RESEARCH ARTICLE

Extramedullary Waldenström macroglobulinemia

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Disease assessment in Waldenstrom Macroglobulinemia (WM) is dependent on the percent involvement of B-cell neoplasm in the bone marrow and IgM paraprotein in the serum. A subset of patients also demonstrates extramedullary involvement, which is infrequently examined. The role of extramedullary involvement in the diagnosis and prognosis of WM is poorly understood. The purpose of this study is to report the characteristics of WM patients with extramedullary disease (EMD). Nine hundred and eight-five patients with WM were evaluated at one academic center and the presence of EMD was assessed in these patients. Forty-three (4.4%) patients were identified to have EMD. Nine (21%) patients presented with involvement at WM diagnosis, while 34 (79%) developed EMD post-therapy for WM. Most frequent EMD sites involved were pulmonary (30%), soft tissue (21%), cerebrospinal fluid (23%), renal (8%), and bone (9%). The median overall survival at 10 years was 79% (95% CI: 57–90%). This is the first study to describe the clinical characteristics, response and overall survival in patients with extramedullary WM. Further studies to define the molecular characteristics of this entity and mechanisms of its development are warranted.
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Introduction

Waldenström macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by bone marrow (BM) infiltration of B-lymphocytes, lymphoplasmacytoid cells, and plasma cells along with production of a serum monoclonal immunoglobulin M (IgM) [1,2]. In 1944, Jan Gosta Waldenström described the entity by identifying two patients with lymphadenopathy, oronasal bleeding, anemia, thrombocytopenia, elevated erythrocyte sedimentation rate, high serum viscosity, and infiltration of the BM by lymphoid cells. According to the Revised European American Lymphoma (REAL) and World Health Organization (WHO) classifications, the BM infiltrate is termed lymphoplasmacytic lymphoma (LPL) [2–5].

WM is a rare cancer with an incidence rate of about three cases per million people per year in the United States [6–8]. Patients with WM can present with an extensive range of signs and symptoms related to the monoclonal serum protein and/or to the tumor infiltration [2–5]. Frequent clinical presentations are related to cytopenias, especially anemia because of BM replacement by tumor cells. Patients may also present with symptoms related to hyperviscosity. Approximately 20% of patients experience hepatosplenomegaly and lymphadenopathy, and some patients may present with B symptoms including night sweats, fever, and weight loss. Other common manifestations include neuropathy, cryoglobulinemia, skin rash (Schnitzler syndrome) [9], cold-agglutinin hemolytic anemia, and amyloidosis [10,11].

Tissue infiltration of other organs by neoplastic cells is rare and can involve various organs and tissues. Pulmonary involvement in the form of masses, nodules, diffuse infiltrate, or pleural effusions have been described with WM [12]. Malabsorption, diarrhea, bleeding, or obstruction may indicate involvement of the gastrointestinal tract at the level of the stomach, duodenum, or small intestine. Direct infiltration of the central nervous system (CNS) constitutes the rarely observed Bing–Neel syndrome, which is characterized clinically by headache, vertigo, ataxia, diplopia, impaired hearing, and eventually coma. Ocular, periorbital, and retro-orbital infiltration may be observed. Several case reports and small case series have identified extramedullary cases of WM [13]. In this study, we reviewed the records of 985 patients seen at one academic institution to define the clinical presentation, prognosis, and response to therapy in extramedullary WM.

Methods

Patient recruitment. A retrospective analysis was performed on a database of patients diagnosed with WM and seen at the Dana-Farber Cancer Institute (DFCI) in Boston, MA. Approval for this protocol was obtained from DFCI and was in accordance with the Declaration of Helsinki. Nine hundred and eighty-five patients with WM were identified between June 1994 and April 2013. The diagnosis of WM was made according to the consensus recommendations [11]. Medical files were reviewed for patients who had a positive biopsy of one or more extramedullary site at WM diagnosis or during follow-up visit at DFCI. Cases with involvement of lymph nodes, spleen, and amyloid deposits

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TABLE I. Baseline Demographics

