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Gastrointestinal, Hepatic and Pancreatobiliary Involvement by Plasma Cell Neoplasms: Clinicopathologic Correlations in a Retrospective Cohort of 116 Cases

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ABSTRACT

Aims: Plasma cell neoplasms (PCNs) may involve the gastrointestinal (GI) tract in two forms: plasmacytoma (PC), an isolated lesion which lacks marrow involvement, and extramedullary myeloma (EMM). However, previous literature on PCNs involving the GI tract, liver and pancreas is limited. We evaluated the clinicopathologic features of the largest series of GI PCNs to date.

Methods and Results: Six institutional archives were searched for GI, liver and pancreas cases involved by PCNs. Medical records were reviewed for clinical and imaging features. Histopathologic features evaluated included involved organ, tumor grade and marrow involvement. Overall, 116 cases from 102 patients were identified. Tumors most presented as incidental findings (29%). The liver was most involved (47%), and masses/polyps (29%) or ulcers (21%) were most common findings. Most cases had high-grade morphology (55%). The majority (74%) of GI PCNs were classified as EMM due to the presence of marrow involvement at some point during the disease course, occurring within a year of marrow diagnosis in 46% of patients. PC was classified in 26% of patients due to the lack of marrow involvement. Most (70%) patients died from disease within 10 years (median 14.1) of diagnosis and more than half (58%) died within 6 months.

Conclusion: PC and EMM involving the GI tract, liver and pancreas have a wide range of clinicopathologic presentations. Tumors may occur virtually anywhere in the GI tract or abdomen and may precede the diagnosis of marrow involvement. Both GI PC and EMM are associated with a poor prognosis.

Keywords: Plasmacytoma, extramedullary myeloma, plasma cell myeloma, multiple myeloma, amyloid

INTRODUCTION

Plasma cell neoplasms (PCNs) encompass several hematologic disorders resulting from the clonal proliferation of plasma cells and resultant overproduction of monoclonal immunoglobulins (M protein), resulting in monoclonal gammopathy. Plasma cell myeloma, also known as multiple myeloma (MM), is defined as the presence of ≥10% clonal plasma cells in the marrow.[1] Plasmacytoma (PC) is defined as a localized clonal plasma cell proliferation that by definition does not involve the marrow.[1] When myeloma involves extramedullary sites as well as the marrow, this is termed extramedullary myeloma (EMM). EMM is usually a feature of advanced disease, and may manifest as localized organ-based proliferations of plasma cells, organomegaly, or rarely involvement of skin and/or soft tissue. EMM may present prior to the discovery of myeloma in the marrow, and cases initially presenting as PC must be distinguished from EMM by marrow evaluation. Deposition of amyloidogenic monoclonal immunoglobulin light chains can also occur among patients with PCNs, resulting in amyloidosis.[1]

Most of the literature describing EMM in the GI tract, liver and pancreatobiliary system consists of case reports and small series, and no large studies detailing their unique clinicopathologic characteristics exist. Historically, the liver is the most common site of involvement,[2–4] but rare cases involving diverse sites such as the upper aerodigestive tract,[5] stomach[6] and colon[7] have been reported, and some authors have described patients with peritoneal disease who presented with ascites.[8–11] GI PCs are even less common, but have been rarely reported in the stomach,[12] small intestine,[13,14] colon[12] and retroperitoneum.[15] The described signs and symptoms of GI PC and EMM vary widely and range from asymptomatic patients to those with fatigue, abdominal pain, GI bleeding, amyloidosis, organomegaly, polyps, ulcers or obstructing masses that simulate

carcinomas.[16–24] Interestingly, the available data suggest that patients with PC have a worse prognosis than those with EMM, often with relapsing disease or marrow involvement that can occur years after surgical resection.[16]

As most of the reports of GI involvement by PCNs are in the form of case reports or small case series, we performed a multi-institutional study to describe the clinicopathologic features of GI PCNs in detail. We retrospectively collected a large cohort of cases and evaluated their pathologic, endoscopic and clinical characteristics. To our knowledge, this is the largest series of GI PC and EMM cases collected to date.

METHODS

The archives of six large academic medical centers (Cleveland Clinic [Cleveland, Ohio], Beth Israel Deaconess Medical Center [Boston, Massachusetts], University of Arkansas for Medical Sciences [Little Rock, Arkansas], University of Chicago [Chicago, Illinois], University of Michigan [Ann Arbor, Michigan] and Weill Cornell Medicine [New York, New York]) were searched for PC or EMM that involved the GI, liver or pancreas over the past 10-24 years. Associated marrow biopsies were retrieved and reviewed when available. Plasmablastic lymphomas, which are distinct from myeloma with plasmablastic features, and post-transplant lymphoproliferative disorders were specifically excluded. Clinical characteristics that were evaluated included patient age, gender, signs and symptoms at presentation, laboratory values, involved organ(s), endoscopy findings, imaging findings, International Staging System (ISS) stage, types of treatment and patient outcome. Pathologic characteristics evaluated included tumor growth pattern, tumor grade and absence or presence of amyloid. Histologic growth

pattern was classified as follows: Tumors were designated as diffuse if there was a large, infiltrating visceral mass or a transmural tumor involving the GI tract. Lesions were designated as focal if they were single, well-circumscribed nodules or polyps, or confined to the mucosa. While we recognize that histologic grading systems are currently infrequently used for myeloma, several are well-reported, have historic prognostic significance and have similar features.[1,25,26] Similar to those grading schemes, we used a simple classification scheme so that we could compare different tumor morphologies with other analyzed variables. Tumors were classified as low-grade (LG) if the neoplastic plasma cells were mature, featuring small-to-intermediate cell size, distinct perinuclear clear zone, eccentric nuclei, indistinct-to-small single nucleolus and low mitotic rate. High-grade (HG) tumors had blastic or anaplastic features including large or pleomorphic cell size, variable-to-indistinct perinuclear clear zone, central nuclei, prominent or multiple nucleoli and high mitotic rate including atypical mitoses.[1,25] Laboratory studies, including serum and urine protein electrophoreses, flow cytometry, cytogenetic analyses and molecular studies, were also evaluated when available. All cases were diagnosed according to the revised 4th edition World Health Organization classification.[27]

Statistical analyses were performed using Microsoft Excel for Mac Version 16.57. Significance testing was performed using Chi-Square test if at least 5 patients or cases and two-tailed Fisher exact test if fewer than 5 patients or cases were present per statistical group with $\alpha = 0.05$ and subtraction of unknown cases from totals.

RESULTS

One hundred and sixteen tumors from 102 unique patients were identified, including 22 patients with PC and 63 patients with EMM. Marrow involvement was unknown in 17 patients and, therefore, they were excluded from subclassification as PC or EMM. Age ranged from 15-86 years (median 63), and there was a slight male predominance (55%, 56 patients).

Clinical Characteristics

The clinical features of the study cases are summarized in **Table 1**. The liver (47%, 48 patients, **Figure 1**), stomach (24%, 24 patients, **Figure 2**) and small bowel (18%, 18 patients) were most commonly involved. Thirteen patients presented with multifocal disease, 12 with two sites of involvement and 1 with three sites of involvement. The presenting signs and symptoms were known for 86% (88) of patients. Most patients presented with GI bleeding (15%, 15 patients), followed by abdominal pain (10%, 10 patients) and elevated liver enzymes/transaminitis (9%, 9 patients). A visible nodule or mass was present in 63% (64 patients) of patients who underwent imaging studies (76%, 77 patients), and an ulcer or polyp was present in 8% (8 patients) and 5% (5 patients) of patients, respectively, who underwent endoscopic studies (37%, 38 patients). Eighteen percent (18 patients) of patients' PCNs were found incidentally during evaluation for another disorder, and 11% (11 patients) of patients' PCNs were found during routine myeloma follow-up.

