ACTA ONCOLOGICA
2022, VOL. 61, NO. 6, 780–784
https://doi.org/10.1080/0284186X.2022.2054289

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Complete pathologic response (pCR) following neoadjuvant pembrolizumab monotherapy in treatment-naive locally advanced, mismatch repair protein-deficient (dMMR) colonic cancer: a case report and literature review

Alfonso Tan-Garcia[a], Lai Mun Wang[b,c], James Chi-Yong Ngu[d] and Lynne Goh[b,c]

[a]Department of Anatomical Pathology, Singapore General Hospital, Singapore, Singapore; [b]Pathology Section, Department of Laboratory Medicine, Changi General Hospital, Singapore; [c]Pathology Academic Clinical Programme, SingHealth Duke-NUS Academic Medical Centre, Singapore; [d]Department of General Surgery, Changi General Hospital, Singapore, Singapore

ARTICLE HISTORY Received 16 January 2022; Accepted 14 March 2022

Introduction

Colorectal cancer is the third most commonly diagnosed malignancy and second leading cause of cancer-related mortality globally with a 5-year survival rate of <15% among patients with metastatic disease [1]. Immune checkpoint inhibitors (ICIs) targeting co-inhibitory pathways such as programmed death-1/programmed death ligand-1 (PD-1/PD-L1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) have shown improved outcomes in various advanced cancers [2] and represent a novel therapeutic strategy in colorectal cancer. ICIs are effective against mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) colorectal tumours, which comprise approximately 15% of all and 5% of metastatic colorectal cancers [3], and show poor response against mismatch repair-proficient (pMMR) colorectal carcinomas [4]. This has been attributed to the increased tumour mutational burden (TMB) of dMMR tumours resulting in the expression of greater quantities of immunogenic neoantigens by tumour cells [5].

Pembrolizumab, a humanised anti-PD-1 monoclonal antibody, was first approved by the United States Food and Drug Administration (US FDA) for chemotherapy-refractory dMMR/MSI-H metastatic colorectal cancer [6–8]. Most recently, pembrolizumab has been approved by both US FDA [9] and European Commission [10] as first-line treatment in unresectable and/or metastatic dMMR/MSI-H colorectal cancer. This is based on KEYNOTE-177, a phase 3 randomised clinical trial which evaluated treatment-naïve, dMMR/MSI-H metastatic colorectal cancer patients and found an objective response rate of 43.8%, increased progression-free survival, improved long-term quality of life and fewer adverse events compared to standard of care chemotherapy [11,12]. Thus far, in assessing treatment response to pembrolizumab, most case reports and clinical trials such as KEYNOTE-177 employ a clinical-radiologic assessment.

In addition to pembrolizumab, the US FDA has also approved nivolumab in 2017 and the combination of nivolumab and ipilimumab in 2018 for the treatment of dMMR/MSI-H metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan, based on results from the CheckMate 142 trial [13–15]. In the NICHE study, 12 out of 20 patients with non-metastatic dMMR colorectal cancer treated with the neoadjuvant combination of nivolumab and ipilimumab showed a complete pathologic response (pCR) in the primary tumour resection [4]. Similar results of pCR were achieved with combination nivolumab and ipilimumab in treatment-naive locally advanced rectal cancer [16]. Nivolumab monotherapy was also successful in achieving pCR in several other cases of locally advanced and metastatic dMMR colorectal cancer [17,18].

To our knowledge, there have been no published reports of pCR in the primary tumour site following surgical resection in patients with colorectal carcinoma treated with first-line pembrolizumab monotherapy apart from preliminary results presented at the European Society for Medical Oncology Congress 2021 of a phase 2 open-label, single centre trial of MSI-H/dMMR non-metastatic solid tumours with localised unresectable or high risk resectable with measurable disease by Ludford et al. [19]. Among the 8 of 35 patients (27 colorectal cancer and 8 non-colorectal cancer) who underwent surgery, pCR was noted in 4. In addition, detailed histologic descriptions of the primary tumour site post-pembrolizumab treatment are lacking. Here, we present a case of pCR in a 79-year-old female with locally-advanced dMMR transverse colonic cancer treated with first-line pembrolizumab monotherapy, detail its histologic treatment effect and review the existing literature.

