CASE REPORT





Koki Tamai^{1,2}, Hajime Hirose^{2*}, Yo Akazawa², Yukihiro Yoshikawa¹, Masatoshi Nomura¹, Hiroshi Takeyama², Masahiro Tokunaga³, Mitsuyoshi Tei¹, Shu Okamura² and Yusuke Akamaru¹

Abstract

Background Concomitant multiple myeloma (MM) and other primary malignancies is rare. Therefore, the treatment outcomes of patients with these conditions have not been well discussed. Lenalidomide is an oral thalidomide analog drug used for MM. Recently, the antitumor effect of lenalidomide has been gaining attention, and lenalidomide has been applied for managing solid tumors. The current case showed the treatment course of a patient treated with lenalidomide for concomitant MM and colon cancer with peritoneal dissemination.

Case presentation A 74-year-old female patient receiving treatment for MM was diagnosed with mucinous adenocarcinoma of the transverse colon. The patient was clinically diagnosed with stage IIIC T4aN2M0 disease. Subsequently, laparoscopic colectomy with lymph node dissection was planned. However, intraperitoneal observation revealed peritoneal dissemination that had sporadically and widely spread. Therefore, palliative partial colectomy was performed to prevent future hemorrhage or obstruction. The patient was discharged on the 10th postoperative day without postoperative complication. Based on the patient's preference, lenalidomide was continually administered for MM without systemic chemotherapy. The patient survived for > 36 months without any signs of tumor progression.

Conclusion The current case first showed the treatment course of concomitant MM and colon cancer. The antitumor effect of lenalidomide can possibly contribute to 3-year progression-free survival in patients with mucinous adenocarcinoma of the colon with peritoneal dissemination.

Keywords Lenalidomide, Mucinous adenocarcinoma, Peritoneal dissemination, Multiple myeloma

*Correspondence:

Hajime Hirose

kckmk.gorilano35@gmail.com

¹ Department of Gastroenterological Surgery, Osaka Rosai Hospital,

1179-3 Nagasone-Kitaku, Sakai, Osaka 591-8025, Japan

² Department of Surgery, Suita Municipal Hospital, Kishibeshinmachi 5-7, Suita City, Osaka 564-8567, Japan

³ Department of Hematology, Suita Municipal Hospital, Kishibeshinmachi

5-7, Suita City, Osaka 564-8567, Japan

Background

Multiple myeloma (MM) is a hematologic malignancy in which cancerous plasma cells accumulate in the bone marrow. Concomitant MM and other primary malignancies are rare. However, patients with MM occasionally develop second primary malignancies (SPM) [1, 2]. However, due to its rarity, the treatment course of patients with these conditions has not been well discussed.



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

Lenalidomide is an oral thalidomide analog drug used for MM, and it has immunomodulatory and antiangiogenetic effects. Due to its antitumor effect, several attempts have been made recently to treat solid tumors with lenalidomide alone or in combination with chemotherapy [3].

Herein, we report a case of concomitant MM and mucinous adenocarcinoma of the colon with peritoneal dissemination in a patient with 3-year progression-free survival after lenalidomide treatment without systemic chemotherapy.

Case presentation

A 74-year-old female patient presented with discomfort due to upper abdominal pain. She was diagnosed with MM and was treated with lenalidomide (15 mg/day) for 3 years before visiting the institution. Colonoscopic examination revealed a tumor in the transverse colon, which could not pass through the endoscope (Fig. 1a). Based on the biopsy results, the tumor was diagnosed as mucinous adenocarcinoma. Computed tomography (CT) scan of the abdomen showed irregular circumferential thickening of the transverse colon with enlarged lymph nodes. However, it could not detect distant metastasis (Fig. 1b). Biochemical analysis revealed a high level of carcinoembryonic antigen at 7.9 (normal range: < 5.0) ng/mL and carbohydrate antigen 19-9 at 6372.9 (normal range: < 37.0) U/mL. The patient was clinically diagnosed with stage IIIC T4aN2M0 disease (TNM classification, 8th version).

Laparoscopic colectomy with lymph node dissection was planned 20 days after halting lenalidomide. However, intraperitoneal observation revealed that the nodules strongly suspected of peritoneal dissemination were sporadically and widely spread in the abdominal cavity (small mesentery, descending mesentery, and bilateral upper abdominal wall) (Fig. 2). Due to peritoneal dissemination, radical surgery was not suitable. Then, palliative laparoscopic partial colectomy without sufficient lymph node dissection was conducted to prevent future hemorrhage or obstruction. The surgical



Fig. 1 Preoperative examinations. a Colonoscopy confirmed an obstructive tumor in the transverse colon. b Computed tomography scan showed thickening of the transverse colon (solid arrow) with enlarged lymph nodes (dashed arrow)



Fig. 2 Intraperitoneal surgical view. Small nodules were sporadically and widely spread in the abdominal cavity. a Left lateral abdomen. b Descending mesentery. c Small mesentery

duration was 207 min, and the volume of blood loss was 10 mL.