Statistically significant clinical characteristics between PC and EMM cases included site and presenting signs and symptoms. EMM was significantly more likely to involve the liver ($p < 0.01$), and was less likely to present incidentally during evaluation for another disorder ($p = 0.01$). EMM was also more frequently associated with renal failure than PC ($p = 0.03$). Age,

gender, endoscopic findings and imaging findings were not significantly different between PC or EMM.

Pathological Characteristics

The pathologic features of the study cases are summarized in **Table 2**. Most (54%, 55 patients) cases showed HG morphologic features with a diffuse growth pattern (57%, 58 patients) of tumor cells (**Figure 3**). Eighty-five patients (83%) had a marrow biopsy at some point during their care, and was involved in 62% (63) of these patients. Most neoplasms in the marrow showed HG morphologic features (35%, 34 patients), which were concordant with the tumor grade in the GI tract in 81% (44 of 54) of patients. There were no significant differences between PC and EMM of the GI tract with respect to any histologic features.

Disease Course of Plasmacytoma and Extramedullary Myeloma

Outcome data for patients with PCN of the GI tract are summarized in **Table 3.** Overall, half (51) of patients developed additional disease at other sites in the aerodigestive tract, solid viscera, lymph nodes, retroperitoneum and/or soft tissue. Nearly all (95%, 97) patients also had at least one of the clinical CRAB manifestations (hypercalcemia, renal insufficiency, anemia and bone lesions) typical of PCNs. Fifty-three percent (54) of all patients had renal insufficiency (64% or 14 of 22 PC patients, 56% or 35 of 63 of EMM patients), 88% (89) had anemia (86% or 19 of 22 PC patients, 92% or 57 of 63 EMM patients) and 67% (68 patients) had bone lesions (55% or 12 of 22 PC patients, 76% or 48 of 63 EMM patients). Serologic data were available for 82 (80%) patients, most of whom had IgG (51%, 52 patients) or IgA (32%, 31 patients) M protein. Twenty-two percent (22) of patients had a free light chain (FLC) in the serum and/or

urine, including 4 (4%) patients with two M proteins, 11 (11%) patients with a single M protein and a FLC and 1 (1%) patient with two M proteins and a FLC; 10 (10%) patients had only a FLC. Two (9%) patients with PC had two M proteins and none of them had a FLC. For patients with EMM, 1 (2%) had two M proteins, 8 (13%) had one M protein and a FLC and 1 (2%) had two M proteins and a FLC; 7 (11%) had only a FLC. The overall Kappa/Lambda ratio was 1.1 for all patients. Interestingly, only 4 (4%) patients developed amyloidosis, all of whom had EMM. Data regarding the ISS stage at the time of presentation, when applicable, was available for 66 (65%) patients, 50% (22 of 44 patients) of whom who were stageable had ISS stage 3.

Available flow cytometry information revealed a clonal plasma cell population in 63 of the 85 patients with known bone marrow involvement; the remaining 22 (22%) patients had unknown flow cytometry information. Additional immunophenotypic and cytogenetic characteristics were not available for enough of the study patients to include for evaluation.

Treatment information was available for 90 (89%) of the patients, most of whom (88%, 79 patients) received chemotherapy. Twenty-one percent (19 patients) received concomitant radiation, and 43 (42%) received a hematopoietic stem cell transplantation (HSCT). In 7 (24%) patients who initially presented as PC seemingly confined to the GI tract, the time interval to the discovery of marrow involvement and true classification as EMM ranged from 5 days to 4.3 weeks (median 2.7 weeks). On the other hand, 48 (76%) patients who presented with marrow involvement by myeloma often developed EMM within 1 year after initial diagnosis (median 1.5 years, range 2 weeks to 15.8 years). Seven (7%) patients were found to have EMM at the time of autopsy. Outcome data were available in 94 (92%) patients. Most died from disease (70%, 71 of

all patients; 55% or 12 of 22 PC patients and 73% or 46 of 63 EMM patients). Median time from diagnosis to death among all patients was 14.1 weeks and, excluding autopsy, 58% (34 of 59 patients) died from disease within 6 months from diagnosis. There were no significant differences regarding outcomes among patients with PC compared with those who had EMM.

Prognostic Factors

Features associated with a poor prognosis are summarized in **Table 4.** Statistically significant characteristics among deceased patients included liver involvement ($p < 0.01$), presence of FLCs ($p = 0.02$), bone lesions ($p = 0.0466$), ISS stage 3 ($p = 0.04$) and treatment with chemotherapy ($p < 0.01$) without radiation ($p = 0.02$).

No other characteristics were found to be statistically significant between alive and deceased patients. However, there were some unique clinicopathologic differences observed. Deceased patients were more often female (65%, 46 of 71 patients versus 35%, 8 of 23 patients) with multifocal disease (14%, 10 of 71 patients versus 9%, 2 of 23 patients) that showed HG morphology (55%, 39 of 71 patients versus 43%, 10 of 23 patients) compared with patients who did not die of disease during the follow-up period. Patients who died of disease were also more likely to have involvement of the gallbladder (58%, 41 of 71 patients versus 27%, 6 of 23 patients), pancreas (8%, 6 of 71 patients versus 5%, 1 of 23 patients) and/or soft tissue (6%, 4 of 71 patients versus 0%) with frequent marrow involvement (79%, 56 of 71 patients versus 52%, 12 of 23 patients), IgM (3%, 2 of 71 patients versus 0%) or IgD (1%, 1 of 71 patients versus 0%) M proteins, multiple M proteins and/or FLC (37%, 26 of 71 patients versus 26%, 6 of 23 patients) and/or CRAB features (see Table 4).

The clinicopathologic characteristics associated with death among all patients are summarized in **Table 5**.

DISCUSSION

Most previous reports of GI, hepatic and pancreatobiliary involvement by PC or EMM in the literature have been in the form of case reports or small case series. In this retrospective, multi-institutional study, we were able to collect 116 cases from 102 unique patients, the largest cohort to date, along with detailed pathologic and clinical data.

Clinically, we found that the liver, stomach and small bowel were the most common sites of involvement, confirming prior studies in which the liver was the most commonly involved organ.[1] We also found multiple cases of PCNs presenting simultaneously in 2 or more GI sites, which has been infrequently reported.[2–4] GI bleeding was the most common presenting finding, followed by abdominal pain and elevated liver enzymes; many cases were incidentally found. Fifty-three percent of patients had renal insufficiency, 88% had anemia and 75% had bone lesions. The majority of patients had IgG M protein, and 27% had a serum and/or urine FLC. The most common imaging finding was a nodule or mass. Thirteen percent of patients had their PCN found during routine follow-up of their myeloma, and 20% had their PCN found during evaluation for an unrelated reason. EMM was less likely than PC to present incidentally during evaluation for another disorder, and EMM was also more frequently associated with renal failure. Overall, half of patients developed additional sites of disease in a wide range of places after the diagnosis of their GI PCN, including the aerodigestive tract, solid organs, lymph nodes,

retroperitoneum and soft tissue. Interestingly, only 4 patients developed amyloidosis, all of whom had EMM. In the entire cohort, EMM was almost three times more common than PC, supporting previous literature that also indicates that EMM is much more common than true PC.[7,28]

Marrow involvement was eventually established in 24% of patients who initially presented as PC with no known marrow involvement. In contrast, 46% of patients who initially presented with marrow involvement developed EMM within one year. Our data emphasize that the appearance of extramedullary GI disease in patients initially presenting with marrow involvement can sometimes occur many years after initial diagnosis, with GI disease detected when patients are symptomatic or undergo routine screening for other purposes. Seventy percent of all patients died of disease, the majority within 6 months. Statistically significant characteristics among deceased patients included liver involvement, presence of a FLC and presence of bone lesions.