Case presentation

A 79-year-old Chinese woman with a history of diverticulosis and endometrial hyperplasia without atypia was

CONTACT Lynne Goh lynne.goh.y.l@singhealth.com.sg Department of Laboratory Medicine, Changi General Hospital, 2 Simei Street 3, 529889, Singapore

referred for significant weight loss of 10 kg over two months. Initial blood investigations showed microcytic hypochromic anaemia. Colonoscopy revealed a circumferential, stenosing mass in the transverse colon and the biopsy a dMMR (MLH-1 and PMS-2-deficient) moderately-differentiated adenocarcinoma (Figure 1(A)). Staging CT-scan showed a 7.4 cm transverse colon mass invading into small bowel and multiple enlarged mesocolic lymph nodes (Figure 1(B)) without distant metastases (cT4N + M0, stage III). Given the tumour's large size and dMMR status, the patient underwent a transverse loop colostomy creation followed by neoadjuvant treatment with pembrolizumab prior to surgical resection. Five cycles of intravenous pembrolizumab (200 mg/cycle) were administered at monthly intervals with no significant adverse effects (Figure 1(C)). Serum carcinoembryonic antigen (CEA) normalised from a pre-treatment level of 875 μg/L to 3.78 μg/L after 3 cycles of pembrolizumab (Figure 1(D)). Interval CT-scans showed a reduction in mesocolic nodal size and the tumour downsized to 4 cm after 2 cycles with no further reduction subsequently (Figure 1(E,F)). A week after completion of neoadjuvant therapy, she underwent an extended right hemicolectomy with en-bloc small bowel resection. Macroscopically, the proximal transverse colon (tumour site), omentum and two small bowel segments were caked together in gelatinous mucin. Apart from a small amount of luminal mucin and erosion, no tumour mass or scar was grossly evident. The entire tumour bed, including adherent structures and mucin was examined which revealed transmural confluent lakes of acellular mucin extending into the omentum and adherent small bowel wall (Figure 1(G,H)). Acellular mucin was also found in 3 of 76 lymph nodes (Figure 1(I)). No fibrosis, necrosis, significant inflammation or viable tumour cells were identified (Figure 1(E) inset), consistent with pCR. The patient recovered well post-operatively.

Discussion

ICIs directed against PD-1/PDL-1 and CTLA-4 proteins are highly effective and have become the standard of care for patients with metastatic dMMR colorectal cancers. Pathologic response in primary tumours following neoadjuvant pembrolizumab treatment has been described in a total of nine patients from three case series [18,20,21] and two case reports [22,23] (Table 1). Of these nine patients, seven showed pCR while two had partial pathologic response. Among the patients with pCR, two patients had received prior chemotherapy [18,23], one patient prior chemotherapy and concurrent radiotherapy [22] and three patients had concurrent chemotherapy with pembrolizumab treatment [20,21]. The only patient reported in the literature to have demonstrated pCR post neoadjuvant pembrolizumab, without prior or concurrent chemotherapy and/or radiotherapy did not undergo surgical excision of the primary tumour for thorough histologic evaluation but instead had a rectal biopsy performed [21].

In our case, the normalisation of serum CEA post-treatment correlates well with pCR. However, the discordance between radiologic tumour size and pathologic response illustrates the limitation of imaging in assessing treatment response as abundant acellular mucin post-pembrolizumab mimics residual disease radiologically. This discordance has been observed in other reports of patients receiving neoadjuvant pembrolizumab [18,21–23] and combination of nivolumab and ipilimumab [4,18]. It poses a potential challenge in selecting patients who may be cured without undergoing surgery. Alternative modalities of imaging such as PET-CT or MRI may be superior to CT when assessing neoadjuvant treatment response [24].

Given the propensity of pembrolizumab to result in a fibrosis-poor, mucin-rich tumour bed, the specimen should be thoroughly fixed to preserve the integrity of the friable mucin-rich tumour bed and adherent structures. The adherent extra-serosal gelatinous mucin, which forms part of the tumour bed, should be left intact and sampled thoroughly to assess for viable tumour cells. The histologic treatment effect (pCR) of neoadjuvant pembrolizumab monotherapy in colorectal adenocarcinomas in the two microscopically documented cases (including ours) [22,23] manifests as acellular mucin, which contrasts with the 'immune cell-rich' features described in non-small-cell lung carcinoma post-anti-PD-1 immunotherapy [25]. Whether the difference in histologic treatment effect is due to tumour site or anti-PD-1 drug used (pembrolizumab versus nivolumab) requires further investigation. The basis of most tumour regression grading (TRG) systems is the Mandard classification [26], described in oesophageal squamous cell carcinoma, which was modified by Dworak for rectal cancer [27]. Both classification systems describe treatment response based on the ratio of residual tumour cells and extent of fibrosis. Since pembrolizumab appears to entail a mucin-rich, fibrosis-poor treatment effect [18,22], the Modified Ryan Scheme [28] may be most suited for assessment of pathologic response. However, TRG systems for colorectal cancer were derived based on neoadjuvant chemoradiotherapy regimens and it is necessary to devise novel immunotherapy-based scoring systems.

