CASE REPORT

Treatment of relapsed multiple myeloma complicated by cardiac extramedullary plasmacytoma with D-PACE chemotherapy

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SUMMARY

Cardiac extramedullary plasmacytomas (EMPs) are rare and may be seen as a complication of multiple myeloma (MM) or in isolation. Here, we describe a case of cardiac EMP that presented clinically as a congestive heart failure exacerbation in a patient with relapsed and refractory IgG lambda MM. We highlight radiographic imaging in conjunction with laboratory biomarkers at presentation and in response to D-PACE (dexamethasone, cisplatin (Platinol), doxorubicin (Adriamycin), cyclophosphamide and etoposide) systemic chemotherapy.

BACKGROUND

Cardiac extramedullary plasmacytoma (EMP) is a rare complication of multiple myeloma (MM). Coakley *et al* described a case series and review of literature including 34 patients which highlighted the demographics and characteristics of cardiac EMPs; however, information regarding response to specific chemotherapeutic regimens is limited.¹ D-PACE (dexamethasone, cisplatin (Platinol), doxorubicin (Adriamycin), cyclophosphamide, and etoposide) is a chemotherapeutic regimen that has been studied in cases of relapsed and refractory MM with response rates of approximately 50%.^{2,3} However, toxicity is common and progression-free survival is short. Thus, D-PACE is best used as a bridge to definitive therapy such as autologous stem cell transplantation. More information is needed to determine an ideal therapy for cardiac EMPs; however, the rarity of these entities makes randomised, controlled study difficult.

CASE PRESENTATION

A 55-year-old, lifetime non-smoker man with a history of relapsed IgG lambda MM on 13th line treatment (table 1), coronary artery disease status post drug-eluting stent and congestive heart failure with systolic ejection fraction of 30% presented at the emergency department with 5 days of worsening cough, fatigue, dyspnoea on exertion, and orthopnoea. Two days after the onset of symptoms, the patient received cycle 3, day 1 of daratumumab, bortezomib and dexamethasone and was noted to have mild hypoxia on pulse oximetry. He received an X-ray of the chest which was without evidence of airway disease and was started on a course of

azithromycin. Despite treatment with antibiotics, his symptoms progressed.

Initial examination demonstrated a blood pressure of 124/60, pulse of 75, temperature of 99.1°F, respiratory rate of 20 and pulse oximetry of 88% on room air which improved to 93% on 3 L of oxygen via nasal cannula. He was in mild respiratory distress with increased work of breathing. Auscultation of the lungs revealed diffuse rhonchi and wheezes. Cardiac examination revealed distant heart sounds with normal rhythm, 2/6 systolic murmur best heard at the left upper sternal border and an S3 gallop. Neck veins were distended to the angle of the mandible and there was pitting oedema in the lower extremities. The remainder of the examination was unremarkable.

INVESTIGATIONS

Initial chest X-ray revealed mild interstitial oedema. ECG showed normal sinus rhythm with stable left axis deviation and left bundle branch block. Laboratory evaluation was significant for negative troponin, elevated BNP of 474 pg/mL (range 0–100 pg/mL) and normal creatinine of 0.79 mg/dL (range 0.7–1.30 mg/dL). Complete blood count showed haemoglobin of 11.3 g/dL, haematocrit of 33.8%, white blood cell count of $5.3 \times 10^9/L$ with 74% neutrophils and platelet count of $94 \times 10^9/L$. Serum protein electrophoresis (SPEP) and immunofixation revealed a total IgG of 541 mg/dL with 132 mg/dL of monoclonal IgG and serum lambda free light chains of 1447.5 mg/L.

CT scan of the chest with contrast to evaluate for pulmonary embolism (PE) was negative for acute PE but showed a large, infiltrating cardiac mass involving the right atrium and right ventricle extending into the pericardium and narrowing the right pulmonary artery (maximum thickness 8.5×5.4 cm) with associated pericardial nodules and prevascular lymphadenopathy (figure 1A). Cardiac MRI confirmed these findings and MRI characteristics were most consistent with infiltrative malignancy (figure 1B). Cardiac MRI also demonstrated left ventricular ejection fraction (LVEF) of 40%–45% and moderate pericardial effusion without evidence of tamponade.