In terms of the pathologic features, the majority of cases were HG and had a diffuse growth pattern. The marrow was involved at some point during the course of the disease in 74% of patients, and the marrow neoplasm was also usually HG. In 81% of patients, this was concordant with the tumor grade of the PC or EMM. Deceased patients were more likely to have multifocal disease and HG tumors, and to have involvement of the gallbladder, pancreas or soft tissue. However, these associations were not statistically significant.

These data indicate several important points about GI PCNs. First, EMM may present before any disease is found in the marrow, and thus may be the initial finding in a patient with MM. Second,

the distinction between a true PC and EMM with marrow involvement is crucial, as management and prognosis may differ markedly.[8,12–16,18,28] For example, radiotherapy is typically first line therapy for PC,[29–34] while chemotherapy and HSCT are typically employed for treating EMM.[29,33] In addition, progression of marrow disease to EMM may alter management, such as the addition of anthracycline-containing combination chemotherapy.[30,32,34]

Our data also highlighted that GI PCNs indicate a poor prognosis, with most patients succumbing to disease within 6 months. Our results also support prior research showing a worse prognosis in patients who were found to have EMM several years after their marrow diagnosis when compared to patients diagnosed with marrow involvement and EMM were at the same time.[34] Previous literature has also indicated a worse prognosis in patients with PC than EMM, as well as late relapse or marrow involvement (after 5-10 years) following resection of the localized PC.[35] However, this is in contrast to our study, which showed more patients dying with EMM than PC (78% versus 63%), and only rare discovery of marrow involvement in cases that presented as PC (24%).[16]

Plasma cell morphology was notably found to be associated with prognosis, in agreement with multiple older and newer studies.[29,30,32,33,35,36] Specifically, tumors with HG histologic features have long been shown to confer poor prognoses and manifest aggressive clinical behavior; furthermore, decreased overall survival (OS) directly correlates with lesser degrees of plasma cell maturity.[25,27,37–39] The correlation between OS and plasma cell maturity has been upheld in modern studies with current chemotherapeutics, which also show differential response based on tumor grade. For example, OS for LG tumors compared to HG tumors was 20 months versus 8

months from initial biopsy studies performed in the 1980s.[37] OS has increased only slightly in the early 2000s, even with the use of modern treatment modalities, showing the OS for HG tumors as 20 months compared to no significant mortality with LG tumors within the study interval.[25,27] HG morphology further predicts poor response to chemotherapeutics, such as lenalidomide and thalidomide,[37] as well as bortezomib.[37,38] Additionally, modern immunophenotyping and molecular studies have also found correlations with HG morphology, such as MPC-1 negativity by flow cytometry,[37] and lost expression of DEPTOR[37] and IRF4 and EGFR1[38] by molecular studies. Overall, even though grading schemes are infrequently used, our study continues to support that plasma cell maturity is a critical prognostic factor correlated with patient history, clinical progression and survival.

The diagnosis of GI, liver and pancreatobiliary PCNs may present a particular challenge in the GI tract. A diagnosis of PCN may be completely overlooked when considering plasmacytoid neoplasms of the GI tract, and the immunostains that are often used to make this diagnosis mark a wide variety of other entities as well. For example, CD138 is frequently used to confirm a PCN, but CD138 also marks a wide variety of carcinomas, including squamous cell carcinoma, urothelial carcinoma, pancreatic carcinoma and colorectal adenocarcinoma.[39] Conversely, CKIT (CD117), a marker commonly used in the diagnosis of GI stromal tumors (GISTs), consistently marks plasma cells.[40–44] This overlap is particularly important to recognize when dealing with poorly-differentiated neoplasms, PCNs with unusual features such as spindled morphology[45,46] or neoplasms with plasmacytoid morphology such as plasmacytoid GISTs or melanoma.[47,48] In these circumstances, additional plasma cell markers such as CD38 and CD79a, demonstration of kappa or lambda light chain restriction or the presence of aberrant co-expression of markers such

as CD20, CD28, CD52, CD56, CD200 or other myeloid or monocytic markers, may be helpful in identifying plasma cells. Additional markers of other entities in the differential diagnosis of plasmacytoid neoplasms may be useful as well, such as DOG1 for GIST, cytokeratins or other markers for epithelial lineage or melanoma markers.

Numerous other B-cell lymphomas are well known to demonstrate plasmacytoid features, such as lymphoplasmacytic lymphoma, chronic lymphocytic lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma and diffuse large B-cell lymphoma, and these should also be considered in the differential diagnosis.[49–51] For example, extranodal marginal zone lymphoma (EMZL), which most commonly presents in the GI tract, often demonstrates plasmacytoid features and is associated with background nonneoplastic plasma cells; one-third of gastric EMZL show plasmacytoid features.[52,53] Additionally, the background plasma cells may rarely transform into neoplastic plasma cells,[54] further complicating the differential diagnosis. Immunohistochemical, flow cytometric and/or molecular studies are pivotal to demonstrate plasma cell or B-cell differentiation, such as CD38 and CD138 for plasma cells and CD19, CD20, CD22 and CD79a for B-cells. Furthermore, plasma cells show negative to dim CD45, in contrast to B-cells, and plasma cells may demonstrate aberrant expression of B-cell markers, such as CD19 and CD20, but with co-existing CD38 and/or CD138. Molecular studies may demonstrate IGH rearrangements in either plasma cell or B-cell neoplasms, and may show specific molecular rearrangements, such as *MYD88* in monoclonal gammopathy of undetermined significance or lymphoplasmacytic lymphoma, *MALT1* in marginal zone lymphoma or *CCND1* in chronic lymphocytic lymphoma, to aid in proper classification.[55]

We recognize the limitations of this study, including the several decade time frame of our study, during which treatment modalities, diagnostic criteria and standard features of the workup for a PCN changed. In addition, we did not have access to complete clinical and pathologic data on all patients, including cytogenetic and molecular analysis that are now considered standard of care. However, patients for whom a bone marrow biopsy was not available were excluded given the critical distinction between PC and EMM for purposes of data analysis. In addition, we think that we effectively excluded other common entities in the differential diagnosis such as extranodal marginal zone lymphoma and lymphoplasmacytic lymphoma, even without complete data, and our confidence in this is bolstered by the finding of IgG M protein in the majority (60%) of patients and IgM M protein in rare (2%) patients. Finally, even though we did not have access to some data, our conclusions regarding prognosis are the same as those drawn in many prior smaller series studying myeloma in the GI tract.

Additional research in this area is needed, particularly on cytogenetic and molecular characteristics between GI PC and EMM that currently play major roles in prognostic stratification, which we were unable to sufficiently evaluate due to lack of data. Retrospective or prospective studies could compare the established prognostic cytogenetic and molecular features of PCNs to the rare PCNs that involve the GI tract. More focused investigation on immunologic features and progression, including M protein presence and persistence, could also be studied to reveal potential prognostic significance as seen in other studies involving all PCNs.[1,52,53,55] Additional clinical information, such as race, ethnicity and rural-urban status,[29,32,33,36,56] could also expand our understanding of these disorders, as would the opportunity to study international cases.

