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Original Research

Etiology of pulmonary hypertension in multiple myeloma: A case series and literature review

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A B S T R A C T

Background: Multiple myeloma is often complicated by pulmonary hypertension through a variety of mechanisms. These mechanisms include pulmonary hypertension (PH) due to concomitant cardiac amyloid, high output heart failure due to anemia or lytic bone lesions, chronic thromboembolic pulmonary hypertension (CTEPH), toxicity from medications to treat multiple myeloma, and congestive heart failure. This case series highlights the various mechanisms through which multiple myeloma patients develop pulmonary hypertension.

Objectives: To identify the etiologies of pulmonary hypertension and their management among multiple myeloma patients treated at University of California San Diego.

Methods: A retrospective chart review was performed to identify patients with multiple myeloma and pulmonary hypertension who were evaluated at the University of California San Diego between July 2013 and July 2021. Patients also required a right heart catheterization to be included. Demographics, comorbidities, clinical course, and etiology of pulmonary hypertension were obtained from chart review.

Results: There were 11 patients included. Of the 11 patients described, two had PH due to cardiac amyloid, one had PH due to high output heart failure, one had PH due to CTEPH, two had pulmonary arterial hypertension due to medications (carfilzomib), and five had PH due to congestive heart failure. The right heart catheterization and echocardiogram findings of the various mechanisms of PH in multiple myeloma are described.

Conclusions: Pulmonary hypertension in multiple myeloma is a common finding that necessitates further evaluation. The initial evaluation should include an echocardiogram and thorough medication review. Further diagnostic testing should be guided by the patient's history and can include right heart catheterization, cardiac biopsy, ventilation-perfusion scan, and bone scan.

1. Introduction

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells, and represents over 18% of all hematological malignancies, with over 34,000 new diagnoses of multiple myeloma in 2021 [1]. Despite being a primarily hematological disease, multiple myeloma can affect many organ systems, including the pulmonary circulation and cardiovascular system. However, there has been limited data describing patients with multiple myeloma who develop pulmonary hypertension.

Pulmonary hypertension (PH) is defined by elevated pressures in the pulmonary vasculature (mean pulmonary artery pressure greater than or equal to 20 mmHg) and is categorized into five groups based on etiology by the World Health Organization: pulmonary arterial hypertension (PAH, Group 1), PH due to left heart disease (Group 2), PH due to lung disease/hypoxia (Group 3), chronic thromboembolic pulmonary hypertension (CTEPH, Group 4), and PH due to multifactorial mechanisms (Group 5) [2]. Patients with multiple myeloma are at risk for PH in all five groups but this is not well defined.

It has been theorized that patients with MM develop PH at greater rates than the general population. Prior studies have shown between 27 and 32% of patients newly diagnosed with MM had echocardiographic evidence of PH at the time of diagnosis [3,4]. This is in contrast to much lower rates of PH seen with other comorbidities. For example, one recent review of over 50,000 patients found that PH was present in only 3.6% of people with left heart disease, 0.7% with lung disease, and 1.4% with thromboembolic disease, indicating that it is a relatively rare complication of these common diseases [5].

It is unclear why patients with multiple myeloma have a higher incidence of PH than the general population but proposed etiologies include cardiomyopathy related to MM, thrombophilia in MM leading to CTEPH, and adverse effects from chemotherapeutics (dasatinib, carfilzomib) used in MM which can cause PAH [3]. Additionally, AL amyloid complicates up to 15% of MM cases, with cardiac involvement occurring

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in at least 50% of these patients which can manifest as heart failure [6]. Patients with MM are also at risk for high-output heart failure which is thought to be secondary to multiple arteriovenous fistulas in the setting of extensive bony involvement which could also lead to group 2 PH [6]. Most of these prior studies do not include right heart catheterization data, except for one small series of three patients [3,6]. Our case series aims to characterize the etiologies of pulmonary hypertension in multiple myeloma and determine treatment course and prognosis of PH in multiple myeloma.