In conclusion, this case report details the histologic appearance of pCR at the resected primary tumour site of locally-advanced dMMR colonic adenocarcinoma following first-line pembrolizumab monotherapy. As ICIs are expected to find wider use, pathologists are likely to encounter primary colorectal resection specimens following neoadjuvant ICI treatment with greater frequency and should be aware of their unique gross and microscopic features.

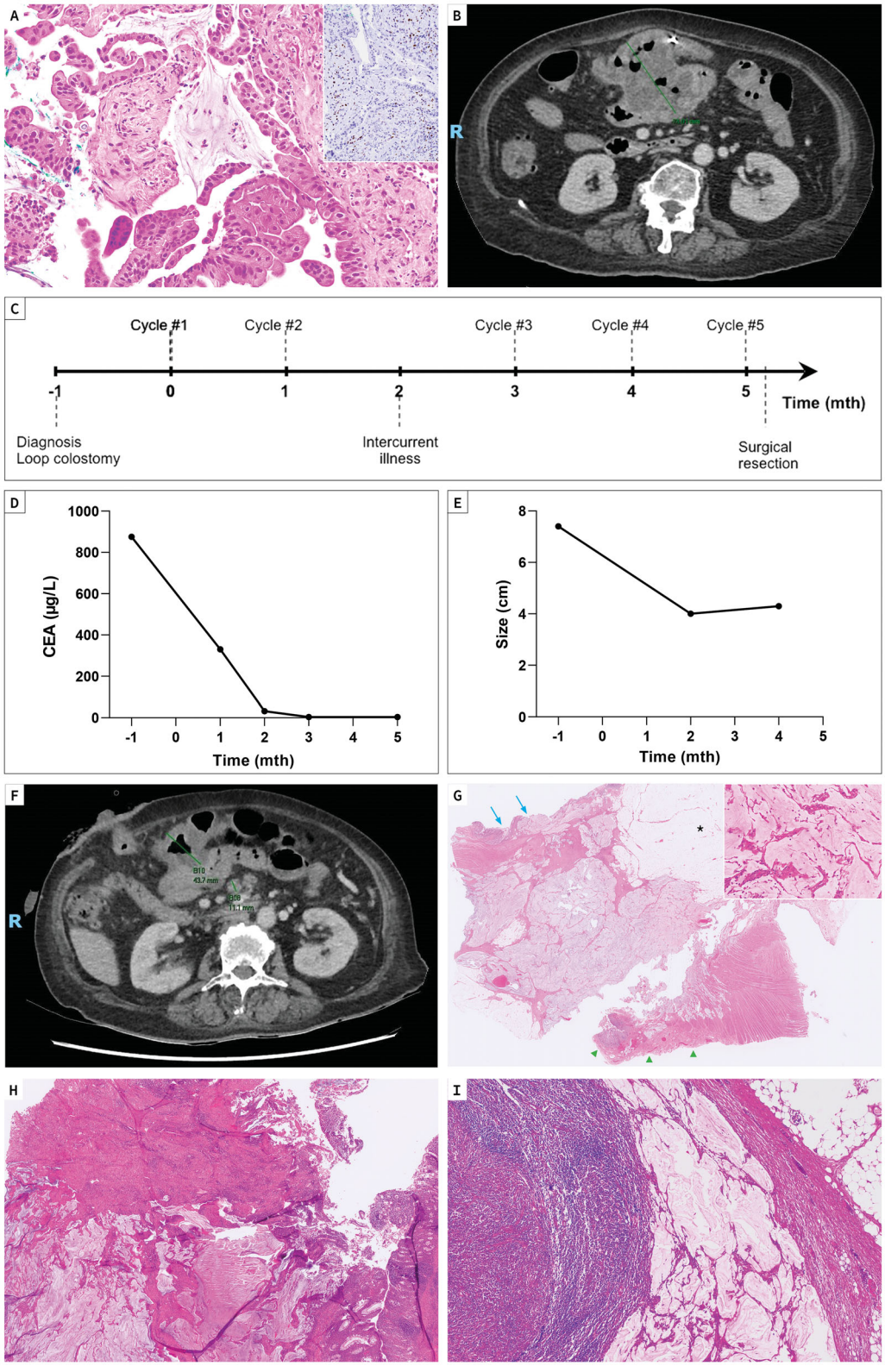

Figure 1. (A) Biopsy of the treatment-naïve transverse colon adenocarcinoma [HE ×200], which was deficient in MLH1 and PMS2 by immunohistochemistry (inset, MLH1, ×200). (B) Axial computed tomography (CT) images showing a 7.4 cm transverse colon tumour invading into small bowel. (C) Timeline of events from point of diagnosis to surgical resection with administration of five cycles of neoadjuvant pembrolizumab at monthly intervals. Between the 2nd and 3rd doses, she was hospitalised for respiratory compromise secondary to atelectasis and bronchitis which was deemed unrelated to ongoing therapy. (D) Plot of serial serum CEA levels (µg/L) measured before and during neoadjuvant therapy. (E) Plot of interval tumour size (cm) measured on computed tomography (CT) imaging before and during neoadjuvant therapy. (F) Axial CT showing downsizing of the primary tumour to 4 cm after two cycles of pembrolizumab. (G) Ultra-low power view of regressed tumour bed with adherent small bowel (colonic tumour site marked with blue arrows, small bowel marked with green arrowheads, omentum with *) [HE, ×0.25], showing copious amounts of acellular mucin (inset, HE ×100) extending transmurally into the adherent small bowel. (H) Low magnification of the primary tumour bed showing luminal erosions and underlying transmural mucin [HE, ×1]. (I) Acellular mucin within a lymph node [HE x40]. The post-pembrolizumab histology corresponded to AJCC 8th edition pathologic stage ypT0N0M0R0, tumour regression grade (TRG) 0/3.

Table 1. Summary of case reports, case series and clinical trials employing neoadjuvant pembrolizumab in colorectal carcinoma.

