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Capillary leak phenotype as a major cause of death in patients with POEMS syndrome

Kenzie Lee[1], Taxiarchis Kourelis[1], Marcella Tschautscher[1], Rahma Warsame[1], Francis Buadi[1], Morie Gertz[1], Eli Muchtar[1], David Dingli[1], Suzanne Hayman[1], Ronald Go[1], Lisa Hwa[1], Amie Fonder[1], Wilson Gonsalves[1], Miriam Hobbs[1], Robert Kyle[1], Prashant Kapoor[1], Nelson Leung[1,2], Moritz Binder[1], Joselle Cook[1], Yi Lin[1], Michelle Rogers[1], S. Vincent Rajkumar[1], Shaji Kumar[1] and Angela Dispenzieri[1]✉

Cause of death (COD) in POEMS (polyneuropathy, organomegaly, endocrinopathies, monoclonal protein and skin changes) syndrome is not well described. We investigated COD in patients with POEMS syndrome treated at Mayo Clinic between 2000 and 2022. Of the 89 deaths, 49 patients had known COD and were the subject of this study. Seventeen patients died of unrelated causes, while 32 patients (65%) died from causes related to POEMS syndrome including secondary malignancies like myelodysplastic syndrome and acute leukemia ($n = 5$) and complications from active therapy ($n = 5$). Notably, 19 patients died with a stereotypic syndrome we termed capillary leak phenotype (CLP), which was characterized by refractory ascites, effusions and/or anasarca that ultimately resulted in hypotension, renal failure and cardiopulmonary arrest. Alternate causes for these symptoms, such as cardiac and hepatic etiologies, were excluded. CLP as a COD was an earlier event with a median time from diagnosis to death of 2.5 years compared to 12.0 years for all other deceased patients ($p = <0.0001$). By definition, treatment of terminal CLP was unsuccessful with median survival of only 4 months after CLP onset. The driver of CLP is unknown, but recognition as an entity should allow for systematic study.

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INTRODUCTION

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathies, monoclonal protein and skin changes) is a rare paraneoplastic syndrome due to an underlying monoclonal plasma cell disorder. While the use of new myeloma-directed therapies and high-dose chemotherapy followed by autologous stem cell transplant (ASCT) has improved overall survival, there is still morbidity and mortality associated with POEMS syndrome [1]. The underlying pathogenesis of POEMS syndrome remains unclear, however there have been features associated with poorer prognosis. In 2017, Wang et al. identified age greater than 50 years, pulmonary hypertension, presence of pleural effusion and estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 as factors associated with inferior overall survival [2]. Papilledema, fingernail clubbing, extravascular volume overload [pleural effusions, peripheral edema and ascites], clinical hypothyroidism, coexisting Castleman disease, and impaired lung diffusion capacity of carbon monoxide (DLCO) have also been identified as risk factors for shorter overall survival [2–10]. While these factors are associated with poorer prognosis, the ultimate cause of death in patients with POEMS syndrome has not been well-described. Several studies have reported the cause of death in a cohort of POEMS patients, but the number of patients has been small and details surrounding the cause of death has been lacking. [1, 8–11] Therefore, the aim of this study was to dissect and describe the causes of death among patients with POEMS syndrome.

METHODS

Patients were included in this study if they met all the following criteria: 1) carried a diagnosis of POEMS syndrome; 2) died during the study period from 2000 to 2022; 3) provided consent for participation in research studies; and 4) had a documented cause of death. POEMS syndrome was defined according to previously described diagnostic criteria [3]. Of the 422 patients with POEMS syndrome that were followed during this period, 89 died. Of these, 49 patients fulfilled all criteria to be included in this study. Baseline characteristics of the other patients who died within this period but had no information about their cause of death were comparable to the final study cohort with the exception of being slightly older and being less likely to have documented extravascular overload at diagnosis (Supplementary Table 1). Three reviewers were involved in the data extraction with one (KL) reviewing the data for all patients. This study was approved by the Mayo Clinic Institutional Review Board.