2. Methods

The Institutional Review Board at University of California, San Diego approved this study. Patients were identified through a retrospective chart review using a data extraction tool in the electronic health record. Adult patients (18 years old or greater) with multiple myeloma and pulmonary hypertension who were evaluated at the University of California San Diego Health between July 2013 and July 2021 were included (Fig. 1). We abstracted International Classification of Diseases, 9th Revision (ICD-9) and 10th Revision (ICD-10) diagnosis codes for multiple myeloma (C90.0), primary pulmonary hypertension (I27.0 or I27.21), and secondary pulmonary hypertension (I27.21). We also required completion of a right heart catheterization (ICD-9 37.21). Demographics, clinical laboratory data, medications, imaging, procedure results, and clinical course were obtained from the electronic medical record and compiled into a secure database for analysis.

The accuracy of ICD-9 and ICD-10 coding for multiple myeloma and pulmonary hypertension was assessed by manual chart review. Confirmation that patients met all inclusion criteria was by review of provider progress or clinic notes, laboratory or biopsy reports, and procedure notes.

3. Results

A total of 62 patients resulted from the initial query in the electronic medical record for patients with an ICD-9 or 10 code for multiple myeloma, pulmonary hypertension, and right heart catheterization (Fig. 1). Of these 62 patients, we excluded 4 patients due to normal pulmonary pressures, 4 due to diagnosis of smoldering multiple myeloma, one with monoclonal gammopathy of unclear significance (MGUS), one who died before bone marrow biopsy confirmation of multiple myeloma diagnosis, one who had a right heart catheterization to place a watchman device and hemodynamic measurements pressures were not obtained, and 40 patients who did not have multiple myeloma. It is unclear why 40 patients without multiple myeloma were classified by diagnostic codes to have the disease. However, on chart review, many of these patients had similar diagnoses (e.g., amyloid without multiple myeloma) and in the early stages of diagnostic work up, providers had coded various tests under the ICD-9 code of multiple myeloma. Ultimately, a total of 11 patients were determined to meet all inclusion criteria: the presence of multiple myeloma, pulmonary hypertension, and a right heart catheterization with measurement of intracardiac pressures (Fig. 1).

Of the 11 patients, two were categorized as having PH from cardiac amyloid, one had high output heart failure, one had chronic thromboembolic pulmonary hypertension (CTEPH), two had PAH due to carfilzomib, and five had congestive heart failure (Table 1). Both patients with concomitant multiple myeloma and cardiac amyloid underwent orthotopic heart transplant. One patient had improvement in pulmonary artery pressures following cardiac transplant, while the second patient had unchanged pulmonary artery pressures after transplant but experienced subjective improvement in dyspnea. One patient was determined to have high output heart failure from anemia and lytic bone lesions. This patient was treated with alendronate and multiple myeloma-specific therapies, with improvement in pulmonary hypertension. The patient with CTEPH was evaluated for pulmonary thromboendarterectomy (PTE) surgery but determined not to be a candidate due to severe cardiomyopathy with a low ejection fraction of 12%. The patient was therefore started on riociguat instead. Two patients developed pulmonary arterial hypertension after the initiation of carfilzomib for multiple myeloma treatment. Both patients experienced an improvement in pulmonary artery pressures after discontinuation of carfilzomib [7]. However, one patient required initiation of PAH-targeted therapy despite permanent discontinuation of carfilzomib. She also had multiple myeloma disease progression after discontinuation of carfilzomib and underwent a second autologous stem cell transplant. Of the five patients with pulmonary hypertension due to congestive heart failure, four had heart failure with preserved ejection fraction (HFpEF) and one had heart failure with reduced ejection fraction (HFrEF). The etiology of heart failure in the patient with heart