Histopathological examination confirmed the diagnosis of mucinous adenocarcinoma with serosal erosion, and one positive lymph node metastasis out of four resected lymph nodes. Moreover, an intraperitoneal nodule, resected intraoperatively, was pathologically diagnosed with peritoneal dissemination (Fig. 3). The final diagnosis was stage IVC (T4aN1aM1c). Histologically, after lenalidomide administration, therapeutic effect was not identified. The patient was discharged on the 10th postoperative day without postoperative complication. Although peritoneal dissemination still remained, the patient refused chemotherapy for colon cancer due to fear of adverse events. She decided to receive treatment with lenalidomide only under the management of the department of hematology. Subsequently, administration of lenalidomide was resumed 30 days after surgery. She underwent outpatient follow-up with blood tests, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels test every 3 months and chest and abdominal CT scan every 6 months. She did not present with any signs of tumor progression for > 36 months on regular follow-up (Table 1).

Discussion

Mucinous adenocarcinoma is a unique subtype of colorectal cancer, and it accounts for 5%-15% of all colorectal cancer cases [4]. The characteristics of mucinous adenocarcinoma include easy filtration and metastasis and chemo- or radiotherapy resistance [5]. Therefore, the tumor is often more advanced upon diagnosis compared with differentiated adenocarcinoma and can be refractory to treatment [6]. In the current case, the patient had peritoneal dissemination, which is associated with a poor survival compared with other metastatic sites. Despite the development of systemic chemotherapy, the prognosis of unresectable peritoneal dissemination remains poor, with a median survival of 11.0-17.9 months [7-9]. Generally, the patient had an unfavorable outcome because of two concomitant conditions (mucinous adenocarcinoma and peritoneal dissemination) with a poor prognosis. However, the patient survived for > 36 months without any sings of tumor progression without systemic chemotherapy. Thus, lenalidomide could have contributed to 3-year progression-free survival.

Lenalidomide is a thalidomide derivative that was approved by the U. S. Food and Drug Administration for treating MM and myelodysplastic syndrome. Lenalidomide has immunomodulatory and antiangiogenetic effects. Lenalidomide, an immunomodulator, inhibits the



Fig. 3 The resected specimen. a Surgical specimen revealed an 80-mm-long circumferential tumor. b Histopathological examination revealed that the intra-abdominal nodules were mucinous and poorly differentiated adenocarcinoma (hematoxylin and eosin staining, × 200)

	Before surgery	Time after surgery (months)												
		1	3	6	9	12	15	18	21	24	27	30	33	36
CEA level (ng/mL)	7.9	2.1	< 1.7	2.3	1.8	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7
CA19-9 level (U/mL)	6373	223	2.3	< 2.1	< 2.1	4.7	< 2.1	< 2.1	< 2.1	< 2.1	< 2.1	< 2.1	< 2.1	< 2.1

 Table 1
 Changes in tumor marker levels before and 3 years after surgery

CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19-9

expression of proinflammatory cytokines [10], reduces the expression of regulatory T-cells [11], stimulates the expression of T-cells inducing cytokine secretion, and promotes natural killer cell cytotoxicity [3]. In addition to these indirect antitumor effects, the antiangiogenetic effect of lenalidomide is suppressing the expression of vascular endothelial factor and basic fibroblast growth factor [12]. Furthermore, lenalidomide induces cell cycle arrest in the G0-G1 phase and apoptosis [13]. Based on these antitumor mechanisms, clinical trials have revealed the effect of lenalidomide monotherapy or combined chemotherapy and antibody therapy against solid tumors, including thyroid, hepatocellular, prostate, lung, and renal cell cancer [3]. In colorectal cancer, the antitumor effect of lenalidomide was revealed in vitro and in vivo [14, 15]. Recent clinical trials have shown that lenalidomide can have antitumor effects [16-18]. However, all these clinical trials were designed to combine lenalidomide with other drugs, such as cytotoxic and antibody drugs, anticipating synergy effects. To the best of our knowledge, this is the first report showing the antitumor effect of lenalidomide monotherapy against colon cancer in clinical settings.

Recently, patients with MM have a high incidence of SPM [1, 2]. Although the pathogenesis of SPM is unclear, the use of alkylating agents, biological factors, genetic predisposition, and immune dysfunctions are a possible mechanism for the development of SPM in patients with MM [1, 19]. Further, growing evidence has revealed that the use of lenalidomide is associated with an increased risk of SPM in MM [20]. Increased surveillance and genetic polymorphisms can explain the increased risk of SPM [20, 21]. Lenalidomide is associated with an increased risk of SPM in patients with MM, with a risk ratio of 1.30 [20]. The incidence of SPM ranges from 6.9% to 18.9% [20, 22, 23]. There are only a few reports on the site of occurrence of SPM in patients with MM treated with lenalidomide. Jackson et al. reported that 4 (6.7%) of 60 solid SPMs were diagnosed as colon cancers [23].