Cause of death was divided into 3 main categories: 1) related to POEMS syndrome and its treatment complications; 2) causes unrelated to POEMS syndrome; and 3) second primary malignancies. The patients who died related to POEMS syndrome were further divided into subcategories: a) death due to complications of POEMS-directed therapy; b) death due to a capillary leak phenotype (CLP); and c) death due to POEMS syndrome, other.

[1]Division of Hematology, Mayo Clinic, Rochester, MN, USA. [2]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA. ✉email: Dispenzieri.angela@mayo.edu

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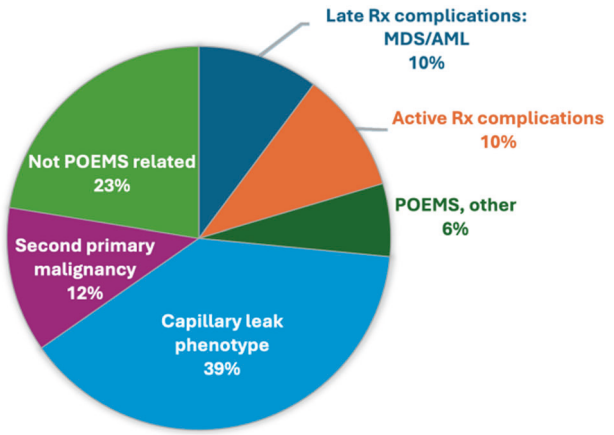

Fig. 1 Causes of death in patients with POEMS syndrome.

The capillary leak phenotype was defined as a course characterized by unrelenting ascites, effusions, and/or anasarca that ultimately resulted in hypotension and cardiopulmonary failure. Patients who were on active therapy and not responding, but died due to infection, were classified as death due to POEMS syndrome. For patients who entered hospice due to POEMS syndrome or who died within 4 months of a documented significant decline in health related to POEMS syndrome such as progression of symptoms or need to change or initiate therapy, the cause of death was classified as due to POEMS syndrome. Deaths that occurred when POEMS syndrome was not active were classified as not related to POEMS.

Statistical analyses were performed using JMP statistical software (SAS, Carey, NC). Fisher exact and Kruskal-Wallis tests were used to define differences among categorical and continuous variables, respectively. Overall survival (OS) was calculated from diagnosis and was estimated using the method of Kaplan-Meier. Survival differences were compared using logrank test.

RESULTS

Baseline characteristics

The median age at diagnosis of POEMS syndrome of the 49 decedents was 56 years (IQR 43, 60), and median age at death was 64 years (IQR 54, 70) (Supplementary Table 1). Patients were diagnosed between 1981 and 2020. By definition, all patients had evidence of both peripheral polyneuropathy and monoclonal plasma cell proliferative disorder. All but 1 patient had a lambda restricted clone. Eighty-six percent of patients had endocrinopathy, sclerotic or mixed sclerotic and lytic bone lesions (84%), and extravascular volume overload (69%). Thrombocytosis and extravascular volume overload were more common in those with known cause of death.

Cause of death in POEMS syndrome

The distribution of cause of death is shown in Fig. 1. Thirty-two (65%) patients died related to POEMS syndrome or its therapy, and 17 (35%) died from unrelated causes or from second primary malignancy (Table 1). By definition, the unrelated causes of death occurred among patients in the observation phase for their POEMS syndrome. These unrelated causes included 6 fatal second primary malignancies comprising 2 instances of metastatic lung cancer and one each of hepatocellular carcinoma, prostate carcinoma, leiomyosarcoma, and metastatic GI neuroendocrine tumor. The remaining 11 unrelated causes of death included pneumonia in 3, heart failure in 3, and one instance each of dementia, sudden death, stroke, intracranial hemorrhage after a fall, and suicide. These 17 patients whose death was not attributed to POEMS or its treatment were diagnosed in a slightly earlier period (median diagnosis year 2003 versus 2004, $p = 0.04$) and at presentation were more likely to have erythrocytosis (50% versus 21%, $p = 0.07$), had fewer bone marrow plasma cells (4% versus 5%, $p = 0.02$), and were more likely to have received radiation as part of their therapy (59% versus 34%, $p = 0.05$) (Table 1). Median time to death for those dying of unrelated causes versus due to complications of POEMS syndrome or its treatment was 12.5 years (95% CI 6.7, 18.4) versus 3.9 years (95%CI 1.3, 9.3), $p = 0.002$ (log-rank), (Fig. 2a).

