The Journal of Dermatology

Concise communication

JDE-2016-1151 revised version R1

Two cases of melanomas paradoxically metastasizing to the intestinal tract during nivolumab therapy

Hajime Miyazawa,[1] Teruki Yanagi,[1*] Yasuyuki Yamaguchi,[1] Keisuke Imafuku,[1] Shinya Kitamura,[1] Hiroo Hata,[1] Jiro Uehara,[2] Nobuki Ichikawa,[3] Yosuke Ohno,[3] Tadashi Yoshida,[3] Shigenori Homma,[3] Hideki Kawamura,[3] Akinobu Taketomi,[3] Hiroshi Shimizu[1]

[1]*Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan*

[2]Department of Dermatology, Asahikawa Medical University, Asahikawa, Hokkaido, Japan

[3]Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Sapporo, Japan

***Correspondence:** Teruki Yanagi. **E-mail:** yanagi@med.hokudai.ac.jp

Department of Dermatology, Hokkaido University Graduate School of Medicine

North 15 West 7, Kita-ku, Sapporo, 060-8638, Japan

Tel: +81-11-7067387 **Fax:** +81-11-7067820

Word count: 1078 words, 2 figures, 0 tables

Funding sources: None

Conflict of interests: None

Running head: Intestinal metastasis in melanoma

Key words: malignant melanoma, intestinal metastasis, nivolumab, weight loss, fecal occult blood test

Abstract

We report two cases of melanomas in patients who developed intestinal metastasis despite other metastatic sites responding to nivolumab and despite the patients having favorable findings such as vitiligo and normal LDH. The first case is an 85-year-old man who had been administered with nivolumab for lung/cutaneous metastases. After 22 courses of nivolumab therapy, fever and anorexia had appeared and his body weight had decreased. An intussusception on the ileocecal valve was revealed by computed tomography, and emergency surgery revealed metastatic lesions on the colon. The second case is an 87-year-old woman treated with nivolumab for lymph node metastases. After 10 courses, laboratory tests had revealed anemia and positive fecal occult blood. Her body weight had decreased. Capsule endoscopy showed scattered tumors and clots, indicating metastases of melanoma. The frequency of symptomatic intestinal metastasis of melanoma is very low. Further, intestinal metastasis of melanoma is difficult to detect through routine examinations. Our cases suggest that fecal occult blood test and decreased body weight are indications of intestinal metastases.

Introduction

Nivolumab is an immune checkpoint inhibitor that prevents programed death (PD) -1/ PD-ligand 1 interaction and is superior to standard chemotherapies, such as dacarbazine, in terms of overall survival (OS) and objective response rates in cases of metastatic malignant melanoma (MM).[1] During nivolumab therapy against metastatic MM, vitiligo is a favorable prognostic factor and high lactate dehydrogenase (LDH) is an unfavorable prognostic factor, in terms of overall survival and progression-free survival (PFS).[2-4] An autopsy study of patients who had had MM found an 80% incidence of metastases to the gastrointestinal tract.[5] However, the incidence of symptomatic gastrointestinal metastatic MM was found to range from 0.8% to 4.7%.[6] We herein present two MM cases in which metastatic lesions suddenly appeared in the intestinal tract and the body weight insidiously decreased during nivolumab therapy, despite partial response (PR) or stable disease (SD) with more favorable prognostic factors, including vitiligo and normal LDH levels.

Nivolumab therapy

At our institution, nivolumab was administered every 3 weeks (2 mg/kg) in a regime approved in Japan, but which differs from that approved by the U.S. Food and Drug Administration. Prior to treatment, laboratory tests and imaging investigations (chest X-ray, computed tomography (CT) and/or ultrasonography) were performed. The CT was performed every 2 courses of nivolumab therapy.