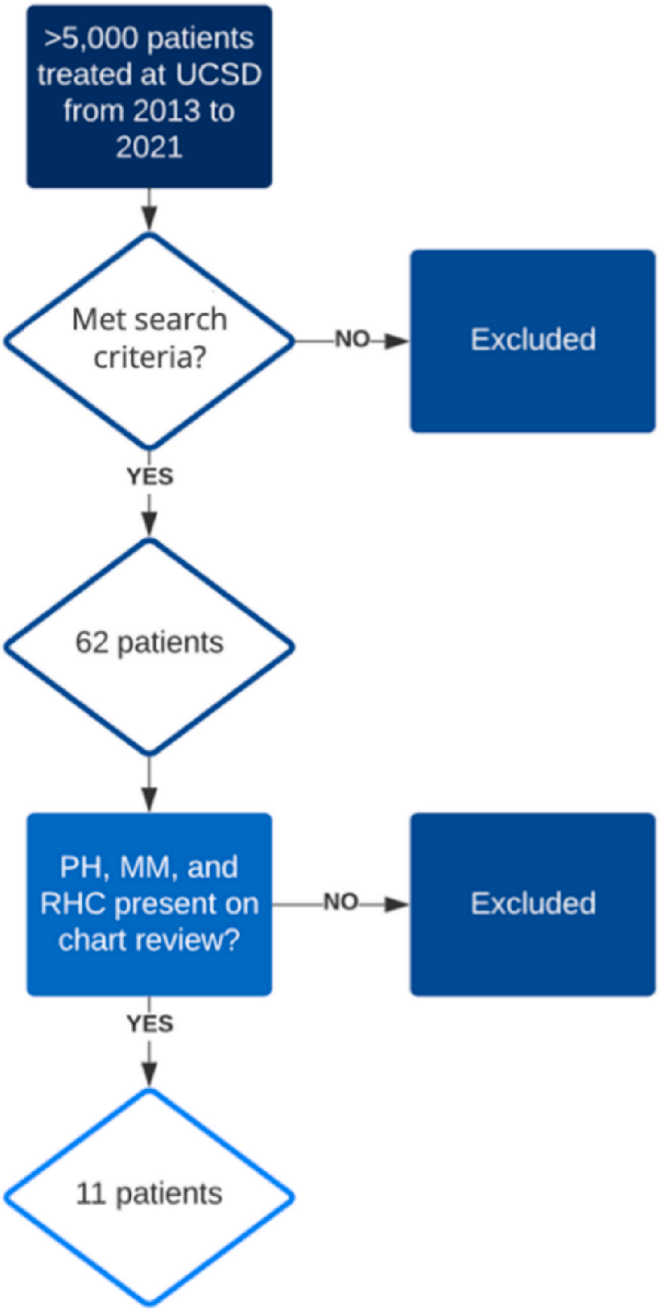

Fig. 1. Patient inclusion criteria. EMR search criteria included a diagnosis of pulmonary hypertension (PH), multiple myeloma (MM), and the presence of a right heart catheterization (RHC).

Table 1
Patients with pulmonary hypertension (PH) and multiple myeloma (MM) were categorized into groups 1–5 based on the World Health Organization (WHO) criteria. Etiology of PH, treatment, echocardiographic findings, and data from right heart catheterization are described above.

Patient #	WHO Group	Etiology of PH	Treatment	RVSP (mmHg)	LVEF	TAPSE (cm)	RA pressure (mmHg)	Systolic/ diastolic (Mean PAP) (mmHg)	PCWP (mmHg)	CO/CI (L/ min)/(L/ min/BSA)	PVR (WU)
1	1	Drug induced	PAH improved after carfilzomib discontinuation	120	67%	1.37	12	85/33 (52)	7	3.2/2.1	14.3
2	1	Drug induced	PAH improved after carfilzomib discontinuation	74	69%	1.38	1	39/14 (23)	7	3.6/2.3	4.4
3	2	HFpEF/severe COPD	Managed with diuretics	82	68%	1.1	12	78/34 (49)	16	4.4/2.4	8.2
4	2	High output heart failure	high output heart failure though to be due to significant anemia	39	48%	1.9	10	46/20 (34)	20	6.9/4.4	2.0
5	2	Amyloidosis	Received OHT, dyspnea resolved thereafter	48	35%	–	15	44/20 (28)	20	3.4/1.6	2.4
6	2	HFpEF	HFpEF thought to be due to longstanding HTN	60	64%	2.5	14	53/22 (35)	18	-/-	–
7	2	HFpEF	Managed with diuretics	58	65%	2.47	0	40/8 (21)	7	5.7/3.4	2.4
8	2	Amyloidosis	PH improved after OHT	83	48%	2.19	10	64/30 (42)	31	3.9/1.7	2.8
9	2	HFpEF	PH improved with diuresis	37	63%	1.64	6	32/14 (20)	13	5.0/3.1	1.4
10	2	HFrEF	Managed with diuretics, digoxin, metoprolol	63	14%	1.07	5	58/24 (36)	26	4.3/2.2	2.3
11	4	CTEPH	Not a candidate for PTE due to EF 12%, treated with riociguat	50	12%	2.22	10	50/30 (36)	–	3.8/1.7	9.5

failure with reduced ejection fraction was determined to be due to prior drug abuse. Many of the patients with HFpEF were thought to be due to long-standing hypertension. All five patients with congestive heart failure were treated symptomatically with diuretics with improvement.

