

## Clinical Case Report

# A plasma cell-based pericardial effusion leading to tamponade in a patient with multiple myeloma – a case report and review of the literature<sup>☆</sup>

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## ABSTRACT

A rare case of extramedullary multiple myeloma causing cardiac tamponade secondary to a plasma cell-based pericardial effusion is described. A systematic search using PubMed (National Library of Medicine) was used to identify a further 27 cases dating back to 1970. Case characteristics, treatment strategies, and survival time following tamponade are discussed. Linear regression demonstrated a weak but statistically significant correlation between survival time following tamponade and treatment with systemic chemotherapy and steroids ( $\beta=16.8$  weeks,  $P=.009$ ). However, this manifestation of extramedullary multiple myeloma still conveys a dismal prognosis with a median survival following tamponade of only 6 weeks based on our review.

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## 1. Introduction

Multiple myeloma (MM) is an atypical plasma cell disorder of the bone marrow that comprises approximately 10% of all hematologic cancers [1]. Extramedullary disease occurs 6–20% of the time and generally confers a poorer prognosis [2]. Cardiac and pericardial involvement has been documented in the literature; however, this type of extramedullary disease remains a rare entity. Additionally, when cardiac or pericardial involvement does occur, the progression to cardiac tamponade occurs >60% of the time [3,4]. Here, we describe a rare case of a plasma cell-based pericardial effusion leading to cardiac tamponade in a patient with known multiple myeloma. The paucity of described cardiac extramedullary disease in MM, specifically regarding the development of cardiac tamponade, warrants careful review of the management and diagnostic strategies employed during these rare cases to benefit future patients afflicted by this condition and possibly develop consensus-based therapies.

## 2. Materials and methods

A PubMed search was undertaken using various combinations of the keywords and phrases, “multiple myeloma”, “cardiac tamponade”, “pericardial effusion”, “plasmacytoma”, “plasma cell”, “extramedullary”, and “malignant effusion”. These articles were reviewed, along with their references, and only those with cytology-proven evidence of plasma cells in the pericardial aspirate were included. In addition, we only included articles in which the patients had a definitive diagnosis of cardiac tamponade. From 1970 to the present, we were able to identify 27 cases of cardiac tamponade secondary to plasma cell-based malignant effusions.

Two-sample *t*-tests, one-way ANOVA, and linear regression were used for various hypotheses testing as described below in section 4. Statistical significance was considered with  $P<.05$ .

## 3. Case description

A 78-year-old female with known MM presented to the emergency department (ED) with bilateral lower extremity weakness, decreased urine output, and progressively worsening dizziness for 1 week. Other pertinent medical history included paroxysmal atrial fibrillation, type 2 diabetes mellitus, hypertension, and hypothyroidism.

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Regarding her MM history, she had been diagnosed with ISS (International Staging System) stage II MM 3 months prior and had just finished her 8th cycle of bortezomib, cyclophosphamide, and dexamethasone (VCD) therapy on the day of presentation. Bone marrow biopsy and aspirate showed hypercellular marrow with 80% involvement by plasma cells, predominantly immature cells. Chromosomal studies showed 48, XX on karyotyping, and FISH testing showed gain of 1q21, deletion 13, and tetrasomy 9, 11, 15. Further workup revealed a serum IgG kappa monoclonal spike. Interestingly, 1 month prior to her formal diagnosis of MM, she had undergone a cholecystectomy and the pathology report documented the presence of plasmacytoma in the wall of her gallbladder; her predominant symptoms of rib pain did not develop until 1 month later, suggesting that she already had extramedullary disease at the time of diagnosis.

Upon arrival to the ED, the patient was afebrile and tachycardic into the 120s with initial blood pressure of 106/66. Physical exam revealed a cachectic-appearing female with distant heart sounds, dyspnea with clear lung fields, and 3+ pitting edema in her lower extremities bilaterally. An EKG showed atrial fibrillation with rapid ventricular response and appreciable electrical alternans, best seen in the pre-cordial leads.

Her constellation of symptoms and physical exam findings prompted a bedside echocardiogram which demonstrated a large, circumferential pericardial effusion with right ventricular diastolic collapse consistent with cardiac tamponade (Fig. 1).