Nuclear positron emission tomography (PET) scan revealed diffuse hypermetabolic osseous lesions consistent with relapsed and progressive MM involving the axial and appendicular skeleton

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Table 1 Patient demographics and treatment history

Age at diagnosis	45	Year of diagnosis	2007
Cytogenetics at diagnosis	55,XY,+3,+5,del(6)(q13q23),+7,+9,+9,+11,add(14)(q32),+15,+15,add(16)(q12.1),add(17)(p13),+19,?add(20)(q11.2),+21,22[2]/46,XY[28]/non-clonal[1]		
Treatment line			
1	Doxorubicin, vincristine, dexamethasone		
2	Bortezomib, dexamethasone		
3	OSU-05155, lenalidomide, temsirolimus		
4	Lenalidomide, dexamethasone		
5	Thalidomide		
	Stem cell collection and storage		
6	Thalidomide, dexamethasone		
7	Dexamethasone		
8	Thalidomide, dexamethasone		
9	Pomalidomide, dexamethasone, clarithromycin		
10	Cyclophosphamide, dexamethasone		
11	Melphalan, prednisone		
12	Melphalan, prednisone		
13	Daratumumab, bortezomib, dexamethasone		
14	D-PACE		

D-PACE, dexamethasone, cisplatin (Platinol), doxorubicin (Adriamycin), cyclophosphamide, and etoposide.

(maximum standardised uptake value (SUV) of 12.6 in parasternal lesion). In the chest, hypermetabolic prevascular lymph nodes, as well as right pericardial/right atrial hypermetabolic tissue, were visualised with a maximum SUV of 6.1.

TREATMENT

The patient was treated for acute decompensated heart failure exacerbation with supplemental oxygen, intravenous Lasix and fluid restriction. Guideline-directed medical therapies for congestive heart failure were continued throughout treatment. After achieving euvolaemia, the patient was started on systemic chemotherapy with oral dexamethasone and 4 days of intravenous cisplatin (Platinol) 10 mg/m², doxorubicin (Adriamycin) 5 mg/m², cyclophosphamide (Cytosan) 400 mg/m² and etoposide (Vepesid) 40 mg/m² (D-PACE) without any acute complications. The patient was discharged from the hospital the day following completion of cycle 1 of chemotherapy.

OUTCOME AND FOLLOW-UP

Four days after being discharged from the hospital, the patient developed fever, vomiting and fatigue. He presented to the emergency department where he was found to be profoundly neutropenic with an absolute neutrophil count of zero. He was treated with intravenous fluids and broad-spectrum antibiotics for febrile neutropenia in the setting of recent chemotherapy. Blood cultures returned positive for *Viridans streptococci*. His hospital course was complicated by hypotension and he required vasopressor support with intravenous norepinephrine. His clinical status stabilised and he was discharged home to complete a 14-day course of intravenous antibiotics which he tolerated well.

Repeat transthoracic echocardiogram performed during admission was significant for reduced LVEF of approximately 20% (40%–45% prior to D-PACE). Contrast-enhanced CT scan of the chest to rule out pulmonary embolism at time of presentation showed interval decrease in size of the previously described infiltrative mediastinal/cardiac mass (approximately 3.8×2.8 cm as compared with 8.5×5.4 cm previously) (figure 1C). SPEP and

Figure 1 CT (A,C) and cardiac MRI (B) at presentation and following cycle 1 of D-PACE (dexamethasone, cisplatin (Platinol), doxorubicin (Adriamycin), cyclophosphamide and etoposide) (C). The infiltrative cardiac mass is highlighted by the white arrow.

immunofixation revealed total IgG of 342 mg/dL, monoclonal protein of 30.1 mg/dL and lambda free light chains of 241 mg/L.

Due to the development of cardiac toxicity with new reduction in LVEF, treatment with D-PACE was discontinued. PET scan 63 days after the previous study demonstrated persistent pericardial/right atrial activity with a maximum SUV of 6.4 (previously 6.1). The patient was referred to Radiation Oncology where he completed a course of radiation therapy to target residual cardiac disease. Unfortunately, his disease progressed rapidly

with resultant decline in his functional status. After risk/benefit discussion regarding risks of worsening heart failure with his primary haematologist, he was started on carfilzomib 20 mg/m², lenalidomide 10 mg and dexamethasone. His course was complicated by multiple pathological fractures and progression of disease despite therapy. The patient died 175 days after initial presentation after choosing to pursue hospice care. Autopsy was declined which prohibited pathological confirmation of the cardiac mass.