	Total $n = 43$	Extramedullary disease presentation	
		At WM diagnosis $n = 9$	Post-WM treatment $n = 34$
Age			
Median (range)	55 (42–70)	58 (47–68)	55 (42–70)
≤ 50	13 (30%)	2 (22%)	11 (32%)
(50, 60]	19 (44%)	4 (44%)	15 (44%)
(60, 70]	11 (26%)	3 (33%)	8 (24%)
> 70	0	0	0
Sex			
Female	20 (47%)	5 (56%)	15 (44%)
Male	23 (53%)	4 (44%)	19 (56%)
β-2 microglobulin (g/dL)			
Median (range)	3.1 (1.3–10.9)	3.8 (1.4–6.1)	2.8 (1.3–10.9)
Missing	23 (53.5%)	3 (33.3%)	20 (58.8%)
Bone marrow (%)			
Median (range)	30 (5–90)	30 (5–80)	30 (5–90)
Missing	5 (12%)	0	5 (15%)
Hemoglobin (g/dL)			
Median (range)	11.8 (3.9–15.0)	12.2 (10.7–15.0)	10.8 (3.9–13.9)
Missing	9 (20.9%)	1 (11.1%)	8 (23.5%)
Platelets (10^9)			
Median (range)	270 (99–600)	292 (99–557)	262 (109–600)
Missing	8 (19%)	1 (11%)	7 (21%)
LDH (UI/L)			
Median (range)	188 (68–1134)	197 (116–1134)	183 (68–478)
Missing	28 (65%)	5 (56%)	23 (68%)
IgM			
Median (range)	2.5 (0.0–9.0)	1.4 (0.6–7.7)	2.7 (0.0–9.0)
Missing	5 (11.6%)	3 (33.3%)	2 (5.9%)

were excluded and only extranodal cases were included in this analysis. Cases with circulating tumor cells were excluded. Fifty biopsy specimens were obtained and examined from 43 patients identified in this study.

Study patients and response evaluation. To be included in this analysis, each of the 43 patients had involvement by LPL in the BM and an IgM paraprotein in the serum. In addition, each patient demonstrated one or more sites of extramedullary involvement by way of biopsy either at WM diagnosis or post-therapy for WM. Medical files of these patients were further reviewed and data regarding patient demographics, initial presentation at diagnosis, and disease prognosis based on the Morel International Prognostic Scoring System (IPSS-WM) study were obtained. Prior medical history including types of therapies for WM and best response to these therapies were also included. Patients were evaluated for clinical response using the criteria established at the Second International Workshop on Waldenström's Macroglobulinemia [14]. Data were collected until the last time of follow-up or death.

Pathology. The diagnosis of LPL was rendered on tissue sections as part of routine clinical care in accordance with the 2008 WHO classification system and consensus definition for WM [3,15]. Pathology specimens were obtained at our institution or at referring institutions, were reviewed by the pathology department at our institution, and the reports were evaluated for confirmation of LPL involvement. Representative histologic sections of the tumors were additionally stained with an anti-CD20 antibody (L26 clone, Dako, Carpinteria, CA) for this study.

Statistical analysis. Patient characteristics were summarized using descriptive statistics. Patient responses to treatment were calculated using 95% exact binomial confidence intervals. Overall survival was defined as the time elapsed between WM diagnosis and last follow-up or death from any cause and was estimated using the Kaplan–Meier method. The median follow-up time was calculated using the reverse Kaplan–Meier method. The 95% confidence intervals for survival analysis were calculated using Greenwood's method of variance estimation. Statistical analyses were performed using the R environment for statistical computing (version 3.1.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics at baseline

The baseline characteristics are shown in Table I. Among the 985 WM patients identified, 43 (4.4%) had evidence of extramedullary involvement. There were 23 (53%) males and 20 (47%) females with a median age of 55 years (range 42–70 years). Ninety-five % were white. At the time of original WM diagnosis, nine (21%) patients were asymptomatic. Laboratory data at WM diagnosis included median β-2-microglobulin of 3.1 g/dL (range 1.3–10.9 g/dL), and percent BM involvement by LPL of 30% (range 5–90%). Among the 43 WM patients identified with EMD, nine (21%) patients presented with involvement at WM diagnosis, and the other 34 (79%) patients presented with EMD post-therapy for WM.