Table 1. Baseline characteristics by whether death was POEMS or treatment related.

Characteristic, *N* (%)	POEMS-related deaths (*N* = 32)	Death not due to POEMS (*N* = 17)
DEMOGRAPHICS		
Year of diagnosis, median (IQR)	2004 (1999, 2011)	2003 (1990, 2006)
Year of death, median (IQR)	2011 (2006, 2016)	2013 (2003, 2020)
Age at diagnosis, median (IQR)	56 (45, 61)	54 (42, 58)
Age Death, y (IQR)	63 (53, 67)	64 (58, 81)
Male Sex, %	72	71
Race, %		
Black	0	12
White	88	71
Unidentified	13	18
POEMS FEATURES[a,b]	*N* = 30	*N* = 13
Polyneuropathy, %	100	100
Hepatomegaly/ Splenomegaly, %	40	38
Lymphadenopathy, %	50	62
Castleman's variant, %	17	23
Endocrinopathy, %	83	77
Skin changes, %	87	69
Papilledema, %	38	15
Extravascular volume overload, %	83	79
Ascites, %	40	14
Bone lesions, %	80	93
Platelet count, median (IQR)	459 (307, 599)	355 (183, 497)
Erythrocytosis, %	21	50
VEGF, pg/mL, median (IQR)	375 (109, 895)	323 (68, 2037)
λ light chain, %	97	100
Immunoglobulin heavy chain, %[c]		
IgA	48	36
IgG	42	57
Other	10	7
BMPC, % median (IQR)[d]	5 (4, 8)	3 (1, 5)
RVSP mmHg, median (IQR)	34 (30, 50)	33 (29, 50)

[a]6 patients did not have complete baseline information so were excluded from the "features" calculations.
[b]There was missing data, so respective denominators used for measures for POEMS-related deaths and death not due to POEMS include: platelet count (28, 12), erythrocytosis (29, 12); VEGF (17, 4), BMPC (26, 10), RVSP (19, 9), DLCO (22, 10).
[c]There was more complete data on immunoglobulin usage so denominators used were 31 and 14, respectively.
[d]$P = 0.02$.
IQR interquartile range, *BMPC* bone marrow plasma cells, *RVSP* right ventricular systolic pressure, *DLCO* diffusion capacity of carbon monoxide, *VEGF* vascular endothelia.
Units for platelet count (x 10^9/L)

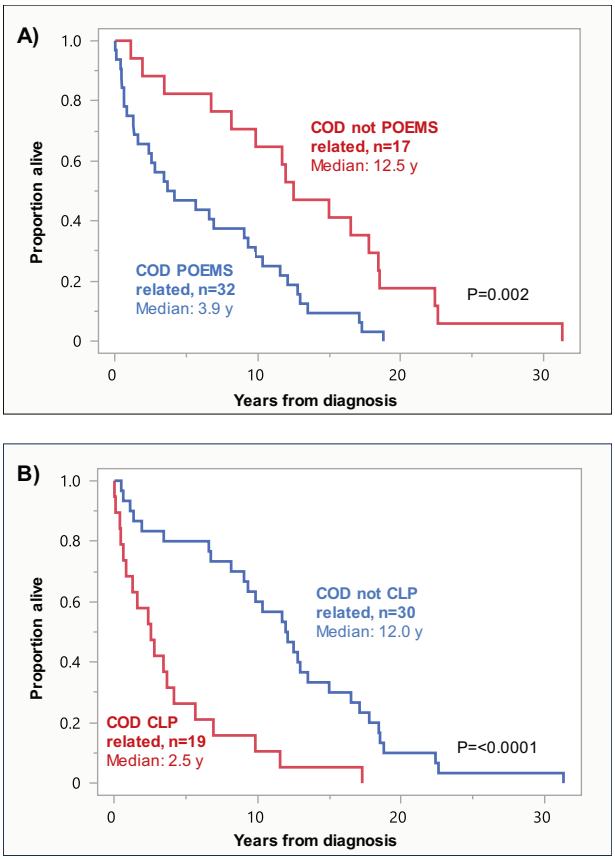

Fig. 2 Time to death by cause of death (COD). Time to death from diagnosis in (**A**) patients who died related to POEMS syndrome ($n = 32$) versus those who died unrelated to POEMS syndrome ($n = 17$) and (**B**) patients with capillary leak phenotype ($n = 19$) versus all other patients with known cause of death ($n = 30$).