To determine the timeline of development of pulmonary hypertension and multiple myeloma, the electronic medical record was reviewed

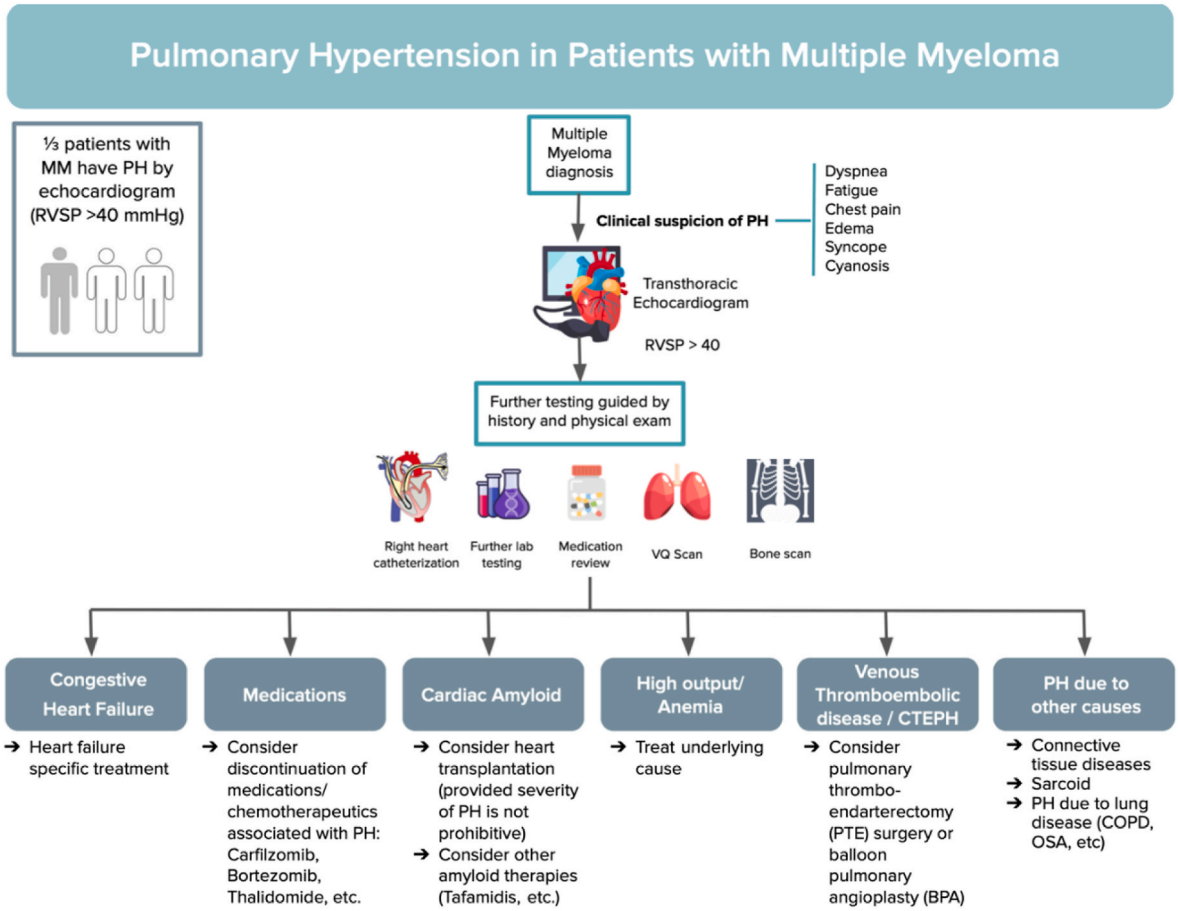

Fig. 2. Diagnostic diagram of patients with multiple myeloma in whom pulmonary hypertension (PH) is suspected. After diagnosis of pulmonary hypertension by echocardiogram, further testing is indicated to clarify the mechanism and severity of PH.

