Clinical and biological features of multiple myeloma involving the gastrointestinal system

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We report 24 cases of multiple myeloma (MM) with involvement of the gastrointestinal (GI) system. We found a strong association with high lactate dehydrogenase levels, plasmablastic morphology, and unfavorable karyotype. GI involvement at the time of initial diagnosis was much rarer than later in the course of the disease. The median survival after diagnosis of GI involvement was 7 months. Among 13 patients treated with stem cell transplantation, the response rate was 92%, and median progression-free survival was 4 months. We conclude that MM involving the GI system is associated with adverse biological features and with short-lasting remissions, even after high-dose chemotherapy.

Key words: gastrointestinal tract, multiple myeloma, plasmacytoma, prognosis, transplantation.

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Involvement of the gastrointestinal (GI) system in the course of multiple myeloma (MM) is extremely rare, and has been described in the medical literature mainly as case reports of single patients. In this study, we retrospectively identified 24 MM patients with direct infiltration of the GI system by MM cells documented by biopsy. We excluded patients with other forms of GI involvement by plasma cell dyscrasias, such as primary extramedullary plasmacytomas, light chain deposition disease, and amyloidosis. We analyzed the clinical and laboratory features of these patients, as well as their treatment outcomes after high-dose chemotherapy and stem cell transplantation (autologous or allogeneic) in order to evaluate whether such an aggressive therapeutic approach had an impact on their survival.

Design and Methods

In a database of 2,584 patients with MM diagnosed and treated at the Myeloma Institute for Research and Therapy (University of Arkansas for Medical Sciences, Little Rock, AR, USA) from August 1997 to November 2003, we identified and analyzed the medical records of 24 patients with involvement of the GI system documented by tissue biopsy. Cytogenetic analysis was obtained from the bone marrow (BM) aspirate and, when possible, from the tumor involving the GI organ. The response to treatment was defined according to Bladé's criteria.[1] Written informed consent, approved by the Institutional Review Board and the Food and Drug Administration, had been obtained according to the Institution and National Cancer Institute guidelines.

Results

The clinical features of the 24 patients are shown in Table 1. Their mean age was 54 years (range, 35-82). Men and women were equally affected (11 and 13 patients, respectively). The GI system was involved at the time of initial diagnosis in only three patients, while in the other 21 patients, it became involved later during the course of the disease. In 14 of 24 (58%) patients, the involvement of the GI system occurred as a manifestation of disease relapse after stem cell transplantation. Myeloma-related renal insufficiency with a serum creatinine >2 mg/dL was present in five patients (21%) at the time of diagnosis. The monoclonal protein secreted by the myeloma cells was IgG κ in ten patients, IgG λ in five, IgA κ in three, IgA λ in two, free κ light chains in one, free λ light chains in one, and two patients had non-secretory disease. In ten patients, the GI system was the only site of macroscopic or symptomatic extramedullary involvement, while the other 14 patients had additional extramedullary disease involving various other organs (Table 1). The prevalence of involvement of other extramedullary sites in patients with GI involvement was significantly higher than that seen in the general population of MM patients (11/24 vs 96/2584, $p<0.001$). Table 2 indicates the GI organs involved by the tumor, and the type of involvement. The organ most commonly involved was the liver (11 patients), followed by pancreas (8 patients), stomach (4 patients), peritoneum, with malignant ascites (3 patients), colon (3 patients), rectum (2 patients), duodenum (2 patients), and ileum (1 patient). The organ involvement by

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Table 1. Clinical characteristics of 24 patients with multiple myeloma involving the gastrointestinal system.

Patient	*Diagnosis*	*Durie-Salmon stage at diagnosis*	*Sites of additional extramedullary involvement*
#1	MM	IIIA	Kidneys, adrenal, SC nodules
#2	MM	IIIA	Spleen
#3	SP→MM	SP→IIIA	Kidney
#4	MM	IIIB	No
#5	MM	IIIA	Kidneys, adrenal, spleen, LN
#6	MM	IIIA	Periorbital soft tissues
#7	MM	IA *	No
#8	MM	IIIA *	No
#9	MM	IIIA	Paraortic LN
#10	MM	IIIA	CNS, pelvic soft tissues
#11	MM	IIIB	No
#12	SP→MM→PCL	SP→IIIA	SC nodules, pleural plaques
#13	MM	IIIB	No
#14	MM	IA *	No
#15	MM	IIIA	No
#16	MM	IIIA	Lungs, perinephric soft tissue
#17	MM	IIIB	No
#18	MM	IIIB	No
#19	MM	IIIA	SC nodules
#20	MM	IIIA	CNS, pleurae, pericardium, testis, LN
#21	MM	IIIA	No
#22	MM	IIIA	Mesenteric LN, SC nodules
#23	MGUS→MM	MGUS→IIIA	Breasts
#24	MGUS→MM	MGUS→IIIA	Mesenteric LN, Parotid gland