In summary, this study comprises the largest clinicopathologic case series to date of GI PCNs, a rare but important manifestation of extramedullary plasma cell myeloma. Our study shows that both GI PC and EMM are associated with a poor prognosis, particularly in patients with EMM. Most of our patients developed their GI PCNs after the diagnosis of MM in the marrow, but the GI PCN was the presenting finding in some cases. The distinction between true GI PC and EMM is fundamental for the appropriate classification, management and prognosis of these patients. Finally, it is important to recognize that, although rare, GI, liver and pancreatobiliary PCNs are important entities in the differential diagnosis of plasmacytoid neoplasms of the GI tract.

ABBREVIATIONS

CRAB: Hypercalcemia, renal insufficiency, anemia, bone lesions

EMM: Extramedullary myeloma

GI: Gastrointestinal

HG: High-grade

HSCT: Hematopoietic stem cell transplantation

ISS: International Staging System

LG: Low-grade

MM: Multiple myeloma

N/A: Not applicable

PC: Plasmacytoma

PCN: Plasma cell neoplasm

SPEP: Serum protein electrophoresis

TPE: Therapeutic plasma exchange

FIGURE LEGENDS

Figure 1. A liver biopsy of a mass lesion in a myeloma patient shows a mass composed of neoplastic plasma cells (A, 8X). Higher power view shows prominent sinusoidal involvement that is common in plasma cell neoplasms of the liver (B, 20X). Prominent sinusoidal involvement is also seen in this autopsy specimen from a myeloma patient with hepatic EMM (C, 8X and D, 20X). High-power views demonstrate plasma cell morphology (E, 40X and F, 40X).

Figure 2. This gastric plasma cell neoplasm shows expansion of the lamina propria by neoplastic plasma cells (A, 8X and B, 20X). High-power views demonstrate plasma cell morphology (C, 40X and D, 40X).

Figure 3. Representative examples of low-grade (LG) and high-grade (HG) plasma cell neoplasms involving the GI tract, liver, and pancreas. LG tumors (A-B, 40X) demonstrated mature plasma cell morphology. HG tumors (C-D, 40X) demonstrated blastic or anaplastic morphology.

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Table 1. Patient Characteristics at Presentation

Characteristics	Overall	Plasmacytoma	Extramedullary Myeloma	P-Value
Total Patients (Total Cases)	102 (116)	22 (26)	63 (71)	**<0.01**
Age (Median, Years)	15-86 (63)	44-85 (62.5)	15-86 (64)	0.59
Gender (% Male/Female)	56/46 (55/45)	15/7 (68/32)	31/32 (49/51)	0.12
Presentation (% Patients)	Abdominal pain: 10 (10)	Abdominal pain: 2 (9)	Abdominal pain: 6 (10)	0.55
	Anemia: 4 (4)	Anemia: 0	Anemia: 4 (6)	1.00
	Ascites: 1 (1)	Ascites: 0	Ascites: 1 (2)	1.00
	Back pain: 3 (3)	Back pain: 0	Back pain: 2 (3)	1.00
	Diverticulitis: 1 (1)	Diverticulitis: 0	Diverticulitis: 1 (2)	1.00
	Dysphagia: 2 (2)	Dysphagia: 0	Dysphagia: 2 (3)	1.00
	Fatigue: 3 (3)	Fatigue: 0	Fatigue: 2 (3)	1.00
	Fever: 4 (4)	Fever: 0	Fever: 4 (6)	1.00
	GI bleeding: 15 (15)	GI bleeding: 3 (14)	GI bleeding: 9 (14)	0.51
	Hemoptysis: 1 (1)	Hemoptysis: 0	Hemoptysis: 1 (2)	1.00
	Incidental during myeloma follow-up: 11 (11)	Incidental during myeloma follow-up: N/A	Incidental during myeloma follow-up: 8 (13)	N/A
	Incidental during workup for another disorder: 18 (18)	Incidental during workup for another disorder: 8 (36)	Incidental during workup for another disorder: 10 (16)	**0.01**
	Jaundice: 2 (2)	Jaundice: 0	Jaundice: 2 (3)	1.00
	Liver failure: 1 (1)	Liver failure: 0	Liver failure: 1 (2)	1.00
	Nausea: 6 (6)	Nausea: 1 (5)	Nausea: 3 (5)	0.63
	Pancreatitis: 1 (1)	Pancreatitis: 0	Pancreatitis: 1 (2)	1.00
	Pneumonia: 1 (1)	Pneumonia: 0	Pneumonia: 1 (2)	1.00
	Rash: 1 (1)	Rash: 0	Rash: 1 (2)	1.00
	Reflux: 1 (1)	Reflux: 1 (5)	Reflux: 0	0.22
	Renal failure: 3 (3)	Renal failure: 3 (14)	Renal failure: 1 (2)	**0.03**
	Shock: 2 (2)	Shock: 0	Shock: 2 (3)	1.00
	Small bowel obstruction: 2 (2)	Small bowel obstruction: 0	Small bowel obstruction: 2 (3)	1.00
	Shortness of breath: 2 (2)	Shortness of breath: 0	Shortness of breath: 2 (3)	1.00
	SPEP spike: 1 (1)	SPEP spike: 0	SPEP spike: 1 (2)	1.00
	Transaminitis: 9 (9)	Transaminitis: 0	Transaminitis: 9 (14)	1.00
	Vomiting: 3 (3)	Vomiting: 1 (5)	Vomiting: 2 (3)	0.52
	Weakness: 6 (6)	Weakness: 1 (5)	Weakness: 4 (6)	0.72
	Weight loss: 3 (3)	Weight loss: 1 (5)	Weight loss: 2 (3)	0.52
	Unknown: 14 (14)	Unknown: 6 (27)	Unknown: 5 (8)	N/A
Involved Site(s) (% Patients)	Ampulla: 1 (1)	Ampulla: 0	Ampulla: 1 (2)	1.00
	Appendix: 1 (1)	Appendix: 0	Appendix: 1 (2)	1.00
	Celiac plexus: 1 (1)	Celiac plexus: 1 (5)	Celiac plexus: 0	0.26
	Colon: 7 (7)	Colon: 2 (9)	Colon: 3 (5)	0.39
	Esophagus: 1 (1)	Esophagus: 1 (5)	Esophagus: 0	0.26
	Gallbladder: 2 (2)	Gallbladder: 1 (5)	Gallbladder: 1 (2)	0.45
	Liver: 48 (47)	Liver: 5 (23)	Liver: 38 (60)	**<0.01**
	Mesentery: 3 (3)	Mesentery: 1 (5)	Mesentery: 2 (3)	0.60
	Pancreas: 7 (7)	Pancreas: 3 (14)	Pancreas: 4 (6)	0.26
	Parotid: 1 (1)	Parotid: 0	Parotid: 0	1.00
	Pharynx: 1 (1)	Pharynx: 0	Pharynx: 1 (2)	1.00
	Retroperitoneum: 1 (1)	Retroperitoneum: 1 (5)	Retroperitoneum: 1 (5)	0.45
	Small bowel: 18 (18)	Small bowel: 4 (18)	Small bowel: 9 (14)	0.45
	Stomach: 24 (24)	Stomach: 7 (32)	Stomach: 11 (17)	0.16
Endoscopic Finding(s) (% Patients)	Bleeding: 3 (3)	Bleeding: 0	Bleeding: 3 (5)	1.00
	Diverticulosis: 1 (1)	Diverticulosis: 0	Diverticulosis: 1 (2)	1.00
	Edema: 1 (1)	Edema: 0	Edema: 1 (2)	1.00
	Erythema: 4 (4)	Erythema: 0	Erythema: 3 (5)	1.00
	Friability: 1 (1)	Friability: 0	Friability: 1 (2)	1.00
	Mass or nodule: 17 (17)	Mass or nodule: 0	Mass or nodule: 12 (19)	1.00
	Luminal narrowing: 1 (1)	Luminal narrowing: 0	Luminal narrowing: 1 (2)	1.00
	Normal: 3 (3)	Normal: 0	Normal: 0	1.00
	Polyp: 5 (5)	Polyp: 0	Polyp: 2 (3)	1.00
	Ulceration: 8 (8)	Ulceration: 1 (5)	Ulceration: 4 (6)	0.19
	Wall thickening: 2 (2)	Wall thickening: 0	Wall thickening: 2 (3)	1.00