Of the 32 patients who died related to POEMS syndrome or treatment complications, the most common cause was a capillary leak phenotype ($n = 19$, see below), followed by active treatment complications ($n = 5$), late therapy complications ($n = 5$), and other POEMS related causes ($n = 3$). The active therapy complications included a bacterial pneumonia, a COVID infection-related death, a sudden death at home 115 days post-autologous stem cell transplant, and a peri-autologous stem cell transplant death characterized by a protracted course including engraftment syndrome, C. difficile colitis, CMV viremia, pancytopenia, esophageal candidiasis, bacteremia, and possible autologous graft-versus-host disease of the colon. The delayed treatment complications as primary cause of death included secondary acute leukemia in 3 and secondary myelodysplastic syndrome in 2. Another 2 patients had early secondary MDS but were classified as death due to CLP and treatment complications because they had active POEMS at their time of death.

The 3 patients who died related to POEMS but did not fit in any of the other 2 categories included one patient who died of complications of non-cirrhotic portal hypertension with varices and two patients who died while on or shortly after discontinuing POEMS-directed therapy due to cachexia and/or decision to enter hospice. Their respective ages at time of death were 61, 76, and 79 years. The liver biopsy of the patient who died of complications of non-cirrhotic portal hypertension with varices only revealed nodular regenerative hyperplasia without fibrosis or cirrhosis. Her serum ascites albumin gradient was elevated.

Capillary leak phenotype (CLP). Uncontrolled terminal CLP was observed in 19 patients and was the most common cause of death in our cohort. It was characterized by a course of unrelenting ascites, effusions, and/or anasarca that ultimately resulted in hypotension, and cardiopulmonary failure. Median time from terminal CLP to death was 4 months. Terminal CLP was part of POEMS syndrome presentation for 6 patients. In contrast for the remainder, CLP occurred much later in the patients' course including 5 patients who developed terminal CLP more than 5 years after POEMS diagnosis (Table 2). Median time to death from POEMS diagnosis for patients succumbing to CLP was 2.5 years (95% CI 0.6, 4.1), Fig. 2b. The only notable differences between those patients who died of uncontrolled CLP versus death due to all other known causes were that the CLP group was diagnosed more recently (median diagnosis year 2007 versus 2002, $p = 0.02$), they were younger at time of death (62 versus 65 years), had higher diagnostic platelet counts (469×10^6/mL versus 415×10^6/mL, $p = 0.04$), and were more likely to have had ascites at POEMS presentation (53% versus 17%, $p = 0.01$), Table 3. They were also less likely to have received ASCT (26% versus 58%, $p = 0.03$).

Eleven of the 19 patients with terminal CLP had complete medical records available during the treatment of the terminal CLP event. A hallmark feature that this cohort shared was overt anasarca and volume overload without a clear explanation. Common causes of ascites and effusions were evaluated and excluded including cardiac and liver dysfunction (Table 4). Six of 7 patients who underwent echocardiogram during an episode of capillary leak had elevated RVSP (range 40 to 67 mmHg) consistent with pulmonary hypertension with intact left ventricular ejection fraction (range 50% to 69%). Two patients underwent right heart catheterization or Swan-Gantz catheter measurements. Hemodynamic studies showed significant pulmonary hypertension for both patients with pulmonary artery systolic pressure of 59 and 84 mmHg (normal <20 mmHg). Both patients had normal cardiac output with a cardiac index of 2.5 and 3.67 L/min/m^2 further supporting that cardiac dysfunction was not the underlying etiology of the volume overload.