At this time, she was immediately taken to the catheterization lab where she underwent pericardiocentesis with drainage of 920 mL of sanguineous fluid. A pericardial drain was placed and there was minimal bloody discharge overnight. After pericardiocentesis, she had normalization of her heart rate and blood pressure and repeat transthoracic echocardiograms at 1 day, 3 days, 32 days, 43 days, and 50 days did not show any evidence of fluid re-accumulation. Cytology of the pericardial fluid demonstrated abundant monoclonal plasma cells that were kappa light chain restricted (Fig. 2). No further cardiac interventions were performed at our institution.

Although her dizziness had resolved post-pericardiocentesis, her bilateral lower extremity weakness continued to progress, and she also had worsening urinary retention. A T-spine MRI revealed an enhancing epidural mass from T6-T9 with anterior cord compression and accompanying edema. She subsequently underwent T6-T10 posterior decompressive laminectomies with debulking of the mass and T6-T10 posterior fusion. Cytology of the mass demonstrated a plasmacytoma with anaplastic features. Due to continued back pain and lower extremity weakness following her laminectomy, she also underwent 11 sessions of palliative external beam radiation.

A final and unfortunate part of her hospital course was the development of obstructive jaundice. An abdominal ultrasound revealed a hypoechoic pancreatic head mass and a CT abdomen showed a 5.2×4.2×4.8 cm heterogenous contrast-enhancing mass in the head of

the pancreas. The mass was not biopsied during this hospitalization. Following the discovery of the pancreatic mass, the patient was transferred to another facility for a second opinion. However, shortly afterwards, the family elected for supportive care and she passed away a total of 5.4 months from the date of MM diagnosis and 9.4 weeks following her tamponade event.

Of note, her VCD chemotherapy regimen was stopped at the time of admission. She did not receive any further systemic or local chemotherapy following her pericardiocentesis. In addition, there was no pericardial radiotherapy or other interventions regarding her malignant effusion. Following her laminectomies, she was put on dexamethasone until the time of discharge.

#### 4. Results

The results of our literature review are summarized in Table 1. There were 28 cases in total, including our reported case. The mean age at presentation was 61.5 (range 30–83); 13 (46%) were female and 15 (54%) were male. Specific immunoglobulin isotypes among those available (25) were 11 IgA (44%), 2 IgD (8%), 10 IgG (40%), and 2 IgM (8%).

Among patients with a MM diagnosis prior to presentation (24), the median time from diagnosis to cardiac tamponade was 18 months (mean 34.0, range 0.5 to 180). There was no significant difference regarding time from diagnosis to cardiac tamponade between males and females (35.1 vs. 32.4,  $P=.89$ ). One-way ANOVA testing using Ig subtype as a predictor variables for time from diagnosis to cardiac tamponade showed no significant differences among Ig subtypes ( $F=0.70$ ,  $P=.57$ ). A simple linear regression was performed using year of case report publication as a predictor variable and time from diagnosis to cardiac tamponade as a response variable, however, no significant correlation was observed ( $\beta=0.60$  months,  $P=.40$ ).

Two patients (7.1%) had primary extramedullary plasmacytomas and negative bone marrow aspiration studies. Solid organ involvement was only recorded with evidence of biopsy-proven plasmacytomas; pericardial infiltration was the most common manifestation, occurring in 10 patients (36%). Atrial masses were the next most common (21%), followed by myocardial infiltration (14%), pancreas (7%), lung (7%), testes (7%), liver (3%), kidney (3%), breast (3%), spinal cord (3%) and gallbladder (3%). Only one of the patients had concomitant AL amyloidosis as demonstrated by the presence of small amounts of AL amyloid in the pericardial membrane [5].

Among patients where there was a reported death (19), the median survival time after tamponade was 6 weeks (mean 11.5, range 0.0–39.1). Among patients who were alive at the time of reporting (9), the median period of reported survival from tamponade was 17 weeks (mean 41.4, range 2–152). There was no significant difference in time between those with reported deaths and those with reported survival (11.5 weeks vs. 41.4 weeks,  $P=.12$ ). The most common cause