As the current case did not have colonoscopy report, it was unclear whether the colon cancer manifested before the onset of MM or developed during MM treatment. If colon cancer was already present upon MM diagnosis, lenalidomide could be a tumor suppressor; thus, it can slow tumor progression. By contrast, if lenalidomide was associated with the development of SPM, whether it is effective in suppressing tumor progression immediately after carcinogenesis or it acts as a tumor suppressor at some point remains unclear. In any case, 3-year progression-free survival was achieved after colectomy. This may be either because the efficacy of lenalidomide was facilitated by reducing tumor burden or because the oncological properties of dissemination, which differed from the primary site, were favorable for lenalidomide. Considering that no apparent therapeutic effect was identified from lenalidomide administration, it may not have a cytocidal effect against the tumor, rather the drug suppressed tumor growth. Zuo et al. reported that first-line therapy with bortezomib and the maintenance use of lenalidomide after lung tumor resection complicated by MM could have helped achieve a satisfactory therapeutic effect for > 3 years without progression despite relapse after the first year [1]. By contrast, Ujiie et al. presented a case with concurrent MM and gastric cancer with rapid liver metastasis progression and subsequent death post gastrectomy and lenalidomide discontinuation [24]. They believed that lenalidomide discontinuation promoted tumor angiogenesis and lowered antitumor immunity. Based on these reports, the continuation of lenalidomide, as in the current case, can be beneficial for tumor suppression.

In the current case, the patient with mucinous adenocarcinoma with peritoneal dissemination survived > 36 months without using systemic chemotherapy. However, the effect and mechanism of lenalidomide against advanced colon cancer remains unclear. Although preclinical and clinical research has validated the antitumor effect of lenalidomide, data accumulation and research on the benefits of lenalidomide are warranted.

Conclusion

Herein, we report the first case of mucinous colon cancer with peritoneal dissemination in a patient with MM treated with lenalidomide. Based on our result, lenalidomide may have contributed to 3-year progression-free survival.

Abbreviations

- CA19-9 Carbohydrate antigen 19-9
- CEA Carcinoembryonic antigen
- CT Computed tomography
- MM Multiple myeloma
- SPM Second primary malignancies

Acknowledgements

We thank Enago (https://www.enago.jp) for proofreading the manuscript.

Author contributions

KT: drafting of manuscript; HH: drafting of manuscript and critical revision of manuscript; YA, HT, MT: acquisition of data; YY, MN, MT, YA: critical revision of manuscript; SO: analysis and interpretation of data, critical revision of manuscript. All authors approved the final version for publication, agreed to be accountable for all aspects of the work, and ensure that any questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

Funding

No funding or other financial support was received for this study.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

Written informed consent for publication of clinical details and clinical images was obtained from the patient's relative.

Competing interests

The authors have no conflicts of interest to declare.

Received: 19 December 2023 Accepted: 4 February 2024 Published online: 07 February 2024

References

- Ji SH, Park JO, Lee J, Oh MJ, Lim DH, Park BB, et al. Three cases of synchronous solid tumor and multiple myeloma. Cancer Res Treat. 2004;36:338– 40. https://doi.org/10.4143/crt.2004.36.5.338.
- Dong HH, Li J, Kang L, Wei Q, Li Y. Simultaneous multiple myeloma and non-small cell lung carcinoma: a case report and review of the literature. Oncol Lett. 2022;23:195. https://doi.org/10.3892/ol.2022.13315.
- Segler A, Tsimberidou AM. Lenalidomide in solid tumors. Cancer Chemother Pharmacol. 2012;69:1393–406. https://doi.org/10.1007/ s00280-012-1874-2.
- Fadel MG, Malietzis G, Constantinides V, Pellino G, Tekkis P, Kontovounisios C. Clinicopathological factors and survival outcomes of signet-ring cell and mucinous carcinoma versus adenocarcinoma of the colon and rectum: a systematic review and meta-analysis. Discov Oncol. 2021;12:5. https://doi.org/10.1007/s12672-021-00398-6.
- Huang A, Yang Y, Shi JY, Li YK, Xu JX, Cheng Y, et al. Mucinous adenocarcinoma: a unique clinicopathological subtype in colorectal cancer. World J Gastrointest Surg. 2021;13:1567–83. https://doi.org/10.4240/wjgs.v13.i12. 1567.
- Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore). 2015;94: e658. https://doi.org/10. 1097/MD.00000000000658.
- Kerscher AG, Chua TC, Gasser M, Maeder U, Kunzmann V, Isbert C, et al. Impact of peritoneal carcinomatosis in the disease history of colorectal cancer management: a longitudinal experience of 2406 patients over two decades. Br J Cancer. 2013;108:1432–9. https://doi.org/10.1038/bjc. 2013.82.
- Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the analysis and research in cancers of the digestive system (ARCAD) database. Lancet Oncol. 2016;17:1709–19. https:// doi.org/10.1016/S1470-2045(16)30500-9.
- Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol. 2012;30:263–7. https://doi.org/10. 1200/JCO.2011.37.1039.
- 10. Crane E, List A. Immunomodulatory drugs. Cancer Investig. 2005;23:625– 34. https://doi.org/10.1080/07357900500283101.
- Scott GB, Carter C, Parrish C, Wood PM, Cook G. Downregulation of myeloma-induced ICOS-L and regulatory T cell generation by lenalidomide and dexamethasone therapy. Cell Immunol. 2015;297:1–9. https:// doi.org/10.1016/j.cellimm.2015.05.002.
- 12. Hanashima Y, Sano E, Sumi K, Ozawa Y, Yagi C, Tatsuoka J, et al. Antitumor effect of lenalidomide in malignant glioma cell lines. Oncol Rep. 2020;43:1580–90. https://doi.org/10.3892/or.2020.7543.