TABLE II. Patients with EMD Sites Involved

	Total $n = 43$	Extramedullary disease presentation	
		At WM diagnosis $n = 9$	Post-WM treatment $n = 34$
EMD site[a]			
Bone	4 (9%)	0	4 (12%)
Breast	1 (2%)	0	1 (3%)
Colon	1 (2%)	0	1 (3%)
Small bowel	1(3%)	0	1 (3%)
Conjunctiva	1 (2%)	0	1 (3%)
CSF	10 (23%)	0	10 (29%)
Gallbladder	1 (2%)	1 (11%)	0
Liver	1 (2%)	1 (11%)	0
Neck	2 (5%)	0	2 (6%)
Prostate	1 (2%)	0	1 (3%)
Pulmonary	13 (30%)	3 (33%)	10 (29%)
Renal	4 (8%)	2 (22%)	2 (6%)
Skin	2 (5%)	0	2 (6%)
Soft tissue	9 (21%)	3 (33%)	6 (18%)

[a] Patients may have multiple sites of EMD which is reflected in column percentages totaling more than 100%.

Extramedullary presentation at WM diagnosis (nine patients)

Eight of these nine patients presented with only a single extramedullary site while one patient had two sites of involvement at WM diagnosis. Extramedullary sites involved in this group included soft tissue from an upper lip mass, upper arm mass, orbital mass, and presacral mass ($n = 3$; 33%); pulmonary ($n = 3$; 33%); renal ($n = 2$; 22%); liver ($n = 1$; 11%); and gallbladder ($n = 1$; 11%), Table II.

Extramedullary presentation post-therapy for WM (34 patients)

Thirty-four (79%) patients developed EMD post-therapy for WM. Of these patients, 29 had only a single extramedullary site of involvement while five patients had multiple sites of involvement post-therapy for WM. None of these cases represented transformation to intermediate-grade lymphoma. Among the patients with multiple extramedullary sites, four patients had two sites of involvement and one patient had four different sites of involvement. Extramedullary sites involved in this group included pulmonary ($n = 10$; 29%); cerebrospinal fluid, CSF ($n = 10$; 29%); soft tissue from nasopharyngeal mass, hard palate mass, abdominal wall mass, neck/upper back mass, chest wall mass, and thigh mass ($n = 6$; 18%); bone ($n = 4$; 12%); renal ($n = 2$; 6%); neck mass ($n = 2$; 6%); skin ($n = 2$; 6%); breast ($n = 1$; 3%); conjunctiva ($n = 1$; 3%); small bowel ($n = 1$; 3%); prostate ($n = 1$; 3%); and colon ($n = 1$; 3%) (Fig. 1 and 2). For patients with Bing–Neel syndrome, the majority of the patients were diagnosed with the presence of leptomeningeal enhancement on MRI or enhancement at the Cauda Equina. All of the patients demonstrated the presence of malignant cells in the CSF except for one patient who had enhancement of the optic nerve and periventricular area along with infiltration of the extra-occular muscles. In this patient, the CSF showed no malignant cells but showed the presence of IgH rearrangement in the spinal