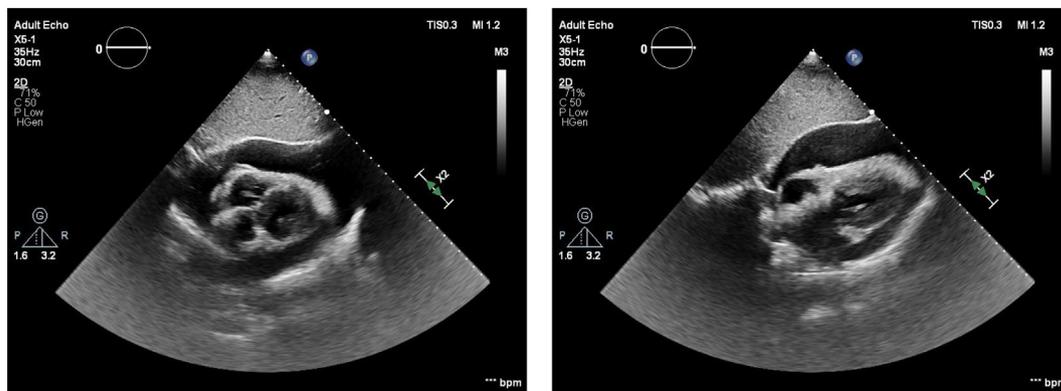
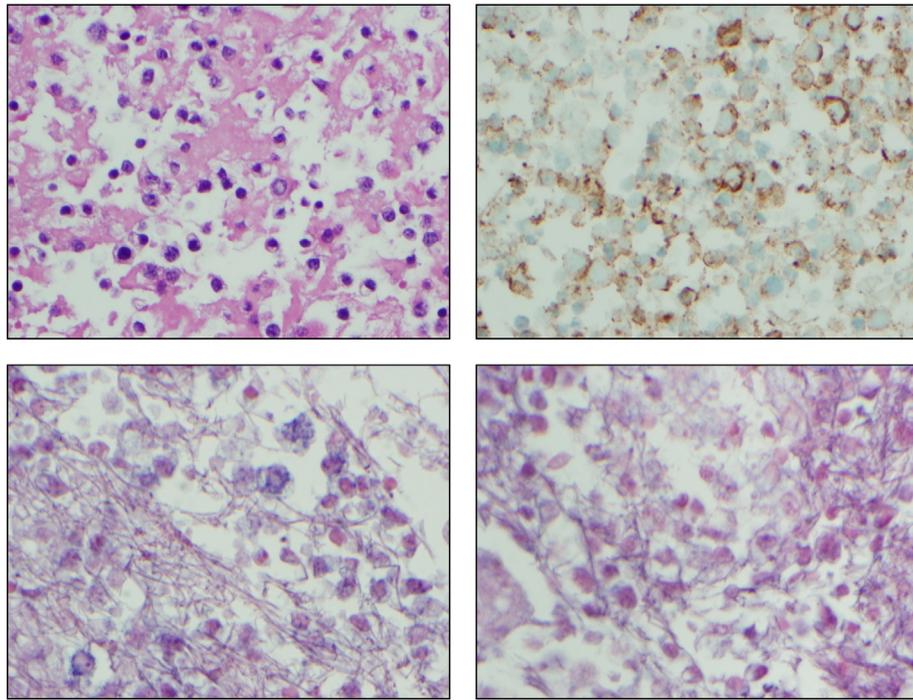


Fig. 1. Transthoracic echocardiography demonstrating a large, circumferential pericardial effusion with right ventricular diastolic collapse.



**Fig. 2.** Presence of monoclonal kappa light chain-restricted plasma cells in pericardial aspirate. Top left: H&E staining of pericardial aspirate at 40× magnification; Top right: CD138 immunohistochemical staining of cell block demonstrating brown reactivity and presence of plasma cells; Bottom left: Kappa light chain tissue in situ hybridization demonstrating kappa light chain reactivity; Bottom right: Lambda light chain tissue in situ hybridization demonstrating a lack of lambda light chain reactivity.

of death in those reported was progressive disease (42%), followed by pneumonia (21%), cardiac tamponade (16%), sepsis (11%), pulmonary embolism (5%), and cardiac arrest (5%).