DISCUSSION

MM is characterised by the neoplastic proliferation of plasma cells within the bone marrow which results in the clonal production of immunoglobulins. EMPs comprise approximately 4% of all plasma cell neoplasms and can be isolated or as a complication of MM.⁴ EMPs occurring within the heart or pericardium are exceedingly rare.

The patient in this case presented clinically as an acute decompensated heart failure exacerbation. He was found to have an extensive, PET avid mass involving the right atrium, right ventricle and pericardium without evidence of pericardial tamponade. Due to evidence of progression of his MM including SPEP and immunofixation showing elevated monoclonal IgG with high levels of lambda free light chains, and progressive disease within the bone marrow on PET imaging, his cardiac disease was presumed to be attributable to cardiac EMP and biopsy was deferred. D-PACE chemotherapy was initiated with partial response as evidenced by interval decrease in the size of the cardiac mass on imaging and a 77% and 83% reduction in monoclonal IgG and serum lambda free light chains, respectively. Despite initial response to therapy, treatment with D-PACE was stopped secondary to cardiac toxicity (left ventricular systolic dysfunction, Common Terminology Criteria for Adverse Events (CTCAE) grade 3) and bacteraemia. The patient's disease was refractory to subsequent therapy and ultimately resulted in his death.

Coakley *et al* recently published a review of extramedullary cardiac MM that included 34 cases since 1990.¹ Typical findings in patients with cardiac EMPs include pericardial effusion with or without cardiac tamponade. Clinically, these patients present with respiratory distress and/or volume overload. Diagnosis is made using cardiac imaging and can be confirmed with biopsy for cases in which the aetiology is unclear. Overall, cardiac EMPs portend a poor prognosis as demonstrated by a 57.5% death rate within 15 months of diagnosis. Many of the cases in the literature highlight the presentation and diagnosis of cardiac EMPs; however, few have documented response to chemotherapeutic agents with concurrent imaging and laboratory studies. Chemotherapeutic regimens aimed at treating cardiac EMPs have included combinations of bortezomib, lenalidomide, melphalan, vincristine, doxorubicin, mercaptopurine, peplo-mycin and cisplatin; however, treatment with D-PACE has not been previously documented.^{5,6}

The combination of oral dexamethasone with the continuous infusion of cisplatin (Platinol), doxorubicin (Adriamycin), cyclophosphamide and etoposide (D-PACE) has been studied in patients with relapsed and refractory MM. Response rates of approximately 50% have been reported.^{2,3} Toxicity is common with up to 98% of patients experiencing at least one treatment-related adverse event, although fewer patients experience

severe adverse events as defined by the National Cancer Institute's CTCAE (CTCAE grade 3–5).⁷ Cardiac toxicity is less common with only 11% of patients experiencing congestive heart failure or volume overload in one study.³ Despite a reasonable response rate to treatment, median progression-free survival is short, suggesting that D-PACE should be used as a bridge to definitive therapy such as stem cell transplantation. Given this patient's initial response to D-PACE in the setting of advanced disease, it may be reasonable to consider D-PACE as an option for treating cardiac EMPs.

In summary, cardiac EMP is a rare complication of MM. Although little is known about optimal treatment of cardiac EMPs, this case suggests that D-PACE may be considered as a potential chemotherapeutic option in the setting of advanced disease in select patients. However, adjunct or definitive therapies will likely be required for adequate treatment due to short progression-free survival and/or toxicity. Therapeutic benefit versus the risk of toxicity must be weighed on a case-by-case basis to determine the best treatment in patients presenting with this rare entity.

Learning points

- ▶ Cardiac extramedullary plasmacytoma is a rare complication of multiple myeloma
- ▶ Cardiac extramedullary plasmacytoma should be considered patients with multiple myeloma who present with congestive heart failure or cardiac tamponade
- ▶ D-PACE (dexamethasone, cisplatin (Platinol), doxorubicin (Adriamycin), cyclophosphamide, and etoposide) may be considered as salvage therapy in cases of advanced multiple myeloma but it can also be cardiotoxic.

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