Liver dysfunction was considered given the presence of anasarca, ascites, and hypotension, but patients had no evidence of liver nodularity on available imaging or other sequelae of cirrhosis such as esophageal or gastric varices. Peritoneal fluid analysis and serum-ascites albumin gradient (SAAG) were inconsistent. Three patients had SAAG less than 1.1 which would indicate non-portal hypertension, while 3 had SAAG greater than 1.1. No patient met criteria for spontaneous bacterial peritonitis at the time of paracentesis. The ascites was often refractory to diuretic management and 8 patients required repeated paracentesis for symptomatic management.

Seven patients experienced shock requiring intravenous vasopressors. Shock was distributive in nature with severe peripheral vasodilation, hypotension and end-organ hypoperfusion, apart from one patient who had obstructive shock caused by cardiac tamponade requiring emergent pericardiocentesis. Other causes of distributive shock such as sepsis, adrenal crisis, and drug reactions were ruled out.

Only after developing anasarca, refractory ascites, and pleural effusions, did these patients experience progressive renal failure. Median creatinine during an episode of capillary leak was 2.1 mg/dL. Only one patient had evidence of nephrotic range proteinuria. No patient had a light chain cast nephropathy phenotype. Diuresis was typically unsuccessful, and 6 patients required hemodialysis for both volume removal and renal clearance. Dialysis presented another challenge as it was commonly poorly tolerated due to hypotension. Renal pathology was available for two patients and both showed thrombotic microangiopathy.

VEGF levels during the terminal episode of CLP were measured in 11 patients with median level of 257 pg/dL (range 63.2–1785; normal range <96.2 pg/mL). Median IL-6 level for the 4 patients with measurements was 20.6 pg/mL (range 3.1–36.76; normal range 0.31–5 pg/mL).

Table 2. Treatment course among patients dying of uncontrolled capillary leak phenotype (CLP).

Pt ID#	Sex	Age at death (y)	POEMS Dx to onset of terminal CLP (y)	CLP onset to death (y)	POEMS Diagnosis to death (y)	No. of treatment lines	Treatment lines before onset of CLP					Treatment lines after onset of CLP			
1	M	66	0.0	0.5	0.5	2						CP	Rd		
2	M	51	0.0	0.6	0.6	3						CP	KCd	Dara	
3	M	66	0.0	0.6	0.6	1						TP			
4	F	29	0.2	0.5	0.8	2	Rad					CP			
5	F	62	0.3	0.1	0.4	2						CP	Rd		
6	M	34	0.4	0.1	0.6	2						CP	MP		
7	M	37	0.9	0.3	1.3	2	Rad					Unk			
8	M	79	1.4	0.1	1.6	3	Rad	MP				Vd			
9	F	64	1.9	0.6	2.6	1						DRd			
10	M	48	2.1	0.3	2.4	3	P					TP	CP		
11	F	61	2.1	0.7	2.8	2	ASCT					IRD			
12	F	72	3.3	0.1	3.4	2	MP					MP			
13	M	62	3.5	0.1	3.7	7	Rad	Rad	MP	MP	Rad	D	MP		
14	M	52	3.6	0.5	4.2	5	Rd	ASCT				Rd	Bev	CP	
15	M	55	5.3	0.3	5.7	6	ASCT	Id	Rd			Dara	KCd	Bev	
16	M	49	6.2	0.7	6.9	4	D					Bev, P	MP	CP	
17	M	65	9.6	0.2	9.8	5	ASCT					VCd	IRD	Dara	VCd
18	M	67	11.3	0.3	11.6	5	Rad	CP	Vd	ASCT		Vd			
19	M	64	16.8	0.4	17.2	7	Rad	MP	CP			VR	T	Bev	V

Bold line demarcates the onset of CLP from POEMS syndrome diagnosis of 5 years.
ASCT autologous stem cell transplant, *Bev* bevacizumab, *C* cyclophosphamide, *CP* cyclophosphamide and prednisone, *D* dexamethasone, *Dara* daratumumab, *DRd* daratumumab, lenalidomide (Revlimid), dexamethasone, *Id* ixazomib, dexamethasone, *IRD* ixazomib, lenalidomide, dexamethasone, *KCd* carfilzomib, cyclophosphamide, dexamethasone, *MP* melphalan and prednisone, *P* prednisone, *Rad* Radiation, *Rd* lenalidomide and dexamethasone, *TP* thalidomide and prednisone, *Unk* unknown, *V* bortezomib, *VCd* cyclophosphamide, bortezomib, dexamethasone, *VR* bortezomib and lenalidomide.