	Unknown: 64 (63)	Unknown: 21 (95)	Unknown: 38 (60)	N/A
Imaging Findings (% Patients)	Ascites: 1 (1) Cirrhosis: 1 (1) Hepatomegaly: 3 (3) Hepatosplenomegaly: 1 (1) Mass or nodule: 64 (63) Mesenteric fat stranding: 1 (1) Normal: 4 (4) Pleural effusion: 1 (1) Steatosis: 1 (1) Wall thickening: 4 (4) Unknown: 25 (24)	Ascites: 1 (5) Cirrhosis: 0 Hepatomegaly: 0 Hepatosplenomegaly: 0 Mass or nodule: 11 (50) Mesenteric fat stranding: 0 Normal: 1 (5) Pleural effusion: 0 Steatosis: 0 Wall thickening: 1 (5) Unknown: 9 (41)	Ascites: 0 Cirrhosis: 1 (2) Hepatomegaly: 3 (5) Hepatosplenomegaly: 0 Mass or nodule: 42 (67) Mesenteric fat stranding: 1 (2) Normal: 3 (5) Pleural effusion: 1 (2) Steatosis: 1 (2) Wall thickening: 3 (5) Unknown: 12 (19)	0.20 1.00 1.00 1.00 0.16 1.00 0.61 1.00 1.00 0.61 N/A

Total percentages may not equal 100% due to rounding. Sum of characteristics may not equal total patients due to multiple features in the same patient. Sum of PC and EMM cases does not equal total patients due to 17 patients with unknown bone marrow involvement. P-values in bold are statistically significant ($\alpha = 0.05$). Abbreviations: GI, gastrointestinal; N/A, not applicable; SPEP, serum protein electrophoresis.

Table 2. Pathologic Characteristics

Characteristics	Overall	Plasmacytoma (n = 22)	Extramedullary Myeloma (n = 63)	P-Value
GI Tumor Growth Pattern at Presentation (% Patients)	Diffuse: 58 (57) Focal: 19 (19) Polypoid: 4 (4) Unknown: 21 (21)	Diffuse: 12 (55) Focal: 2 (9) Polypoid: 2 (9) Unknown: 6 (27)	Diffuse: 36 (57) Focal: 14 (22) Polypoid: 1 (2) Unknown: 12 (19)	0.73 0.95 0.14 N/A
GI Tumor Grade at Presentation (% Patients)	LG: 39 (38) HG: 55 (54) Unknown: 8 (8)	LG: 7 (32) HG: 13 (59) Unknown: 2 (9)	LG: 19 (30) HG: 38 (60) Unknown: 6 (10)	0.89
Marrow Involvement During Disease Course (% Patients)	Yes: 63 (62) No: 22 (22) Unknown: 17 (17)	N/A	N/A	N/A
Marrow Neoplasm Grade (% Patients)	LG: 20 (20) HG: 35 (34) N/A: 24 (24) Unknown: 23 (23)	N/A	LG: 20 (32) HG: 35 (56) Unknown: 8 (13)	N/A
Concordant GI and Marrow Neoplasm Grades (% Patients)	Yes: 44 (43) No: 10 (10) N/A: 22 (22) Unknown: 26 (25)	N/A	Yes: 44 (70) No: 10 (16) Unknown: 9 (14)	N/A

Total percentages may not equal 100% due to rounding. Abbreviations: GI, gastrointestinal; HG, high-grade; LG, low-grade; N/A, not applicable.

Table 3. Disease Course of Patients with Plasmacytoma versus Extramedullary Myeloma

Characteristics	Overall	Plasmacytoma (n = 22)	Extramedullary Myeloma (n = 63)	P-Value
ISS Stage at Presentation (% Patients)	1: 10 (10) 2: 12 (12) 3: 22 (22) N/A: 22 (22) Unknown: 36 (35)	N/A	1: 8 (13) 2: 10 (16) 3: 19 (30) Unknown: 26 (41)	N/A
Immunology (% Patients) **Sub-Total (% Patients)**	IgA: 32 (31) Kappa: 15 (15) Lambda: 17 (17) IgD: 1 (1) Kappa: 0 Lambda: 1 (1) IgE: 0 IgG: 52 (51) Kappa: 32 (31) Lambda: 20 (20) IgM: 2 (2) Kappa: 0 Lambda: 2 (2) FLC: 22 (22) Kappa: 11 (11) Lambda: 11 (11) Overall K/L: 1.1 Kappa: 58 (57) Lambda: 51 (50) Multiple: 16 (16) Unknown: 20 (20)	IgA: 7 (32) Kappa: 4 (18) Lambda: 3 (14) IgD: 0 Kappa: 0 Lambda: 0 IgE: 0 IgG: 12 (55) Kappa: 7 (32) Lambda: 5 (23) IgM: 1 (5) Kappa: 0 Lambda: 1 (5) FLC: 0 Kappa: 0 Lambda: 0 Overall K/L: 1.2 Kappa: 11 (50) Lambda: 9 (41) Multiple: 2 (9) Unknown: 4 (18)	IgA: 20 (32) Kappa: 9 (14) Lambda: 11 (17) IgD: 1 (2) Kappa: 0 Lambda: 1 (2) IgE: 0 IgG: 33 (52) Kappa: 23 (37) Lambda: 10 (16) IgM: 1 (2) Kappa: 0 Lambda: 1 (2) FLC: 15 (24) Kappa: 8 (13) Lambda: 7 (11) Overall K/L: 1.3 Kappa: 40 (63) Lambda: 30 (48) Multiple: 17 (27) Unknown: 10 (16)	0.93 0.43 0.76 1.00 1.00 1.00 1.00 0.74 0.74 0.42 0.46 1.00 0.46 1.00 1.00 1.00 0.86 0.99 N/A
Time Interval from Marrow to EMM Diagnosis (Median) **Sub-Total (% Patients)**	N/A	N/A	2 weeks-15.8 years (1.5 years) 0-4 years: 35 (56) 5-9 years: 9 (14) 10-14 years: 2 (3) 15-20 years: 2 (3) N/A: 9 (14) Unknown: 6 (10)	N/A
Time Interval from Apparent GI PC to Subsequent Marrow Involvement (Median) **Sub-Total (% Patients)**	N/A	N/A	5 days-4.3 weeks (2.7 weeks) 0 - <1 weeks: 2 (3) ≥1 - <2 weeks: 1 (2) ≥2 - <3 weeks: 1 (2) ≥3 - <4 weeks: 1 (2) ≥4 - <5 weeks: 2 (3)	N/A
Development of Additional GI Sites (% Patients)	Yes: 51 (50) No: 51 (50)	Yes: 10 (45) No: 12 (55)	Yes: 32 (51) No: 31 (49)	0.67
Development of CRAB Features (% Patients)	Hypercalcemia Yes: 36 (35) No: 64 (63) Unknown: 2 (2) Renal insufficiency Yes: 54 (53) No: 47 (46) Unknown: 1 (1) Anemia Yes: 89 (88) No: 12 (12) Unknown: 1 (1) Bone lesions Yes: 68 (67) No: 23 (23) Unknown: 11 (11)	Hypercalcemia Yes: 6 (27) No: 16 (73) Unknown: 0 (0) Renal insufficiency Yes: 14 (64) No: 8 (36) Unknown: 0 (0) Anemia Yes: 19 (86) No: 3 (14) Unknown: 0 (0) Bone lesions Yes: 12 (55) No: 4 (18) Unknown: 6 (27)	Hypercalcemia Yes: 24 (38) No: 37 (59) Unknown: 2 (3) Renal insufficiency Yes: 35 (56) No: 27 (43) Unknown: 1 (2) Anemia Yes: 57 (90) No: 5 (8) Unknown: 1 (2) Bone lesions Yes: 48 (76) No: 10 (16) Unknown: 5 (8)	0.31 0.56 1.88 1.86