- Martinez-Høyer S, Karsan A. Mechanisms of lenalidomide sensitivity and resistance. Exp Hematol. 2020;91:22–31. https://doi.org/10.1016/j. exphem.2020.09.196.
- Liu WM, Henry JY, Meyer B, Bartlett JB, Dalgleish AG, Galustian C. Inhibition of metastatic potential in colorectal carcinoma in vivo and in vitro using immunomodulatory drugs (IMiDs). Br J Cancer. 2009;101:803–12. https://doi.org/10.1038/sj.bjc.6605206.
- Leuci V, Maione F, Rotolo R, Giraudo E, Sassi F, Migliardi G, et al. Lenalidomide normalizes tumor vessels in colorectal cancer improving chemotherapy activity. J Transl Med. 2016;14:119. https://doi.org/10. 1186/s12967-016-0872-2.
- Bertino EM, McMichael EL, Mo X, Trikha P, Davis M, Paul B, et al. A phase I trial to evaluate antibody-dependent cellular cytotoxicity of cetuximab and lenalidomide in advanced colorectal and head and neck cancer. Mol Cancer Ther. 2016;15:2244–50. https://doi.org/10.1158/1535-7163. MCT-15-0879.
- 17. Said R, Kakadiaris E, Piha-Paul S, Fu S, Falchook G, Janku F, et al. Phase I clinical trial of lenalidomide in combination with bevacizumab in patients with advanced cancer. Cancer Chemother Pharmacol. 2016;77:1097–102. https://doi.org/10.1007/s00280-016-3000-3.
- Said R, Ye Y, Hong DS, Naing A, Falchook G, Fu S, et al. Phase I clinical trial of lenalidomide in combination with 5-fluorouracil, leucovorin, and oxaliplatin in patients with advanced cancer. Cancer Chemother Pharmacol. 2016;77:575–81. https://doi.org/10.1007/s00280-015-2952-z.
- Zuo W, Zhu X, Yang J, Mei Z, Deng M, Lin Q, et al. Bortezomib combined with lenalidomide as the first-line treatment for the rare synchronous occurrence of multiple myeloma and pulmonary adenocarcinoma: a case report. Medicine (Baltimore). 2017;96: e5787. https://doi.org/10.1097/MD. 000000000005787.
- Saleem K, Franz J, Klem ML, Yabes JG, Boyiadzis M, Jones JR, et al. Second primary malignancies in patients with haematological cancers treated with lenalidomide: a systematic review and meta-analysis. Lancet Haematol. 2022;9:e906–18. https://doi.org/10.1016/S2352-3026(22)00289-7.
- Mitchell JS, Li N, Weinhold N, Försti A, Ali M, van Duin M, et al. Genomewide association study identifies multiple susceptibility loci for multiple myeloma. Nat Commun. 2016;7:12050. https://doi.org/10.1038/ncomm s12050.
- Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, et al. Final analysis of survival outcomes in the phase 3 first trial of upfront treatment for multiple myeloma. Blood. 2018;131:301–10. https:// doi.org/10.1182/blood-2017-07-795047.
- Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20:57–73. https://doi.org/ 10.1016/S1470-2045(18)30687-9.
- Ujiie N, Enomoto Y, Takido N, Kawaharada Y, Zuguchi M, Kubota Y. Rapid progression of gastric cancer with liver metastasis after discontinuation of lenalidomide in a patient with concurrent multiple myeloma: a case report. Int J Surg Case Rep. 2021;81: 105834. https://doi.org/10.1016/j. ijscr.2021.105834.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.