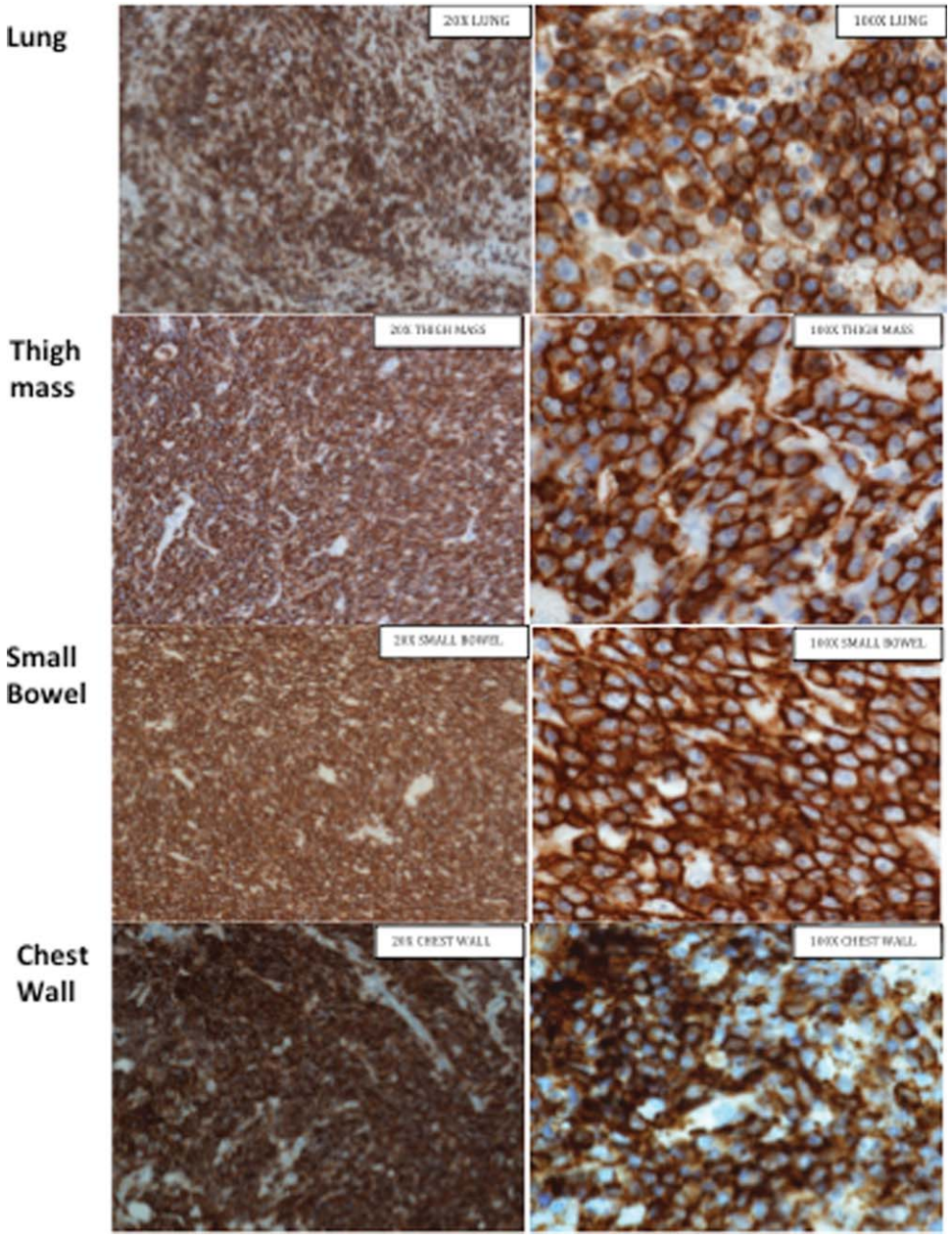

Figure 1. Immunohistochemical detection of CD20 expression in EMD sites. Four examples of extramedullary sites of involvement with LPL. There is strong immunoreactivity for CD20 in all the areas. 20× and 100× images are shown for lung, thigh, small bowel, and chest wall masses, respectively.

fluid. For the patients with pulmonary involvement, three had involvement in the parenchyma of the lung with a lung mass or pulmonary nodules and were proven to have malignant cells by biopsy or bronchioalveolar lavage. The other patients showed pleural effusions by CT scan imaging and cytology proven presence of malignant cells. Median time to extramedullary presentation from WM diagnosis in this group was 71.5 months (range 2–210 months) or approximately six years.

Immunohistochemical and molecular characteristics of EMD specimens

Fifty samples obtained from 43 patients were evaluated by pathology review at our institution as part of routine clinical care. All patient specimens analyzed were consistent with LPL. Immunoglobulin kappa or lambda light chain expression was analyzed in 45 specimens by either flow cytometry or by *in situ* hybridization, of which 40 (88%) samples were kappa and five (12%) samples were lambda. Figure 1 shows representative immunohistochemical detection of CD20 expression in EMD of the lung, thigh, small bowel, and chest wall. For the cases in which molecular analysis of DNA isolated from biopsies was performed ($n = 6$), a clonal immunoglobulin heavy chain gene rearrangement was identified in all cases indicating the presence of a clonal B-cell population.