**patients with involvement of the GI system at presentation.*
CNS: central nervous system; LN: lymph nodes; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; PCL: plasma cell leukemia; SC: subcutaneous; SP: solitary plasmacytoma.

tumor cells was in the form of macroscopic nodules or masses in 26 organs, and diffuse microscopic infiltration in eight organs. In ten of 24 patients, the GI involvement was initially asymptomatic, and found only incidentally by imaging studies (computed tomography or positron emission tomography) (6 patients), or at autopsy (4 patients). The reported symptoms and signs are shown in Table 2. Sixteen of 24 patients (67%) had a lactate dehydrogenase (LDH) level >250 IU/L (institutional upper limit of normal), and the median LDH level was 377 IU/L (range, 127-1047). The median bone marrow plasmacytosis at the time of GI involvement was 60% (range, 5-90%). The morphologic features of plasma cells in the affected GI organ were classified as Bartl grade I (*Marschalko-like*) in three patients, grade II (either *asynchronous* or *polymorphous*) in 14 patients, and grade III (*plasmablastic*) in seven patients. The prevalence of plasmablastic morphology in patients with MM involving the GI system was significantly higher than that seen in the total population of MM patients (7/24 vs 163/2536, $p<0.001$). The cytogenetic analysis of the bone marrow showed a complex karyotype in 16 patients, (including monosomy 13 in 11 patients), and normal results in six patients, as shown in Table 3. The prevalence of unfavorable cytogenetic abnormalities in the bone marrow was significantly higher than that seen in the general population of MM patients (14/20 vs

Table 2. Sites and types of myelomatous lesions, and related clinical manifestations, in 24 patients with multiple myeloma involving the gastrointestinal system.

Patient	*Involved GI organs*	*Clinical manifestations*
1	Colon (left pericolic mass) Pancreas (diffuse infiltration)	None (incidental finding at CT). Later: bile duct obstruction and jaundice
2	Duodenum (nodules) Liver (mass)	Nausea, vomiting (diagnosis at EGD done to rule out GVHD)
3	Stomach (diffuse infiltration) Peritoneum (ascites) Pancreas (peripheral mass)	Nausea, dyspepsia, ascites
4	Liver (diffuse infiltration + nodule, 0.5×0.4 cm)	Liver failure, with serum bilirubin 8.3 mg/dL (liver involvement documented at autopsy)
5	Liver (diffuse infiltration)	None (GI involvement found at autopsy)
6	Pancreas (mass, 5 cm)	Jaundice, due to obstruction of CBD
7	Stomach (mass, 4×10 cm) -Rectum (? size)	Upper GI bleeding (with melena and anemia). *H. Pylori* was found within the gastric mass
8	Colon (right colonic mass, 6.5x6.5 cm)	Weight loss, abdominal discomfort
9	Liver (diffuse infiltration) Pancreas (nodule)	None (incidental finding at autopsy)
10	Liver (multiple lesions, largest 7.3×6.0 cm)	Abdominal pain
11	Liver (multiple lesions, largest 1.5 cm)	None (incidental finding at CT)
12	Liver (multiple lesions, largest 6.5 cm)	None (incidental finding at CT)
13	Liver (multiple small nodules)	Altered LFT, with serum bilirubin 1.8 mg/dL
14	Rectum (polyp, 1.8 cm)	Tenesmus, hematochezia
15	Peritoneum (nodule, 2.0×2.0, ascites)	Ascites (myeloma cells found in ascitic fluid)
16	Pancreas (mass in pancreatic head, 8x7 cm) Duodenum (infiltration)	Abdominal pain, nausea, vomiting, altered LFT (with serum bilirubin 5.3 mg/dL) due to obstruction of CBD. Later: UGI bleeding
17	Liver (two masses, largest 2.3×3.5 cm)	None (incidental finding at CT)
18	Liver (multiple masses, largest 4.5×5.9 cm)	None (incidental findings at PET scan)
19	Stomach (diffuse infiltration) Pancreas (peripheral mass) Peritoneum (ascites)	Gastric outlet syndrome, with nausea and vomiting. Ascites (myeloma cells found in ascitic fluid)
20	Liver (eight focal lesions, largest 1.2 cm)	None (incidental finding at autopsy)
21	Pancreas (mass in pancreatic head, 3.5×2.0)	None (incidental finding at autopsy)
22	Cecal mass (8.5×8.3 cm)	Lower GI bleeding
23	Stomach (nodular thickening of the fundus)	None (incidental finding at PET scan)
24	Ileum (mass, 5.2×4.7 cm) Pancreas (mass, 3.2×2.4 cm in head)	Small bowel obstruction

CBD: common bile duct; CT: computerized tomography; EGD: esophagogastroduodenoscopy; GI: gastrointestinal; GVHD: graft-versus-host disease; LFT: liver function tests; PET: positron-emission tomography; UGI: upper gastrointestinal.