Study	Study design	Age	Gender	Extent of disease	No. of patients	MMR status	Previous treatment (% patients)	Pembrolizumab regimen	Pembrolizumab dose (mg)	No. of cycles	Concurrent treatment	Clinical response (% patients)	Specimen assessed	Type of specimen	Pathologic response	Histology of regressed tumour site
Current study	Case report	79	Female	Locally advanced	1	dMMR	None	Neoadjuvant	200	5	None	cPR	Primary tumour	Resection	pCR	Acellular mucin
Liu *et al* (2020) [20]	Case series	51	Female	Locally advanced	1	dMMR/ MSI-H	None	Neoadjuvant	240	2	Chemotherapy	cPR	Primary tumour	Resection	pCR	N/A
		54	Male	Metastatic	1	dMMR/ MSI-H	None	Neoadjuvant	200	6	Chemotherapy	SD	Primary tumour	Resection	pCR	N/A
		34	Male	Locally advanced	1	dMMR/ MSI-H	None	Neoadjuvant	200	4	None	cPR	Primary tumour	Resection	pPR	N/A
Demisse *et al* (2020) [21]	Case series	81	Male	Locally advanced	1	dMMR	None	Neoadjuvant	200	11	None	cPR	Primary tumour	Biopsy	pCR	N/A
		38	Female	Locally advanced	1	dMMR/ MSI-H	None	Neoadjuvant	N/A	N/A	Chemotherapy	N/A	Primary tumour	Resection	pCR	N/A
Yang *et al* (2021) [22]	Case report	64	Male	Metastatic	1	dMMR/ MSI-H	Chemotherapy	Neoadjuvant	200	4	Radiotherapy	cPR	Primary tumour	Resection	pCR	'only mucus'
Tominaga *et al* (2022) [23]	Case report	45	Male	Metastatic	1	MSI-H	Chemotherapy	Neoadjuvant	N/A	12	None	cPR	Primary tumour	Resection	pCR	Ulceration, fibrosis and cyst-like spaces
Ludford *et al* (2021) [18]	Case series	33	Male	Metastatic	1	dMMR	Chemotherapy	Neoadjuvant	N/A	3	None	SD	Primary tumour	Resection	pPR	N/A
		48	Female	Metastatic	1	dMMR	Chemotherapy	Neoadjuvant	N/A	4	None	SD	Primary tumour	Resection	pCR	N/A
Andre *et al* (2020) KEYNOTE-177 [11]	Phase 3 open-label trial	–	–	Metastatic	153	dMMR/ MSI-H	None (75)	Neoadjuvant	200	At least 1	None	cCR (11), cPR (33)	N/A	N/A	N/A	N/A

MSI-H: microsatellite instability-high, dMMR: mismatch repair protein deficient, cCR: clinical complete response, cPR: clinical partial response, pCR: pathologic complete response, pPR: pathologic partial response, SD: stable disease, N/A: not assessed or data not available.