Among patients with reported deaths, there was no significant difference in time from tamponade to death between males and females (11.8 weeks vs. 11.0 weeks,  $P=.89$ ). In addition, there was no significant

**Table 1**  
Characteristics of reported cases

Case	Age	Sex	MM Hx	Solid Organ Involvement	Ig	Treatment before tamp	Treatment after tamp	PRT	Survival	COD
Ours	78	F	3.2 m	Spinal cord, gallbladder	IgGκ	Chemo	Pcs, CS	N	9.4 w	PD
1 [6]	39	F	51 m	N/A	IgAλ	Chemo, HSCT	Pcs, chemo	N	> 82 w	N/A
2 [4]	61	F	9 m	N/A	IgA	Chemo, HSCT	Pcs, chemo	N	17.2 w	PD
3 [7]	79	F	N/A	AM (R, L)	IgAλ	N/A	Chemo, RT	N	> 152 w	N/A
4 [8]	45	F	157 m	Breast, AM (R)	IgM	Chemo, RT, HSCT	PcW, chemo	N	> 75 w	N/A
5 [9]	83	F	15 m	N/A	N/A	Chemo	Pcs	N	3 w	PD
6 [10]	68	M	59 m	AM (R, L)	IgA	Chemo	Pcs, chemo	Y	> 7 w	N/A
7 [11]	55	M	42 m	N/A	IgAκ	CS, chemo, HSCT	Pcs, CS	N	6 w	PNA
8 [12]	72	M	72 m	PI	IgGκ	Chemo	Pcs, PcW, chemo	N	> 26 w	N/A
9 [13]	53	F	1° EMP	Lung, PI, AM (R)	IgD	N/A	Pcs, chemo	N	> 6 w	N/A
10 [3]	73	F	12 m	N/A	IgG	Chemo	Pcs, CS	N	39.1 w	PD
11 [3]	69	F	18 m	PI	IgG	N/A	Pcs, PcW, chemo	N	15 w	Sepsis
12 [14]	76	M	36 m	AM (R, L), testes	IgAλ	Chemo	Pcs	Y	>6 w	N/A
13 [15]	48	F	36 m	N/A	IgA	Chemo, HSCT	Pcs	N	0.3 w	Tamp
14 [15]	30	M	0.5 m	PI	IgMκ	Chemo	Pcs	N	0.1 w	Arrest
15 [16]	74	M	1° EMP	AM (R, L), lung	IgAκ	N/A	Pcs, chemo	Y	15 w	PD
16 [17]	78	M	0.7 m	PM	IgGλ	Chemo	Pcs, IPI, chemo	N	26 w	PNA
17 [5]	39	M	3 m	PI	IgAκ	Chemo	Pcs (x2), PcW, colchicine	N	> 2 w	N/A
18 [18]	71	M	180 m	PI	IgGκ	Chemo, RT	Pcs, IPI	N	3 w	Sepsis
19 [18]	70	M	3 m	PI	IgD	RT, chemo	Pcs, IPI, chemo	N	6 w	PNA
20 [19]	56	M	36 m	PM	IgG	Chemo	Pcs, PcW, CS	Y	12 w	PNA
21 [20]	67	M	10 m	N/A	IgAλ	Chemo	Pcs, IPI	N	2 w	PE
22 [21]	66	M	6.4 m	PI	IgGκ	Chemo	Pcs, IPI, chemo	N	30.4 w	PD
23 [22]	42	M	21 m	MI	N/A	Chemo, RT	Pcs (x2), IPI, chemo	Y	29.7 w	PD
24 [23]	71	F	N/A	N/A	IgG	N/A	Pcs, chemo	Y	> 17 w	N/A
25 [24]	50	F	18.2 m	MI, PI, pancreas, liver, kidney	IgG	Chemo	Pcs (x2), PcW	N	4.1 w	PD
26 [25]	66	F	4.6 m	MI, PI	N/A	Chemo	N/A	N	0 w	Tamp
27 [26]	43	M	22 m	MI, pancreas, testes	IgA	RT, chemo	Pcs	N	0 w	Tamp

Abbreviations: MM Hx, time from MM diagnosis to cardiac tamponade; Ig, immunoglobulin subtype; tamp, cardiac tamponade; PRT, pericardial radiotherapy; Survival, time from cardiac tamponade to death. Values with > symbol indicate time from tamponade to known survival at time of report; COD, cause of death; m, months; w, weeks; chemo, chemotherapy; Pcs, pericardiocentesis; CS, corticosteroid; PD, progressive disease; N/A, not reported; HSCT, hematopoietic stem cell transplant; AM, atrial mass; R, right atrium; L, left atrium; RT, radiotherapy; PcW, pericardial window; PNA, pneumonia; 1° EMP, primary extramedullary plasmacytoma; PI, pericardial infiltration; PM, pericardial mass; IPI, intrapericardial injection; MI, myocardial infiltration.

difference in time from tamponade to reported survival between males and females (10.2 weeks vs. 66.4 weeks,  $P=.10$ ). Linear regression was performed using age and MM history (as defined in Table 1) as predictor variables for both time from tamponade to death and time from tamponade to reported survival, but no significant associations or interactions were observed. One-way ANOVA tests were performed using Ig subtypes as predictor variables for both time from tamponade to death ( $F=1.54$ ,  $P=.26$ ) and time from tamponade to reported survival ( $F=0.34$ ,  $P=.80$ ); once again, no significant differences were observed based on Ig subtype.