to determine if each patient had an echocardiogram or right heart catheterization before the date of multiple myeloma diagnosis. Four of the eleven patients did not have an echocardiogram or right heart catheterization before multiple myeloma diagnosis. One patient with CTEPH (WHO group 4) had existing pulmonary hypertension proven by right heart catheterization prior to multiple myeloma diagnosis. Both patients with likely medication-induced PAH due to carfilzomib had worsening pulmonary hypertension after multiple myeloma diagnosis. Four patients with WHO group 2 pulmonary hypertension due to left heart disease experienced either new or worsening pulmonary hypertension after multiple myeloma diagnosis.

4. Discussion

This case series highlights the different mechanisms by which patients with multiple myeloma develop pulmonary hypertension: pulmonary arterial hypertension due to chemotherapeutics (group 1), pulmonary hypertension due to left heart failure often from concomitant amyloidosis (group 2), pulmonary hypertension due to high output heart failure due to lytic lesions/anemia (group 2), and pulmonary hypertension due to CTEPH from thrombophilia (group 4). This case series is unique in that each patient with echocardiographic evidence of pulmonary hypertension and multiple myeloma received a right heart catheterization to characterize the etiology of pulmonary hypertension (Table 1). Based on previous studies, roughly one-third of patients newly diagnosed with multiple myeloma have concomitant pulmonary hypertension [3,4].

As demonstrated by this case series, determining not only the presence but also the etiology of pulmonary hypertension by right heart catheterization is essential as it has key implications for treatment (Fig. 2). Invasive hemodynamics allow for evaluation of the cardiac output, pulmonary artery pressures, and pulmonary capillary wedge pressure to help differentiate the various etiologies of pulmonary hypertension. As part of the work up for pulmonary hypertension in MM, patients should be screened for chronic thromboembolic pulmonary hypertension with a VQ scan as MM is associated with a very high risk for pulmonary embolism [8]. Additionally, a thorough medication review to identify medications associated with the development of PAH is needed in all MM patients with pulmonary hypertension.

4.1. Medication-induced PAH

In our case series, there were two patients with pulmonary arterial hypertension associated with therapy for MM. They both had improvement in PA pressures and symptoms with discontinuation of the offending medication (carfilzomib). Notably, several medications used in the treatment of multiple myeloma have been associated with PH, such as carfilzomib and dasatinib, as well as some monoclonal antibodies and immune regulators [7,9]. Dasatinib-induced PAH can improve with discontinuation of the medication, with one study finding improvement in NYHA functional class and pulmonary arterial pressures on repeat right heart catheterization [9]. However, roughly one-third of patients had persistent PAH even after discontinuation of dasatinib and required long-term targeted PAH therapies [10]. Two additional small case series have shown improvement in hemodynamics with discontinuation of carfilzomib [7,12]. However, similar to dasatinib-induced PAH, there were patients with persistent PAH despite permanent discontinuation of the offending medication. On the other hand, leflunomide is an immune modulator commonly used in multiple myeloma treatment regimens [11]. There have been reports of leflunomide being associated with PAH, but a recent series found pulmonary hypertension associated with leflunomide was rare and more common in patients with other PH risk factors.[11]

Recently published European Society of Cardiology guidelines on cardio-oncology recommend baseline echocardiography before starting therapy with proteasome inhibitors (carfilzomib) or dasatinib [13]. Long-term follow-up should be performed for all patients treated with therapeutics that are associated with the risk of PAH. Repeat echocardiography should be completed in patients who develop signs or symptoms suggestive of pulmonary hypertension or heart failure [13]. Drug-induced PAH in multiple myeloma may continue to grow in subsequent years as additional new chemotherapeutics are being developed for the treatment of multiple myeloma. When PH is identified in a patient with multiple myeloma, medication review is an important step to identify possible offending medications.