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Table 3. Morphologic features and cytogenetic analysis of plasma cells in 24 patients with multiple myeloma involving the gastrointestinal system.

Patient	Bartl grade in BM	Bartl grade in GI organ	Cytogenetic analysis in BM	Cytogenetic analysis in GI organ
#1	III (plasmablastic)	III (plasmablastic)	Complex, -13	[same as in BM]
#2	I (n/a)	I (n/a)	Normal	n/a
#3	III (plasmablastic)	n/a	Normal	n/a
#4	II (asynchronous)	II (asynchronous)	n/a	n/a
#5	II (asynchronous)	II (asynchronous)	Complex	n/a
#6	II (polymorphous)	II (asynchronous)	Complex, -13	n/a
#7	I (Marschalko-like)	I (Marschalko-like)	Normal	n/a
#8	II (n/a)	II (n/a)	Complex	n/a
#9	I (Marschalko-like)	I (Marschalko-like)	Complex, -13	n/a
#10	III (plasmablastic)	III (plasmablastic)	Complex, -13	Complex [different from BM]
#11	II (n/a)	n/a	Normal	n/a
#12	III (plasmablastic)	n/a	Complex, -13	Complex [different from BM]
#13	II (asynchronous)	II (asynchronous)	Normal	Complex
#14	II (polymorphous)	n/a	Normal	n/a
#15	n/a	III (plasmablastic)	Complex	[same as in BM]
#16	III (plasmablastic)	III (plasmablastic)	Complex, -13	n/a
#17	II (asynchronous)	II (asynchronous)	Complex, -13	n/a
#18	II (polymorphous)	II (polymorphous)	Complex, -13	[same as in BM]
#19	II (n/a)	II (n/a)	Complex	[same as in BM]
#20	II (polymorphous)	II (polymorphous)	Complex, -13	n/a
#21	II (polymorphous)	II (polymorphous)	Complex, -13	n/a
#22	III (plasmablastic)	III (plasmablastic)	Complex	n/a
#23	II (asynchronous)	II (asynchronous)	Normal	n/a
#24	II (polymorphous)	n/a	Complex, -13	n/a

The morphologic classification of tumor plasma cells was based on the report of Bartl et al.,[3] who differentiated six histologic types (Marschalko type, small cell type, cleaved type, polymorphous type, asynchronous type, and blastic type), and combined these types into three prognostic grades: low (I), intermediate (II), and high (III). -13: monosomy 13; BM: bone marrow; GI: gastrointestinal; n/a: not available.

762/1629, p=0.0017). The karyotype of plasma cells involving the GI system was available for seven patients. All karyotypes were complex, displaying various trisomies, monosomies, translocations, and other aberrations (*data not shown*).

After diagnosis of GI involvement, 13 patients were treated with high-dose chemotherapy followed by stem cell transplantation, either autologous (9 patients) or allogeneic (4 patients). The overall response rate was 92%, with three patients achieving complete responses, nine having partial responses, and one patient having progressive disease. The median overall survival was 7 months (range, 1-18); two patients treated with allogeneic transplant died of complications in the immediate post-transplant period. Among the 11 non-transplanted patients, treated with other therapies (including corticosteroids, thalidomide, and bortezomib), the median survival was 4 months (range, 1-10). In the overall group of 24 patients with MM involving the GI system, the median survival after diagnosis of GI involvement was 7 months (range, 1-54). Our study includes the largest series of MM patients with direct GI involvement by tumor plasma cells. We found that involvement of the GI system in MM patients is a rare event, as we identified only 24 cases in a systematic review of a database of 2584 patients, This prevalence of 0.9% could be an underestimate, since GI involvement in MM may be completely asymptomatic and be incidentally found by imaging studies or at autopsy. However, a preliminary analysis of 58 consecutive patients who underwent positron emission tomography scanning for symptomatic MM showed extramedullary disease in only three of them (5%), with no GI involvement, thus confirming the rarity of direct tumor involvement of the GI organs in MM.