Treatment after MM diagnosis prior to cardiac tamponade was variable between patients. Treatment consisted of various combinations of systemic chemotherapy, corticosteroids, radiotherapy, and hematopoietic stem cell transplantation (HSCT). Please see Appendix A for details regarding specific chemotherapeutic regimens. 86% (24/28) patients received systemic chemotherapy following their diagnosis of MM prior to cardiac tamponade. Eighteen percent (5/28) received radiotherapy and 18% (5/28) received HSCT. The two most common chemotherapeutic agents used were melphalan (54%; 15/28) and cyclophosphamide (29%; 8/28) either alone or in combination with other agents. The two most common chemotherapeutic regimens used were VAD (14%; 4/28) and VCD (11%; 3/28). Corticosteroids were used in combination with other agents in 21 of the 28 cases (75%); there were no cases where corticosteroids were used alone. Multivariate linear regression was performed using systemic chemotherapy, radiotherapy, and HSCT as predictor variables and time from MM diagnosis to tamponade as a response variable. Radiotherapy appeared to be a weak but significant predictor ( $\beta=54.3$  months,  $P=.012$ ). Systemic chemotherapy ( $\beta=-2.1$  months,  $P=.96$ ) and HSCT ( $\beta=32.3$  months,  $P=.13$ ) did not appear to be significant predictors. The overall model fit was  $R^2_{\text{adj}}=0.32$ . A separate interaction analysis did not reveal any significant interactions between the variables.

Treatment after tamponade consisted of various combinations of pericardiocentesis, pericardial windows, corticosteroids alone, chemotherapy, radiotherapy, and intrapericardial injections. Please see Appendix A for specific agents used. Eighty-nine percent (25/28) had pericardiocentesis performed following their tamponade event and 21% (6/28) had pericardial windows. Fourteen percent (4/28) were treated with corticosteroids alone and 50% (14/28) were treated with systemic chemotherapy and corticosteroids. Twenty-one percent (6/28) underwent pericardial radiotherapy, and 21% (6/28) had pericardial

injections using various cytotoxic or sclerosing agents. There was also a single case where colchicine was used following two rounds of pericardiocentesis and creation of a pericardial window. Multivariate linear regression was performed using treatment with corticosteroids alone, treatment with systemic chemotherapy and corticosteroids, pericardial radiotherapy, creation of pericardial window, and intrapericardial injection as predictor variables and time from tamponade to death as the response variable. Corticosteroids alone ( $\beta=16.1$  weeks,  $P=.02$ ) and systemic chemotherapy with corticosteroids ( $\beta=16.8$  weeks,  $P=.009$ ) appeared to be weak but significant predictors while pericardial radiotherapy ( $\beta=0.73$  weeks,  $P=.91$ ), pericardial window ( $\beta=-1.6$  weeks,  $P=.80$ ), and intrapericardial injection ( $\beta=4.1$  weeks,  $P=.46$ ) did not appear to be significant predictors. The overall model fit was  $R^2_{\text{adj}}$  of 0.40. A separate interaction analysis did not reveal any significant interactions between the variables. In addition, the same predictor variables were modeled with time from tamponade to reported survival as a response variable, and no significant correlations or interactions were observed.

A final simple linear regression was performed using year of case report publication as a predictor variable and time from tamponade to death as a response variable, but no significant correlation was observed ( $\beta=0.20$  weeks,  $P=.34$ ). In addition, no correlation was observed when using time from tamponade to reported survival as a response variable ( $\beta=2.2$  weeks,  $P=.19$ ).

## 5. Discussion

Here we present an elderly female with multiple myeloma and clear evidence of extramedullary disease as demonstrated by the presence of plasma cells in her pericardial fluid as well as plasmacytomas in her spinal cord and gallbladder wall. It is unclear whether or not the pancreatic mass discovered late in her hospitalization was also plasmacytoma-based, but this would certainly not be unexpected given her advanced stage of disease [26,27] and the presence of plasmacytoma infiltrate of her gallbladder wall 1 month prior to diagnosis.