Immunophenotypic data for WM patients with extranodal disease

Immunophenotpic data were obtained for extranodal biopsy specimens and samples were analyzed by flow cytometry ($n = 34$), immunohistochemistry ($n = 30$), or both ($n = 14$). All patient specimens analyzed were of B-cell lineage (CD19+, CD20+). Monotypic surface immunoglobulin kappa or lambda light chain was analyzed in all specimens of which 91% were kappa and 9% were lambda.

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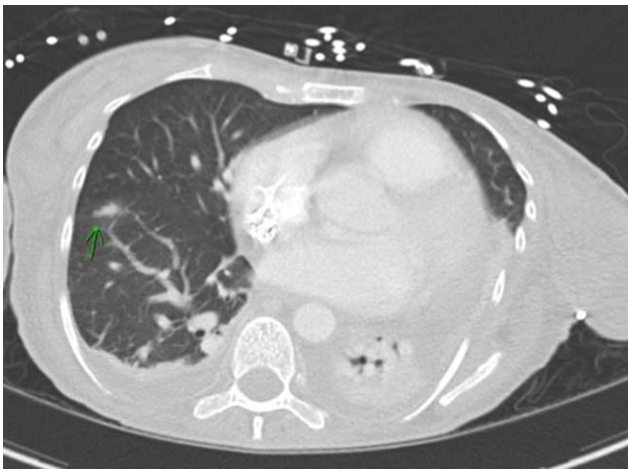

Figure 2. CT scan of the chest showing extramedullary involvement in a patient with WM with a lung mass and pleural effusion.

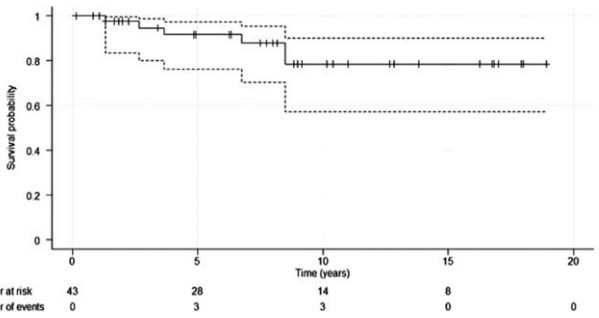

Figure 3. Overall survival (OS) in the patients with EMD. OS was defined as the duration of time from initial WM diagnosis to time of death. Median overall survival time was not reached since more than 50% of patients were still alive. Five-, 10-, and 15-year survival probabilities were 92%, 79%, and 79%, respectively. All censored observations (represented on the curve by vertical marks) were alive at last contact, and their respective dates of last known status are used in the estimation of the overall survival curve. The median follow-up time was 106 months or approximately nine years. The dashed line represents the 95% confidence bounds of the survival probability estimate at a particular time point.

Interventions before and after EMD presentation

At the time of data collection (July 2013), for all 43 patients the median number of lines of therapy was three (range 0–8). In the group of nine patients presenting with EMD at WM diagnosis, four patients (44%) had one subsequent line of therapy, two (22%) had two lines, two (22%) had three lines, and one (11%) had four lines of therapy. The median number of subsequent lines of therapy was two (range 1–4). All of the therapies for these patients were post-diagnosis with EMD. In the group of 34 patients presenting with EMD post-therapy for WM, one (3%) had no prior lines, eight (24%) had one line of therapy, four (12%) had two lines, seven (21%) had three lines, six (18%) had four lines, and eight (24%) had five or more lines of therapy prior to EMD presentation. The median number of prior lines was three (range 0–8).

Among the 43 WM patients presenting with extramedullary involvement at diagnosis or post-therapy for WM, 37 received therapy to reduce the burden of disease. All nine patients with EMD at WM diagnosis received treatment, and eight (89%) achieved a minimal response or better (95% CI: 52–100%). Of the 34 patients who presented with EMD after WM diagnosis, 28 (79%) received therapy, and 22 (65%) achieved a minimal response or better (95% CI: 59–92%).

First therapies that patients received after EMD presentation included cyclophosphamide-based regimens including combinations of rituximab and CVP or CHOP or cyclophosphamide/dexamethasone/rituximab combinations (n = 11; 21%), bortezomib-based regimens including bortezomib and rituximab combinations or bortezomib/dexamethasone/rituximab (n = 8; 15%), and bendamustine-based regimens including bendamustine alone or in combination with rituximab (n = 7; 13%). Other therapies included methotrexate for CNS involvement and everolimus/bortezomib/rituximab or cytarabine and dexamethasone. Twenty-two (85%) of the 26 patients who received rituximab-based therapy to reduce disease burden achieved a minimal response or better (95% CI: 65–96%). We could not report the overall response rate for other therapeutic agents because of the small number of patients.

