow-up, and surgical resection is an effective short-time method for alleviating symptoms.

Figure Legend:

Figure A. Multiple solid masses in the right atrium.

Figure B. CDFI showing significant thinning of the blood flow in the superior vena cava inlet and patent inferior vena cava blood flow.

Figure C. Mild-moderate tricuspid regurgitation.

Figure D. Postoperative TEE showing limited thickening of the upper segment of the interatrial septum and a patent superior vena cava.

Figure E. Multiple space-occupying masses in the right atrium.

Figure F. Arrows show significant thinning of the inner diameter in the residual superior vena cava

Figure G. Intraoperative resection samples.

Figure H. Microscopy showing diffuse tumor cells consisting mainly of immature plasma cells.

Author Contributions:

Shuzhen Wang: Concept, Drafting article.

Ruohan Zhao：Data analysis/interpretation, Drafting article, Critical revision of article.

Feng Xiong：Approval of article.

Kunyue Tan, Chunxia Liu, Lijuan Zhang and Min Xu: Statistics, and Data collection.

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Table 1. Disease characteristics of patients with multiple myeloma presenting with cardiac space-occupying masses in the last 10 years

Patient	Sex/age (years)	Symptoms	MM disease course	Imaging method used for diagnosis	Site and size of mass	Treatment and outcome
Current case	Male/57	Dyspnea and facial edema	1+ year	TTE + CT + TEE	Right atrium, interatrial septum, superior vena cava, partial superior vena cava obstruction, 7.9 × 3.8 cm	Surgery, symptoms alleviated
Guan et al.	Female/44	Precordial pressure sensation	11+ years	CT + TTE + MRI	Left ventricular anterior wall epicardium and aortic and pulmonary artery lateral walls; broad	Chemotherapy, mass shrunk

					area, size unknown	
Fukae et al.	Female/79	Dyspnea and lower limb edema	4+ years	TTE + CT	Right atrial lateral wall, 3.8 × 4.5 cm	Chemotherapy, death
Caro-Fernández et al.	Male/82	Dyspnea	7+ months	TTE + TEE + CT	Right atrial appendage, interatrial septum, left atrium, superior and inferior vena cava inlet; wide area, size unknown	Chemotherapy, death
Nam et al.	Male/54	Dyspnea and abdominal distension	Primary cardiac plasmacytoma	TTE + CT + MRI	Extending from the right atrium to the tricuspid valve and inferior vena cava inlet, 9.2 × 6.2 cm	Surgery + chemotherapy, unknown

Vrettou et al.	Male/73	Mild dyspnea on exertion	26+ years	TTE + MRI	Right ventricular apical myocardium involving the distal interventricular septum, 5.7 × 2.2 cm	Chemotherapy + radiotherapy, mass shrunk
Blau et al.	Male/72	Dyspnea on exertion, cough	Unknown	TTE + MRI	Large mass in the right atrium, partial obstruction of the right ventricular inflow tract and the inferior vena cava, 10 × 6 cm	Radiotherapy, unknown
Behzadnia et al.	Male/57	Dyspnea and bilateral lower limb	2+ years	TTE + TEE + CT	Large mass in the right atrium, partial obstruction of the right	Surgery, good

		edema			ventricular inflow tract and tricuspid valve, inferior vena cava occlusion, 5.8 × 4.5 cm	
Andrea et al.	Male/62	Nocturnal dyspnea, weakness	Primary cardiac plasmacytoma	TTE + CT	Right atrial mass involving the right atrial appendage and interatrial septum, 3.2 × 2.8 cm	Chemotherapy + radiotherapy, good
Stawis et al.	Female/45	Shortness of breath and dyspnea	13+ years	TTE + CT	Right atrial mass extending to the superior and inferior vena cava inlets, 6.7 × 3.3 cm	Chemotherapy, mass shrunk
Vigo et al.	Female/79	Dyspnea and chest	Unknown	TTE + CT	Right atrial mass encasing	Radiotherapy, mass shrunk

		pain			the interatrial septum and extending to the left atrium, 4.2 × 5.3 cm	
Paulus et al.	Male/68	Shortness of breath and dyspnea	5+ years	TTE + TEE + CT	Right atrial mass encasing the interatrial septum and involving the left atrium; size unknown	Chemotherapy + radiotherapy, mass shrunk