Acknowledgements

We would like to thank the Department of Anatomical Pathology, Singapore General Hospital, for digital imaging facilities.

Author contributions

Manuscript writing and figures: A.T-G., L.G. and L.M.W.; Grossing and histology: L.M.W.; Patient care and surgery: N.C.Y.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Alfonso Tan-Garcia http://orcid.org/0000-0001-8059-730X

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

References

[1] Keum NN, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713–732.
[2] Vaddepally RK, Kharel P, Pandey R, et al. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers. 2020;12(3):738–719.
[3] Bonneville R, Krook MA, Kautto EA, et al. Landscape of microsatellite instability across 39 cancer types. J Clin Oncol Precis Oncol. 2017;2017:PO.17.00073.
[4] Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage Colon cancers. Nat Med. 2020;26(4):566–576.
[5] Mandal R, Samstein RM, Lee KW, et al. Genetic diversity of tumors with mismatch repair deficiency influences anti-PD-1 immunotherapy response. Science. 2019;364(6439):485–491.
[6] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–2520.
[7] Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–413.
[8] Le DT, Kim TW, van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite Instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. J Clin Oncol. 2020;38(1):11–19.
[9] Casak SJ, Marcus L, Fashoyin-Aje L, et al. FDA approval summary: pembrolizumab for the first-line treatment of patients with MSI-H/dMMR advanced unresectable or metastatic colorectal carcinoma. Clin Cancer Res. 2021;27(17):4680–4684.
[10] Trullas A, Delgado J, Genazzani A, et al. The EMA assessment of pembrolizumab as monotherapy for the first-line treatment of adult patients with metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer. ESMO Open. 2021;6(3):100145.
[11] André T, Shiu K-K, Kim TW, et al. Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. N Engl J Med. 2020;383(23):2207–2218.
[12] Andre T, Amonkar M, Norquist JM, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(5):665–677.
[13] Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18(9):1182–1191.
[14] Andre T, Lonardi S, Wong M, et al. Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC): first report of the full cohort from CheckMate-142. J Clin Oncol. 2018;36(4_suppl):553–553. [Internet].
[15] Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol. 2018;36(8):773–779.
[16] Trojan J, Stintzing S, Haase O, et al. Complete pathological response after neoadjuvant short-course immunotherapy with ipilimumab and nivolumab in locally advanced MSI-H/dMMR rectal cancer. Oncologist. 2021;26(12):e2110–e2114.
[17] Zhang J, Cai J, Deng Y, et al. Complete response in patients with locally advanced rectal cancer after neoadjuvant treatment with nivolumab. Oncoimmunology. 2019;8(12):e1663108.
[18] Ludford K, Cohen R, Svrcek M, et al. Pathological tumor response following immune checkpoint blockade for deficient mismatch repair advanced colorectal cancer. J Natl Cancer Inst. 2021;113(2):208–211.
[19] Ludford K, Raghav K, Murphy MAB, et al. 1758O neoadjuvant pembrolizumab in localized/locally advanced solid tumors with mismatch repair deficiency. Ann Oncol. 2021;32:S1210.
[20] Liu DX, Li DD, He W, et al. PD-1 blockade in neoadjuvant setting of DNA mismatch repair-deficient/microsatellite instability-high colorectal cancer. Oncoimmunology. 2020;9(1):e1711650-1-5.
[21] Demisse R, Damle N, Kim E, et al. Neoadjuvant immunotherapy-based systemic treatment in MMR-deficient or MSI-high rectal cancer: case series. JNCCN J Natl Compr Cancer Netw. 2020;18(7):798–804.
[22] Yang J, Bi F, Gou H. Complete pathologic response after concurrent treatment with pembrolizumab and radiotherapy in metastatic colorectal cancer: a case report. Onco Targets Ther. 2021;14:2555–2561.
[23] Tominaga T, Nonaka T, Fukuda A, et al. Pathological complete response to pembrolizumab in patients with metastatic ascending Colon cancer with microsatellite instability. Clin J Gastroenterol. 2022;15(1):134–139.
[24] Koo PJ, Kim SJ, Chang S, et al. Interim fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography to predict pathologic response to preoperative chemoradiotherapy and prognosis in patients with locally advanced rectal cancer. Clin Colorectal Cancer. 2016;15(4):e213–e219.
[25] Cottrell TR, Thompson ED, Forde PM, et al. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol. 2018;29(8):1853–1860.
[26] Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73(11):2680–2686.
[27] Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis. 1997;12(1):19–23.
[28] Ryan R, Gibbons D, Hyland JMP, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology. 2005;47(2):141–146.