Development of Amyloidosis (% Patients)	Yes: 4 (4) No: 97 (96) Unknown: 1 (1)	Yes: 0 (0) No: 22 (100) Unknown: 0 (0)	Yes: 4 (6) No: 58 (92) Unknown: 1 (2)	1.00
Treatment Received (% Patients)	Chemotherapy Yes: 79 (78) No: 11 (11) Unknown: 12 (12)	Chemotherapy Yes: 13 (59) No: 3 (14) Unknown: 6 (27)	Chemotherapy Yes: 52 (83) No: 6 (10) Unknown: 5 (8)	1.91
	Radiation Yes: 19 (19) No: 71 (70) Unknown: 12 (12)	Radiation Yes: 5 (23) No: 11 (50) Unknown: 6 (27)	Radiation Yes: 10 (16) No: 48 (76) Unknown: 5 (8)	0.22
	Hematopoietic stem cell transplant Yes: 43 (42) No: 47 (46) Unknown: 12 (12)	Hematopoietic stem cell transplant Yes: 9 (41) No: 7 (32) Unknown: 6 (27)	Hematopoietic stem cell transplant Yes: 28 (44) No: 30 (48) Unknown: 5 (8)	0.57
	Therapeutic plasma exchange Yes: 1 (1) No: 90 (89) Unknown: 11 (11)	Therapeutic plasma exchange Yes: 0 (0) No: 16 (73) Unknown: 6 (27)	Therapeutic plasma exchange Yes: 1 (2) No: 57 (90) Unknown: 5 (8)	1.00
Patient Outcome (% Patients)	Alive: 23 (23) Deceased: 71 (70) Unknown: 8 (8)	Alive: 7 (32) Deceased: 12 (55) Unknown: 3 (14)	Alive: 13 (21) Deceased: 46 (73) Unknown: 4 (6)	0.20
Time Interval from Diagnosis to Death (Median)	0 days-10.0 years (14.1 weeks)	1.4 weeks-63.1 weeks (22.6 weeks)	0 days-9.8 years (13.1 weeks)	0.09
Sub-Total (% Patients)	0-4 years: 63 (62) 5-9 years: 1 (1) 10-14 years: 2 (2) N/A: 23 (23) Unknown: 13 (13)	0-4 years: 8 (36) 5-9 years: 0 10-14 years: 0 N/A: 7 (32) Unknown: 7 (32)	0-4 years: 44 (70) 5-9 years: 0 10-14 years: 1 (2) N/A: 13 (21) Unknown: 5 (8)	0.09 1.00 1.00 N/A N/A

Total percentages may not equal 100% due to rounding. Sum of characteristics may not equal total patients due to multiple features in the same patient. Abbreviations: CRAB, hypercalcemia, renal insufficiency, anemia, bone lesions; EMM, extramedullary myeloma; GI, gastrointestinal; ISS, International Staging System; N/A, not applicable; PC, plasmacytoma.

Table 4. Selected Characteristics Comparing Alive versus Deceased Patients among All Patients with Known Outcome.

Characteristics	Alive (n = 23)	Deceased (n = 71)	P-Value
Time Interval from Marrow to EMM Diagnosis (Median)	4.3 weeks-12.3 years (1.7 years)	0 days-15.8 years (1.4 years)	1.96
Sub-Total (% Patients)	0-4 years: 5 (22)	0-4 years: 38 (54)	1.96
	5-9 years: 3 (13)	5-9 years: 7 (10)	0.18
	10-14 years: 1 (4)	10-14 years: 2 (3)	0.40
	15-20 years: 0	15-20 years: 2 (3)	1.00
	N/A: 13 (57)	N/A: 16 (23)	N/A
	Unknown: 1 (4)	Unknown: 6 (8)	N/A
Time Interval from Apparent GI PC to Subsequent Marrow Involvement (Median)	5 days-18 weeks (3.7 weeks)	6 days-4.4 weeks (3.4 weeks)	2.00
Sub-Total (% Patients)	0-4 weeks: 3 (13)	0-4 weeks: 4 (6)	2.00
	5-9 weeks: 1 (4)	5-9 weeks: 0	0.56
	10-14 weeks: 0	10-14 weeks: 0	1.00
	15-20 weeks: 1 (4)	15-20 weeks: 0	0.56
	N/A: 17 (74)	N/A: 61 (86)	N/A
	Unknown: 1 (4)	Unknown: 6 (8)	N/A
Development of Additional GI Sites (% Patients)	Yes: 13 (57)	Yes: 36 (51)	0.63
	No: 10 (43)	No: 35 (49)	
Development of CRAB Features (% Patients)	Hypercalcemia	Hypercalcemia	0.10
	Yes: 5 (22)	Yes: 30 (42)	
	No: 17 (74)	No: 41 (58)	
	Unknown: 1 (4)	Unknown: 0	
	Renal insufficiency	Renal insufficiency	0.40
	Yes: 10 (43)	Yes: 38 (54)	
	No: 13 (57)	No: 33 (46)	
	Unknown: 0	Unknown: 0	
	Anemia	Anemia	2.00
	Yes: 16 (70)	Yes: 67 (94)	
	No: 7 (30)	No: 4 (6)	
	Unknown: 0	Unknown: 0	
	Bone lesions	Bone lesions	**0.0466**
	Yes: 13 (57)	Yes: 53 (75)	
	No: 9 (39)	No: 13 (18)	
	Unknown: 1 (4)	Unknown: 5 (7)	
Development of Amyloidosis (% Patients)	Yes: 1 (4)	Yes: 3 (4)	0.69
	No: 22 (96)	No: 67 (94)	
	Unknown: 0	Unknown: 1 (1)	
Treatment Received (% Patients)	Chemotherapy	Chemotherapy	**<0.01**
	Yes: 5 (22)	Yes: 60 (85)	
	No: 15 (65)	No: 5 (7)	
	Unknown: 3 (13)	Unknown: 6 (8)	
	Radiation	Radiation	**0.02**
	Yes: 8 (35)	Yes: 10 (14)	
	No: 12 (52)	No: 55 (77)	
	Unknown: 3 (13)	Unknown: 6 (8)	
	Hematopoietic stem cell transplant	Hematopoietic stem cell transplant	0.11
	Yes: 7 (30)	Yes: 36 (51)	
	No: 13 (57)	No: 29 (41)	
	Unknown: 3 (13)	Unknown: 6 (8)	
	Therapeutic plasma exchange	Therapeutic plasma exchange	1.00
	Yes: 0	Yes: 1 (1)	
	No: 21 (91)	No: 64 (90)	
	Unknown: 2 (9)	Unknown: 6 (8)	
Treatment Received (% Patients)	Chemotherapy	Chemotherapy	**<0.01**
	Yes: 5 (22)	Yes: 60 (85)	
	No: 15 (65)	No: 5 (7)	