4.2. Cardiac amyloidosis

An important cause of PH in multiple myeloma patients is concomitant cardiac amyloid. Immunoglobulin light chain (AL) amyloid complicates up to 15% of multiple myeloma cases, with cardiac involvement occurring in at least 50% of these patients which can manifest as heart failure [6]. In these patients, misfolded immunoglobulin light chains are deposited as amyloid fibrils in the myocardium [14]. Echocardiographic features suggestive of amyloid include septal wall thickness >12 mm, profoundly decreased left ventricular tissue Doppler (e'<5 cm/s), reduced global longitudinal strain with apical sparing pattern [14,15]. The European Society of Cardiology (ESC) recommends obtaining serum and urine electrophoresis with immunofixation, serum free light chain ratio, and bone tracer cardiac scintigraphy (PYP scan) in patients with clinical suspicion of cardiac amyloidosis [16]. Cardiac scintigraphy reveals increased uptake of bone tracer in patients with cardiac ATTR amyloidosis, and is typically negative in patients with AL cardiac amyloid [16]. Patients with AL cardiac amyloid can be diagnosed either by positive endomyocardial biopsy or an extracardiac biopsy positive for amyloid and echocardiographic/cardiac MRI criteria [15].

Heart failure in patients with cardiac involvement of AL amyloid can lead to the development of group II PH (due to left heart failure). Identifying these patients early is critical, as the median survival from onset of heart failure is approximately 6 months [17]. It is important to note that newer cardiac amyloid therapies such as tafamidis are only to be used in the treatment of ATTR amyloid [16]. The treatment course for patients diagnosed with AL cardiac amyloid is complicated and should include a multidisciplinary team preferably at amyloid center of excellence [16]. Chemotherapy suppressing light chain production by plasma cells is the mainstay of treatment of AL amyloidosis. Selected patients could be candidates for cardiac or multi-organ transplantation [15]. Our series identified two patients with concomitant multiple myeloma and cardiac amyloid. In both of these patients, the cardiac amyloidosis manifested as heart failure and the diagnosis was confirmed with an endomyocardial biopsy. One patient initially had a fat pad biopsy which was negative for amyloidosis followed by a positive endomyocardial biopsy. The second patient had a cardiac MRI suggestive of cardiac amyloidosis and had a confirmatory endomyocardial biopsy. Both patients underwent a successful orthotopic heart transplant.

4.3. Heart failure (group II pulmonary hypertension)

In addition to infiltrative cardiomyopathies, congestive heart failure due to other etiologies is an important cause of group 2 PH in this subset of patients. Heart failure with reduced or preserved ejection fraction can lead to elevated left atrial pressure leading to post-capillary pulmonary hypertension [18]. Treatment for PH due to left heart failure consists of guideline-directed medical therapy for heart failure, and underlying etiologies. There have been various studies evaluating the use of PAH targeted therapies in group 2 PH, however no benefit has been found and some have shown harm. The patients in this series identified to have PH due to left heart failure were managed with diuretics and other heart failure-directed therapies.

Similar to the general population, there are many etiologies to consider when evaluating multiple myeloma patients with heart failure: ischemic cardiomyopathy, valvular heart disease, tachycardia-induced

cardiomyopathy, stress-cardiomyopathy, myocarditis, uncontrolled hypertension, endocrine abnormalities (hyperthyroidism), and others. We wanted to highlight two etiologies of left heart failure that are specifically linked to multiple myeloma: medication induced and high output heart failure.

1. Medication Induced Left Heart Failure

Left heart failure induced by proteasome inhibitors is an important and increasing etiology of heart failure in this subset of patients [19]. Carfilzomib as previously described is not only associated with the development of pulmonary arterial hypertension but is also associated with an increase in heart failure and arrhythmias [19]. The ENDEAVOR trial compared carfilzomib to bortezomib in 465 patients and found a significantly higher rate of cardiovascular complications in the carfilzomib group including hypertension (24.8% vs. 8.7%), cardiac failure (8.2% vs. 2.8), and ischemic heart disease (2.6% vs. 1.9%) [19]. In these patients, it is important to identify potential cardiac toxicities that may be contributing to the development of heart failure.

b. High Output Heart Failure

Another important cause of heart failure in multiple myeloma patients is high output heart failure commonly thought to be due to bone lytic lesions and severe anemia. Additionally, high output heart failure can be a rare presenting sign of multiple myeloma [21]. One patient in the series was discovered to have high output heart failure likely due to severe anemia in the context of multiple myeloma diagnosis. The anemia observed in multiple myeloma is thought to be multifactorial due to bone marrow infiltration and upregulation of hepcidin [22]. Hepcidin inhibits ferroportin leading to decreased iron absorption and anemia of chronic inflammation [22]. Patients with multiple myeloma have increased levels of IL-6 and BMP-2 (bone morphogenic protein 2) which both lead to the upregulation of hepcidin [23].