An assortment of therapies were unsuccessful in treating the CLP including alkylators, corticosteroids, immune modulator drugs, anti-CD38 antibodies, and anti-VEGF antibodies (Table 2). While most therapies were ineffective at treating CLP, two patients stand out because they had prior episodes of capillary leak symptoms which were responsive to anti-plasma cell therapy. Patient ID#18 had an 11.3-year course prior to his third and terminal episode of CLP. At initial presentation, he was hospitalized for anasarca, neuropathy, and 15 kg weight loss, and was found to have restrictive lung disease with severely reduced FEV1 and FVC. He was started on plasma exchange without improvement, followed by radiation therapy to a biopsy-indeterminate T8 lesion. Radiation was terminated after 5 of planned 22 fractions due to worsening respiratory failure. He ultimately required vasopressor support and tracheostomy placement for refractory respiratory failure. Symptoms improved after initiation of combined high-dose corticosteroids and cyclophosphamide, which he continued for a total of 17 months followed by prednisone alone for an additional 24 months. He was able to return to work full time and was treatment-free for nearly 4 years, but he again developed anasarca and respiratory failure. He responded well to bortezomib and dexamethasone both with a reduction in VEGF levels (213 to 44 pg/mL) after 3 cycles and improvement in his ECOG performance status from 3 to 1. Further bortezomib was held for worsening neuropathy, and he underwent ASCT. He clinically improved for another 4 years, but once again relapsed with CLP. This was further complicated by an underlying myelodysplastic neoplasm (del(5)(q13q33)). VEGF level increased from undetectable to 87 pg/mL, and he had worsening anasarca, ascites, profound weakness, hypotension, respiratory failure and renal failure requiring dialysis. Velcade was recommended and he was treated locally without further follow-up at Mayo Clinic. He died shortly thereafter.

The other patient (ID#10) had CLP as a presenting feature two years prior to official POEMS syndrome diagnosis and the terminal episode of CLP. He had diffuse anasarca, large-volume ascites, pleural effusion, and subacute renal failure (creatinine rise from 1.4 mg/dL to 3.8 mg/dL). These symptoms initially resolved with prednisone treatment alone as the diagnosis of POEMS syndrome was not initially recognized. Upon prednisone taper, symptoms recurred with worsening renal function and anasarca. After 22 months of prednisone therapy, he was brought to the hospital in respiratory arrest due to pneumonia. A diagnosis of POEMS syndrome was made, and he was started on thalidomide but this was discontinued within one month due to worsening neuropathy. Cyclophosphamide was initiated, but had no effect on the anasarca, pleural effusions, ascites requiring frequent paracentesis, and severe weakness. He developed multisystem organ failure including respiratory failure requiring intubation with subsequent tracheostomy, hypotension requiring vasopressors, and renal failure requiring dialysis. He died ultimately from cardiac arrest after 3 months of complicated hospitalization.

DISCUSSION

Although the prognosis of patients with POEMS syndrome is typically excellent with 10 year overall survival of 62–77%, patients still die related to the disease. [1, 2, 8–11] In this study 35% of decedents died due to causes other than POEMS or complications of treatment, while the majority died related to POEMS and/or its treatment. In this population of patients with diagnosis dates spanning between 1981 and 2020, 25% having been diagnosed before 1997 when alkylator therapy and radiation were the mainstay of therapy, it is not surprising that 10% of patients died of secondary MDS/AML and another 2 had early MDS that was not the immediate cause of death. Nor is it surprising that 10% of

Table 3. Baseline characteristics by whether capillary leak phenotype was cause of death.