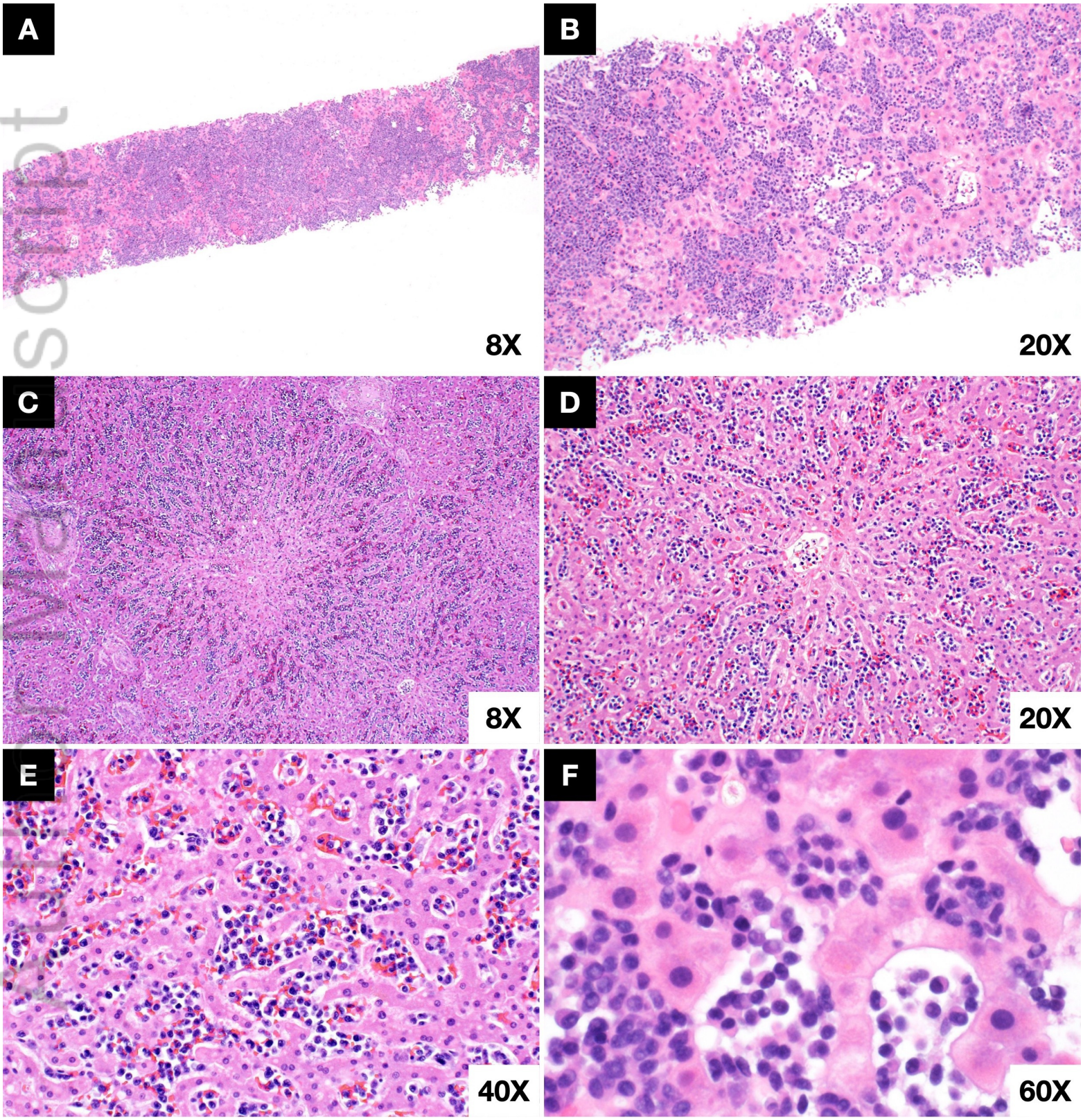
Unknown: 3 (13)	Unknown: 6 (8)	
Radiation	Radiation	**0.02**
Yes: 8 (35)	Yes: 10 (14)	
No: 12 (52)	No: 55 (77)	
Unknown: 3 (13)	Unknown: 6 (8)	
Hematopoietic stem cell transplant	Hematopoietic stem cell transplant	0.11
Yes: 7 (30)	Yes: 36 (51)	
No: 13 (57)	No: 29 (41)	
Unknown: 3 (13)	Unknown: 6 (8)	
Therapeutic plasma exchange	Therapeutic plasma exchange	1.00
Yes: 0	Yes: 1 (1)	
No: 21 (91)	No: 64 (90)	
Unknown: 2 (9)	Unknown: 6 (8)	

Total percentages may not equal 100% due to rounding. Sum of characteristics may not equal total patients due to multiple features in the same patient. P-values in bold are statistically significant ($\alpha = 0.05$). Abbreviations: CRAB, hypercalcemia, renal insufficiency, anemia, bone lesions; EMM, extramedullary myeloma; GI, gastrointestinal; ISS, International Staging System; N/A, not applicable; PC, plasmacytoma.