In addition to anemia, extensive bony involvement causing intramedullary arteriovenous fistulas is thought to contribute to high output heart failure in these patients [21,24]. One case series describes two cases of multiple myeloma that presented with high output heart failure [21]. Both of these patients were treated with anti-angiogenesis therapy of dexamethasone, lenalidomide, and thalidomide and experienced significant improvement in symptoms [21]. Identifying these patients who present with high output heart failure is important as they often fail to respond or can be harmed by traditional heart failure therapies (beta-blockers, diuretics, etc). Treatment of high output heart failure is to treat the underlying cause. In this case, this would involve treating underlying anemia and addressing hemodynamically significant intramedullary arteriovenous fistulas.

4.4. Chronic thromboembolic pulmonary hypertension

In addition to a right heart catheterization, several patients in the series received a VQ scan to evaluate for CTEPH as the underlying etiology of pulmonary hypertension. Multiple myeloma represents a hypercoagulable state, with venous thromboembolism (VTE) rate of approximately 7–10% in the first year [8,25]. When newer immunomodulatory derivatives such as thalidomide and lenalidomide are used, the reported VTE rate increases to as high as 14–26% per year [8]. Many factors are thought to contribute to the high VTE rate observed in MM including increased blood viscosity, high levels of immunoglobulin, procoagulant activity of monoclonal protein, and inflammatory cytokines [8]. The increased incidence of pulmonary embolism can contribute to the development of CTEPH. Although no patients in this series received pulmonary thromboendarterectomy (PTE) surgery to treat CTEPH, this would be a therapeutic option to explore for a patient with CTEPH from presumed thrombophilia in multiple myeloma. Another therapeutic option for a patient with CTEPH unable to undergo surgery would be to consider balloon pulmonary angioplasty [26].

Patients with multiple myeloma are more likely to develop pulmonary hypertension due to a variety of factors. These include thrombophilia predisposing to CTEPH, anemia, and bone lytic lesions leading to high output heart failure, concomitant cardiac amyloid, congestive heart failure, and medication induced PH. This case series highlights the high index of suspicion required to diagnose pulmonary hypertension in this subset of patients and the next steps to determine the etiology and treatment course.

4.5. Study limitations

A limitation of this study is the small number of patients included. Although 62 patients initially met the search criteria, upon chart review, many of these were incorrectly coded and did not meet the study inclusion criteria. Another limitation is the inability to determine a causal relationship between pulmonary hypertension and multiple myeloma due to the retrospective nature of this study. Further larger and prospective studies are needed to better classify this important association.

5. Conclusion

Pulmonary hypertension in multiple myeloma is a common finding due to a variety of contributing factors. Etiologies of pulmonary hypertension in multiple myeloma include medication induced, thrombophilia leading to CTEPH, concomitant cardiac amyloidosis, cardiomyopathy related to multiple myeloma, and high output heart failure. A high clinical index of suspicion is required to diagnose pulmonary hypertension. A diagnosis of pulmonary hypertension in a patient with multiple myeloma warrants further evaluation. The first steps include a thorough medication review, and basic laboratory evaluation with echocardiography, and can also include a right heart catheterization, VQ scan, bone tracer cardiac scintigraphy scan, cardiac MRI, and myocardial biopsy depending on the suspected underlying etiology.

CRediT authorship contribution statement

Taylor Desmarais: design of analysis, Data curation, Writing – original draft, Writing – review & editing, creation of figures. **Jenny Yang:** project conception and design of analysis, Data curation, Writing – review & editing, final approval of manuscript submitted. **Anna Narezkina:** design of analysis, Writing – review & editing, final approval of manuscript submitted. **Timothy Fernandes:** Conceptualization, design of analysis, Data curation, Writing – review & editing, final approval of manuscript submitted.

Declaration of competing interest

Disclosures: Anna Narezkina: consultant for Epsilon Imaging, Janssen, and Pharmacyclics; Timothy Fernandes: consultant for Bayer Pharmaceuticals; the remaining authors have nothing to disclosure.

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Further reading

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