Of those who responded by consensus criteria, the EMD sites also showed disease improvement, although there are no specific criteria of response for these EMD sites. Response in the patients with Bing–Neel syndrome was demonstrated in five patients with resolution of the malignant cells from the CSF. In seven patients with lung or pleural fluid involvement, there was improvement in the pleural fluid/negative cytology of the fluid or resolution/improvement in the pulmonary involvement.

Survival data

At the time of data collection, the median follow-up time was 106 months (range 2–227 months), or approximately nine years. Of the 43 WM patients with EMD, 30(70%) were alive, seven (16%) were lost to follow-up, and six (14%) died as a result of progressive disease. Kaplan–Meier estimates of 5-, 10-, and 15- year survival rates were 92% (95% CI: 76–97%), 79% (95% CI: 57–90%), and 79% (95% CI: 57–90%), respectively (Fig. 3).

Discussion

In this report, we describe a unique entity of extramedullary Waldenström macroglobulinemia. Prior case reports and case series have described some of these cases [13]. However, the clinical characteristics, response rate, and survival of these patients have not been previously examined.

These extramedullary WM cases were defined as the presence of a clonal lymphoplasmacytic infiltrate at anatomic sites distant from the bone marrow or adjacent soft tissue in a patient with underlying WM, and excluding splenic/liver and nodal involvement as well as excluding circulating tumor cells. Interestingly, many of these cases showed involvement in specific organs such as lung, soft tissue, CNS, and gut involvement, indicating possible specific tropism/homing of the malignant cells to those organs. We also found cases of renal involvement with infiltrates of tumor cells, which would suggest a potential etiology of renal failure in some patients with WM. All of the cases with CNS involvement (Bing–Neel syndrome) developed after therapeutic interventions while other cases of lung or soft tissue involvement occurred at the time of diagnosis. In general, most cases presented after therapy and not at the time of initial diagnosis indicating possible clonal evolution/clonal heterogeneity that favors the growth of clones with extramedullary preference with selective pressure after therapeutic agents. Clonal evolution has been described in other B-cell malignancies [16–18].

FISH and cytogenetic studies were not available in all the patients and MYD88 mutation status was not routinely performed in these patients. Therefore, we could not define specific prognostic markers that identify this patient population. Recent studies have demonstrated that MYD88 L265P mutation is present in 70–90% of WM patients [19,20]. Moreover, a recent observation indicated that 20–30% of patients also harbor a CXCR4 WHIM mutation [21,22]. CXCR4 is a chemokine receptor that regulates cell trafficking and has been implicated in tumor dissemination and metastasis in many

malignancies [23–27]. Recent studies have shown that the CXCR4 WHIM mutation was present in EMD and enhanced tumor dissemination and extramedullary involvement in xenograft mouse models [22,23,28,29]. Therefore, CXCR4 may potentially be a factor in the regulation of extramedullary involvement in patients with WM. Future studies to examine molecular characteristics of extramedullary disease including the presence or absence of MYD88 or CXCR4 mutations in patients with extramedullary WM are therefore warranted.

The median overall survival at 10 years was 79% (95% CI: 57–90%), which is comparable to that observed in patients with WM if all IPSS risk factors are included. These data suggest that, unlike in multiple myeloma, extramedullary WM including CNS involvement remains potentially treatable and does not confer a poor prognosis in these patients. However, the current response criteria of WM do not include response for EMD or for Bing–Neel syndrome. Therefore, future response criteria should include adequate criteria for EMD in WM.

We should caution that there are many limitations to this study including being a small retrospective report with some missing information and with no direct comparison to all the other WM patients who did not develop extramedullary disease. Therefore, larger prospective studies to follow up survival and response to therapy in patients with EMD are recommended.

In summary, we report the clinical characteristics, response and overall survival of a rare entity that is observed in patients with WM termed extramedullary WM. Further studies to define the molecular characteristics of this entity and mechanisms of its development are warranted.

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