Characteristic, *N* (%)	Uncontrolled CLP deaths *N* = 19	All other deaths *N* = 30	*P* value
DEMOGRAPHICS			
Year of diagnosis, median (IQR)	2007 (2001, 2014)	2002 (1992, 2007)	0.02
Year of death, median (IQR)	2011 (2005, 2017)	2006 (2006, 2013)	
Age at diagnosis, y, median (IQR)	54 (45, 61)	56 (43, 60)	
Age at death, y (IQR)	62 (49, 66)	65 (58, 74)	0.03
Male Sex, %	73.7	70.0	
Race, %			
Black	0	7	
White	89	77	
Unidentified	11	17	
POEMS FEATURES[a,b]	*N* = 19	*N* = 24	
Polyneuropathy, %	100	100	
Hepatomegaly/ Splenomegaly, %	37	42	
Lymphadenopathy, %	47	58	
Castleman's variant, %	11	25	
Endocrinopathy, %	95	83	
Skin changes, %	84	79	
Papilledema, %	28	33	
Extravascular volume overload, %	84	83	
Ascites, %	53	17	0.01
Bone lesions, %	79	87	
Platelet count, median (IQR)	469 (343, 724)	415 (190, 500)	0.04
Erythrocytosis, %	17	39	
VEGF, pg/mL, median (IQR)	294 (104, 775)	482 (115, 1087)	
λ light chain, %	100	97	
Immunoglobulin heavy chain[c], %			
IgA	42	46	
IgG	42	50	
Other	16	4	
BMPC, % median (IQR)	5 (3, 9)	5 (3, 5)	
RVSP mmHg,c median (IQR)	35 (30, 62)	34 (32, 45)	
DLCO, % predicted, median (IQR)	49 (36, 68)	61 (52, 69)	

[a]6 patients did not have complete baseline information so were excluded from the "features" calculations.
[b]There was missing data, so respective denominators used for measures for uncontrolled CLP and all other deaths include: platelet count (17, 23), erythrocytosis (18, 24); VEGF (10, 11), BMPC (16, 20), RVSP (11, 17), DLCO (13, 19).
[c]There was more complete data on immunoglobulin usage so denominators used were 19 and 26, respectively.
Hgb hemoglobin, *alb* albumin, *VEGF* vascular endothelial growth factor, *IL-6* interleukin 6, *Pl Eff* pleural effusion, *# of Para/thora* number of paracentesis /thoracentesis, *cr* creatinine, *HD* hemodialysis, *SAAG* serum to ascites albumin gradient, *ECHO* echocardiogram, *RVSP* right ventricular systolic pressure, *ECHO LVEF* echocardiogram left ventricular ejection fraction.

patients died of complications of active therapy, one of whom already had early MDS. What was striking was that 39% of patients had a very distinctive preterminal phase, which we called a capillary leak phenotype. The rate may be higher since there were 7 patients with causes of death called "liver disease" and "congestive heart failure" and "cachexia" which may have been instances of this phenotype that were insufficiently evaluated or for whom we lacked detailed clinical information.

The etiology of the CLP phenotype, which is characterized by onset of anasarca with pleural effusion and ascites complicated by hypotension, and ultimately renal or cardiopulmonary failure, is not understood. Despite extensive evaluations, neither right or left-sided heart failure, pulmonary hypertension, nor liver disease fully accounted for the resistant third spacing observed. Hypoalbuminemia was typically present, but at levels that did not explain the degree of capillary leak seen. The CLP seen in POEMS is distinct from that of Clarkson's disease (or idiopathic capillary leak syndrome) in that the latter is episodic, acute, and associated with hemoconcentration; whereas, the POEMS CLP is subacute to chronic and typically unrelenting [12–14]. There are some similarities between the CLP seen in these POEMS patients and the cytokine release syndrome that is seen with T-cell engager therapies though the CLP patients typically do not have fever but they do develop hemodynamic instability and respiratory distress [15]. Information about the cytokine milieu of these patients was sparse, and anti-IL-6 therapies (other than high dose corticosteroids, which all patients received) were not employed. Three patients received bevacizumab (antibodies directed against VEGF) without benefit, 7 received proteasome inhibitors, 8 received IMID therapy and 12 alkylator therapy, all with no apparent benefit.