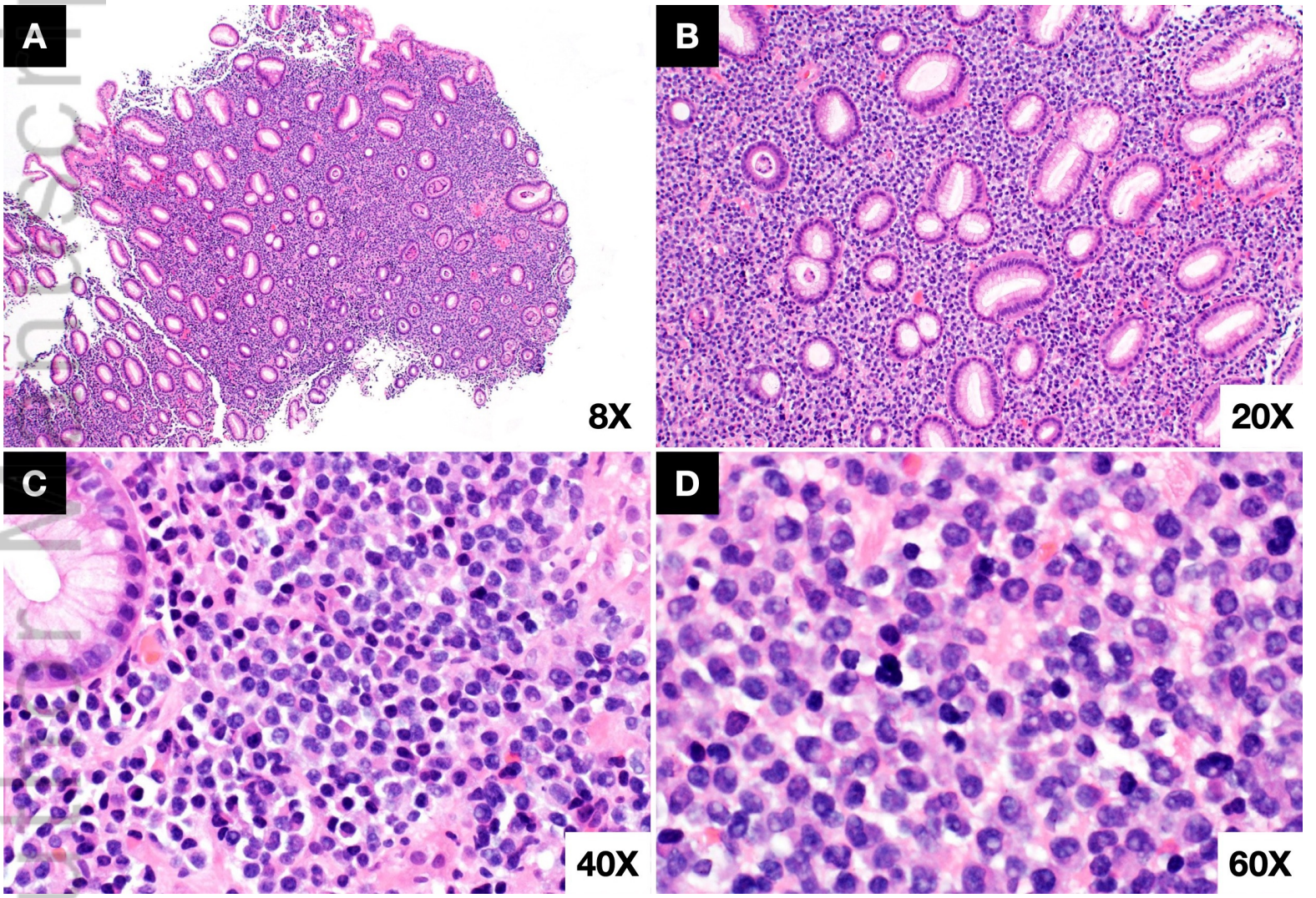
Table 5. Univariate Clinicopathologic Characteristics among all Patients who Died of Disease

Poor Prognosis	P-Value
Amyloidosis	0.69
Bone lesions	**0.0466**
Hematopoietic stem cell transplant	0.11
Chemotherapy	**<0.01**
Female gender	0.33
Free light chains, serum or urine	**0.02**
Gastrointestinal plasma cell neoplasms	N/A
High-grade morphology	0.89
High clinical stage (ISS stage 3)	**0.04**
IgM and IgD M proteins	0.37
Liver involvement	**<0.01**
Multiple M proteins or M protein(s) with serum or urine free light chains	0.64
Multiple sites of disease	0.63
Presentation other than incidental during workup for another disorder	0.38
Radiation (not received)	**0.02**

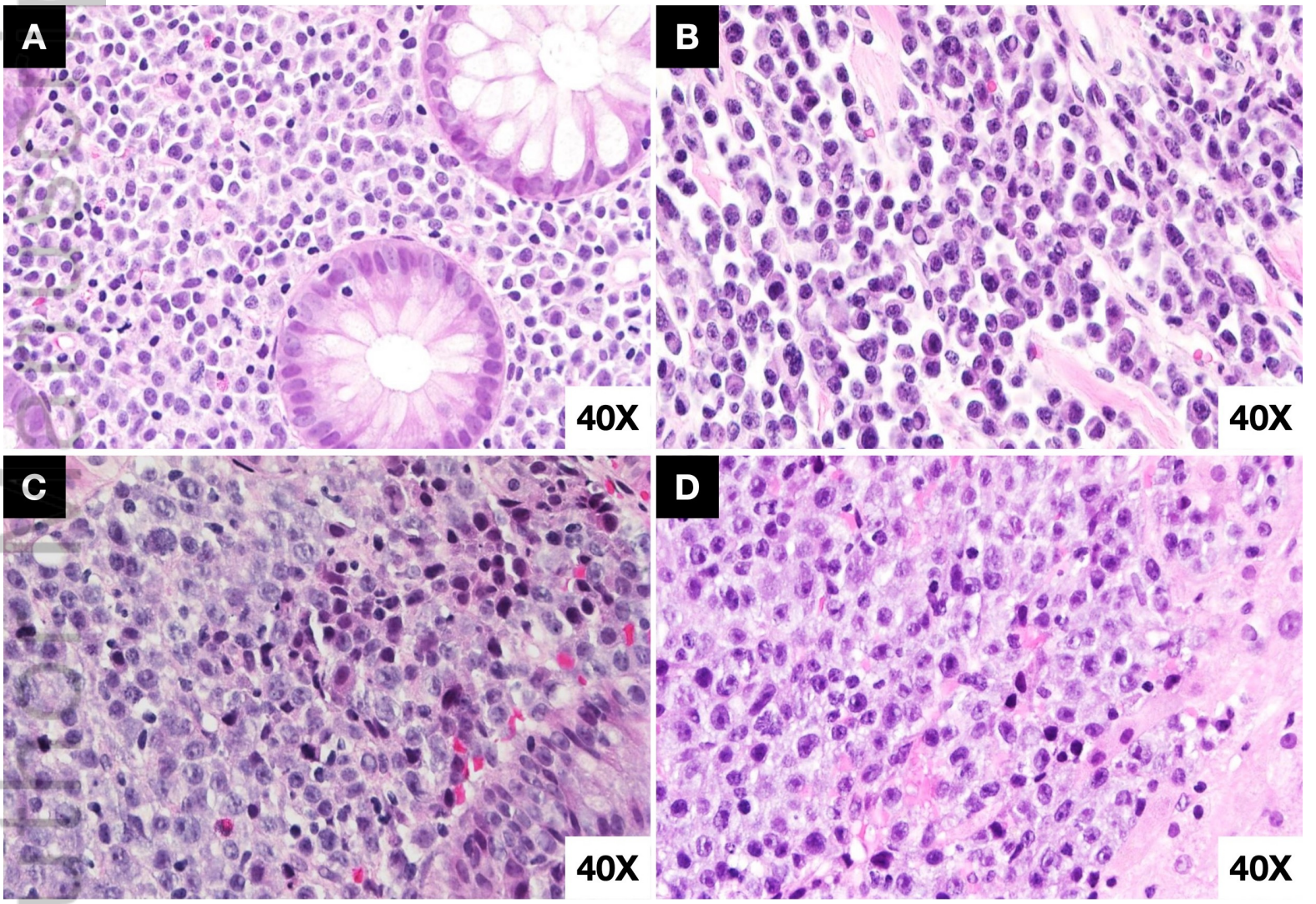
P-values in bold are statistically significant ($\alpha = 0.05$). Abbreviation: ISS, International Staging System.



HIS_14778_Figure 1_GI Plasma Cell Neoplasms.jpg



HIS_14778_Figure 2_GI Plasma Cell Neoplasms.jpg



HIS_14778_Figure 3_GI Plasma Cell Neoplasms.jpg