We found that GI involvement at the time of initial diagnosis of MM is much rarer than GI involvement later in the course of the disease, and it often develops in patients with relapsing disease after stem cell transplantation. MM can involve almost every organ of the GI system. The clinical manifestations are variable, and depend on the affected organ. As with other tumors, MM lesions in the GI system become symptomatic through three main mechanisms: (i) direct invasion of a specific organ (with consequent perforation and hemorrhage in the case of the stomach and intestine, and hepatic failure in the case of the liver); (ii) mechanical pressure due to a mass effect (with gastric outlet syndrome, intestinal obstruction, or jaundice due to biliary tract obstruction); (iii) production of malignant effusion (with development of myelomatous ascites).

The paraprotein produced by plasma cells included several isotypes. Interestingly, we did not find an excess of IgA isotype, as could have been expected considering that IgA is the class of antibody secreted by the lymphoid tissue lining the GI tract. There was an excess of plasmablastic morphology (Bartl grade III), as we previously reported:[2] while plasmablastic morphology is present in only 2% of the general population of MM patients,[3] we observed it in seven of the 24 (29%) patients with GI involvement. There was also an excess of complex karyotypes, with numerous numerical and structural aberrations. Monosomy 13, which is one of the most powerful negative prognostic factors in MM,[4,5] was observed in 46% of our patients, while it is present in only 15% of the general population of MM patients.[6] This association between MM involving the GI system and monosomy 13 may by itself explain the poor outcome of our patients.

The prognosis of our MM patients with GI involvement was poor, even after aggressive treatment. Stem cell transplantation was very effective in inducing tumor remission, but MM relapsed quickly in most patients. These results differ from those achieved in other patients with MM, in whom stem cell transplantation provides long-term remissions (≥5 years) in a substantial percentage of cases.[7] We could not assess the possible benefit of allogeneic transplant in our series, because only four patients were treated with this approach, and two of them died of complications in the immediate post-transplant period. It is possible that a graft-versus-myeloma effect observed in the allogeneic

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setting will improve the outcome in patients with extramedullary MM,[8] and the use of a non-myeloablative approach may eventually prove to be superior in these patients.

In conclusion, the prognosis of our MM patients with involvement of the GI system reflects that of MM with other aggressive biological features, such as monosomy 13 or extramedullary disease in the central nervous system, as previously reported by our group.[9] The generally poor outcome of MM patients with extramedullary disease is best explained by the stroma-independent growth of this disease, a biological characteristic associated with genetic instability and rapid post-transplant relapse.[10] Since stem cell transplants did not provide a significant benefit in terms of durable remissions, novel therapeutic approaches are needed for these patients.

All authors contributed to this article including substantial contributions to concept and design (GT, FC. CKL, SK), analysis and interpretation of data (MPR), drafting the article (GT) and revising it critically (MZ, BB, EK, GT). The authors declare that they have no potential conflicts of interest.

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References

1. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating response in patients with multiple myeloma treated by high-dose therapy and hematopoietic stem cell transplantation. Br J Haematol 1998;102:1115-23.
2. Lamps LW, Moix FM, Zhang FJ, Rochling FA, Spoon FD, Waldron JA. Gastrointestinal involvement by plasma cell myeloma. Mod Pathol 2001; 14:513A.
3. Bartl R, Frisch B, Fateh-Moghadam A, Kettner G, Jaeger K, Sommerfeld W. Histologic classification and staging of multiple myeloma. A retrospective and prospective study of 674 cases. Am J Clin Pathol 1985;87:342-55.
4. Shaughnessy J, Barlogie B. Chromosome 13 deletion in myeloma. Curr Top Microbiol Immunol 1999; 246:199-203.
5. Barlogie B Jr, Shaughnessy JD. Early results of total therapy II in multiple myeloma: implications of cytogenetics and FISH. Int J Hematol 2002;76 Suppl 1:337-9.
6. Sawyer JR, Waldron JA, Jagannath S, Barlogie B. Cytogenetic findings in 200 patients with multiple myeloma. Cancer Genet Cytogenet 1995;82:41-9.
7. Barlogie B, Shaughnessy JD, Tricot G, Jacobson J, Zangari M, Anaissie E, et al. Treatment of multiple myeloma. Blood 2004;103:20-32.
8. Badros A, Barlogie B, Siegel E, Cottler-Fox M, Zangari M, Fassas A, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. J Clin Oncol 2002; 20: 1295-303.
9. Fassas AB, Muwalla F, Berryman T, Benramdane R, Joseph L, Anaissie E, et al. Myeloma of the central nervous system: association with high-risk chromosomal abnormalities, plasmablastic morphology and extramedullary manifestations. Br J Haematol 2002;117:103-8.
10. Tricot GJ. New insights into the role of microenvironment in multiple myeloma. Int J Hematol 2002;76 Suppl 1:334-6.

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