The renal failure that occurs in POEMS CLP appeared clinically to be a secondary phenomenon due to low perfusion as would be suggested by low right atrial pressures and collapsible IVC seen on transthoracic echocardiograms though 2 of the patients demonstrated localized microthromboangiopathy on renal pathology. Thrombotic microangiopathy has been implicated in POEMS-related kidney injury, however the mechanism remains unknown [16].

Although not all capillary leak events in POEMS patients are fatal, as demonstrated by the courses of two patients in this series and by personal experience, CLP is thought to represent progression of POEMS syndrome and is an entity that can be refractory to standard therapies including alkylators, corticosteroid, IMiD, anti-CD38 antibody, and anti-VEGF therapies. It is notable that 2 individuals who had prior CLP had been salvaged earlier in their course by corticosteroids, alkylator, bortezomib, and/or ASCT. However, both had recurrence of CLP that did not respond to similar interventions pre-terminally.

POEMS syndrome remains an enigmatic disease, whose etiology remains elusive. With earlier diagnosis and more plasma cell-directed therapeutic options, patients are living longer [1]. There are, however, still deaths that occur related to the disease, but this has not previously been well described. The best description of COD in POEMS is in the series by Yu et al. which lists "disease progression", cardiopulmonary failure, progressive renal failure, infection, cachexia, and other as causes of death in 91 patients with POEMS [10]. Other series follow suit but often with "unknown" as the primary cause, followed by disease progression and secondary malignancy [1, 8, 9].

Our study is limited by small sample size and incomplete data. Another limitation of this decedent cohort study is selection bias, which could lead to overestimation of CLP as COD in POEMS. Despite these limitations, our findings do bring to the forefront an important entity, the capillary leak phenotype, that is the leading cause of death in patients with POEMS syndrome. Identification of this phenotype may help guide further studies into pathophysiology and best effective treatment.

Table 4. Patient characteristics during terminal episode of capillary leak phenotype.

Pt ID#	Hgb, g/dL	Alb, g/dL	VEGF, pg/mL	IL-6, pg/mL	Shock	Ascites	Pl Eff	# of Para/ Thora	Cr, mg/dL	HD	SAAG	24-hr urine protein, mg	ECHO RVSP, mmHg	ECHO LVEF, %
2	10.2	3.1	63	19	Y	Y	Y	3	1.6	Y	1.5	901	35	68
3	11.1	2.2			NA	Y	Y	0	2.3	N		402	48	50
6	13	3.1			N	Y	Y	1	0.8	N		158		
8	11.5	3.1	1785	3	Y	N	Y	0	1.6	N		229		
9	10.9	2.7	104	11.7	Y	Y	Y	3	2.0	Y	0.7	341	66	77
10	10.5	2.2			Y	Y	Y	>5	2.4	Y	1	180	28	69
11	7	2.6	743		Y[a]	Y	Y	14[b]	0.8		1.7		67	64
12	12.6				Y	NA	Y	0	2.3	N		216		
14	10.2	2.4	283	29.5	N	Y	Y	17	2.5	N	1.5		49	63
15	10.4	2.7	294		Y	Y	Y	NA	3.5	Y	0.8	240	67	
16	8.6	2.6			N	Y	Y	1	2.1	N		119		
17					Y	Y	Y	>15	Unk	Y		290		

Alb albumin, *Pl Eff* Pleural effusion, *# of Para/Thora* Number of paracentesis or thoracenteses, *Cr* creatinine, *HD* hemodialysis, *SAAG* Serum-to-ascites albumin gradient, *ECHO* echocardiogram, *RVSP* right ventricular systolic pressure, *LVEF* left ventricular ejection fraction.
[a]Obstructive shock from cardiac tamponade, all other shock was distributive.
[b]Required pleural drain placement.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Conception, design, data analysis and interpretation: Kenzie Lee and Angela Dispenzieri; provision of study materials of patients, collection of data, writing of manuscript and final approval of manuscript: All authors.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study complies with all relevant ethical guidelines and regulations according to the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board (ID: 19-011683). All patients included had provided consent for participation in research studies.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Angela Dispenzieri.