Pericardial effusions are a rare manifestation of metastatic extramedullary multiple myeloma and are seen in <1% of cases [3]. Progression to cardiac tamponade is an even rarer complication and has only been described in the literature in 27 previous patients, 28 including our index case (Table 1). Unfortunately, the presence of plasma cells in the pericardial aspirate is associated with a poor

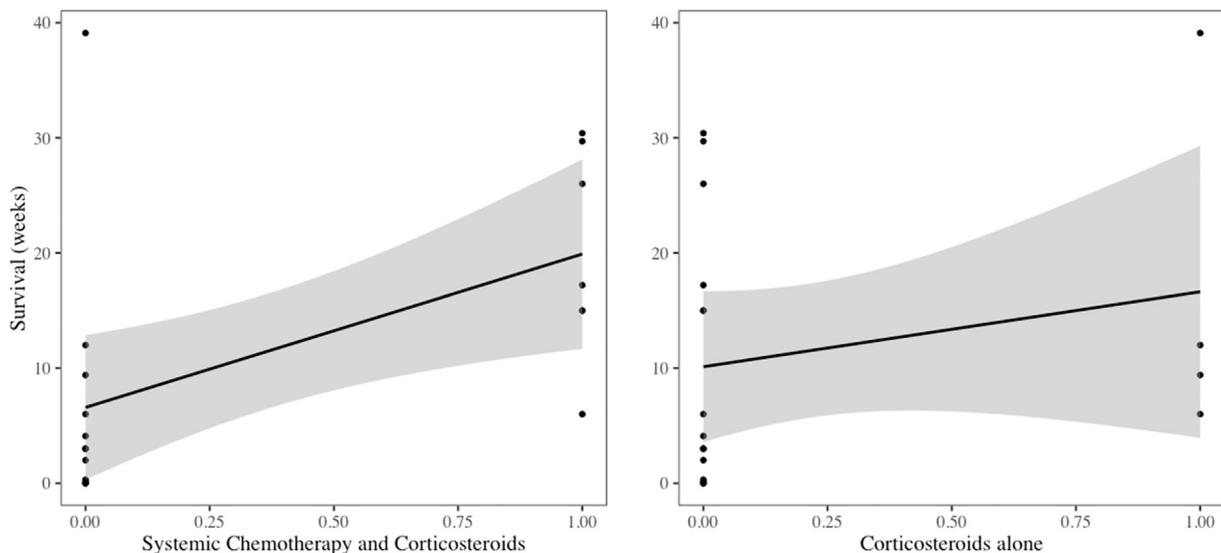


Fig. 3. Plots of corticosteroids alone and systemic chemotherapy with corticosteroids vs. survival following tamponade.

prognosis – an average survival of 14.25 weeks (median 13 weeks) was calculated during one case series [3]. A more recent case series showed that 57.5% of these patients died within 15 months of presentation [4]. Our data show even poorer outcomes with an average survival of only 11.5 weeks (median 6 weeks) and 67.9% of patients (19/28) dying within 9 months of presentation; the remaining 9 patients were still alive at the time of reporting. These data suggest that the presence of cardiac tamponade may be an even more dismal prognostic indicator than the presence of plasma cell-based malignant effusions alone.

Regarding management of the disease, there is no current consensus as this remains a rare entity. Symptomatic drainage via pericardiocentesis or through creation of a pericardial window are commonly advised with cytologic analysis recommended due to its prognostic significance [15]. Treatment beyond drainage has included combinations of chemotherapy and steroids, chemotherapy or steroids alone, pericardial radiation therapy, and intrapericardial injection of sclerosing/chemotherapeutic agents, with mixed results. Our data show a weak but significant correlation between survival following tamponade and use of corticosteroids alone or use of systemic chemotherapy with corticosteroids (Fig. 3). In addition, there is a single case report documenting complete resolution of a plasma cell-based cardiac tamponade using colchicine in a patient with concomitant AL amyloidosis [5]; the effusion was initially refractory following 2 rounds of pericardiocentesis and creation of a pericardial window. However, the follow-up period was only 2 weeks, so there are no data available regarding the long-term outcome. Due to the lack of clinical guidelines, all of these interventions were performed at the discretion of the attending providers. In addition, the poor prognosis at this stage of disease combined with its rarity has not produced enough consistent data to date to objectively evaluate the efficacy of such treatments in a controlled manner. It is therefore imperative that accurate documentation of cardiac and pericardial extramedullary plasmacytomas and their treatment interventions continue to be described in the medical literature. Coakley et al. [4] recommended that the cardiology and hematology communities form a standardized database of cardiac and pericardial extramedullary plasmacytomas to address this gap in knowledge as our imaging and medical record systems become more sophisticated and comprehensive.

**6. Conclusion**

Although this manifestation of multiple myeloma is exceedingly rare, the incidence is likely to increase in the coming decades due to the increasing proportion of the aging population in the U.S. who will be at risk for developing multiple myeloma and its extramedullary complications [28]. In addition, the potential lethality of cardiac tamponade in the setting of a plasma cell-based pericardial effusion warrants further investigation of therapeutic interventions and their efficacy due to both the acute effects of tamponade and its status as a poor prognostic indicator in longitudinal management of the disease. Our data demonstrate a weak but significant association between survival and use of corticosteroids or chemotherapy with corticosteroids, so these interventions may be effective in prolonging life. However, considering that life expectancy following tamponade is still on the order of months regardless of intervention, it remains a very poor prognostic indicator and palliative care should be considered when discussing goals of care with these patients.

**Conflict of interest**

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

**Appendix A. Specific chemotherapeutic agents used during treatment**

Case	Treatment before tamponade	Treatment after tamponade
Ours	VCD	Pcs, CS
1	PAD, M, HSCT, RD, VCD, VBCMP/VBAD	Pcs, carfilzomib and dexamethasone
2	VCD, M, HSCT	Pcs, RVD
3	N/A	Bortezomib, MP, RT
4	VAD, RT, BU/CY, HSCT, RT	PcW, bortezomib, dexamethasone, cyclophosphamide
5	MP	Pcs
6	VAD, thalidomide, milatuzumab, bortezomib, doxorubicin, dexamethasone	Pcs, dexamethasone, bortezomib, lenalidomide, cyclophosphamide
7	CS, etoposide, ifosfamide, HSCT, fludarabine, carmustine, M	Pcs, CS
8	MP	Pcs, PcW, cyclophosphamide, adriamycin, dexamethasone
9	N/A	Pcs, VCMP
10	MP	Pcs, CS
11	N/A	Pcs, PcW, vincristine, adriamycin, dexamethasone
12	MP	Pcs
13	MP, VAD, HSCT	Pcs
14	VAD	Pcs
15	N/A	Pcs, “chemotherapy”
16	CHOP	Pcs, intrapericardial cisplatin and betamethasone, CHOP
17	c-VAMP, M, thalidomide	Pcs (x2), PcW, colchicine
18	“various cytotoxic regimens,” RT	Pcs, intrapericardial cyclophosphamide
19	RT, VCMP	Pcs, intrapericardial cyclophosphamide, VAD
20	MP, interferon	Pcs, PcW, CS
21	MP, vincristine, cyclophosphamide, carmustine, doxorubicin	Pcs, intrapericardial bleomycin
22	MP	Pcs, intrapericardial dexamethasone, VAD
23	MP, interferon, RT	Pcs (x2), intrapericardial OK-432, POP
24	N/A	Pcs, MP
25	Cyclophosphamide, prednisone	Pcs (x2), PcW
26	M	N/A
27	RT, MP, cyclophosphamide	Pcs

VCD, Vincristine, doxorubicin, dexamethasone; Pcs, pericardiocentesis; CS, corticosteroids; PAD, bortezomib, adriamycin, dexamethasone; M, melphalan; HSCT, hematopoietic stem cell transplant; RD, lenalidomide, dexamethasone; VBCMP/ VBAD, vincristine, carmustine, cyclophosphamide, melphalan, prednisone/vincristine, carmustine, doxorubicin, and high-dose dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone; N/A, no treatment reported; MP, melphalan, prednisone; RT, radiotherapy; VAD, Vincristine, doxorubicin, dexamethasone; BU/CY, busulfan, cyclophosphamide; PcW, pericardial window; VCMP, Vincristine, cyclophosphamide, melphalan, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; c-VAMP, cyclophosphamide, doxorubicin, vincristine, methylprednisone; OK-432, picibanil; POP, peplomycin, vincristine, prednisolone.

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