Case presentation

Case 1:

An 85-year-old man had been diagnosed with MM (T4N1aM0, Stage IIIa) on the left great toe, which had been treated with wide local excision. BRAF gene mutation was not inspected. Two months after surgery, multiple in-transit metastases appeared on the left thigh. Despite four courses of dacarbazine (DTIC) chemotherapy, CT showed lung metastases (Fig. 1, b-c). Neither positron emission tomography (PET)-CT nor endoscopy was performed. We switched from the DTIC to nivolumab, whereby he maintained PR status for 1 year (Fig. 1, d-e). During the nivolumab therapy, vitiligo appeared on the whole body, especially on the face and neck. After 22 courses of nivolumab therapy, he suddenly developed a 38.2-degree fever and diminished appetite. His body weight decreased by 5 kg from 55 kg in 10 months (Fig. 1a). Physical examination revealed a palpable mass on the right lower abdomen without signs of acute peritonitis. Laboratory tests revealed elevated C-reactive protein of 12.63 mg/dl (normal: 0.00-0.39 mg/dl). However, no other significant changes, including in LDH level, were seen. CT revealed a severe intussusception on the ileocecal valve (Fig. 1f), and emergency surgery was performed. Histopathologically, the tumour was found to be metastatic MM. Subsequent colonoscopy showed more than 10 metastatic tumors. (Fig. 1g). Two months later, the patient died of metastatic MM.

Case 2:

An 87-year-old woman had been diagnosed with MM (T3aN3M0, Stage IIIc) on the left cheek. BRAF gene mutation was not inspected. She had undergone wide local excision and left cervical lymphadenectomy. At 3.5 years after surgery, lymphadenopathy ap-

peared on the right neck (Fig. 2b). Neither PET-CT nor endoscopy was performed. To treat the metastatic MM of the lymph node, nivolumab therapy was started. Under nivolumab therapy, she maintained SD (Fig. 2c) for 6 months with an adverse skin effect (vitiligo). LDH had been within normal limits throughout the treatments. After the 10 courses of nivolumab therapy, laboratory tests revealed iron-deficiency anemia and positive fecal occult blood. Her body weight decreased by 3.5 kg from 47 kg in 5 months (Fig. 2a). Upper and lower gastrointestinal endoscopy showed neither tumors nor bleeding. Capsule endoscopy showed scattered black tumors with smooth surfaces and clots on the small intense (Fig. 2d). Based on the clinical findings, the diagnosis of metastatic MM of small intense was made. The nivolumab was discontinued and palliative care started.

Discussion

We reported two cases of MM that metastasized to the intestinal tract during nivolumab therapy, although the possibility remains that the intestinal metastasis had preceded the nivolumab therapy. We discuss two points: One is interstitial metastasis in MM, and the other is the significance of vitiligo and LDH level during nivolumab therapy. An autopsy study of 125 patients with MM found the incidence of metastases to the gastrointestinal tract to be 58% in the small intestine (73 patients) and 22% in the colon (28 patients).[5] Several studies have noted that the incidence of symptomatic gastrointestinal metastatic MM ranges from 0.8% to 4.7%.[6] In an autopsy study, the intestinal metastasis of MM was reported in a patient who had undergone nivolumab therapy.[7] We usually use CT to assess the efficacy of nivolumab;[8] however, interstitial metastasis is difficult to detect. In fact, we were unable to detect the metastasis in the intestinal tract by routine examination in either of our two cases. Reportedly, the clinical features of intestinal metastasis of MM are gastrointestinal bleeding (including melena), anemia, vague abdominal pain, and weight loss.[6,9] Hence, body weight should be monitored and fecal occult blood should be tested for in follow-up screening of nivolumab therapy.

Both of our cases showed vitiligo as an adverse effect of the nivolumab therapy. The cumulative incidence of vitiligo in patients with MM who are receiving immunotherapy (PD-1 or cytotoxic T-lymphocyte antigen 4 antibody) has been reported to be 3.4%.[2] Another study reported that vitiligo appeared in 15% of nivolumab therapy cases.[11] Patients who presents vitiligo as skin adverse event have longer OS and PFS.[2] Thus, vitiligo is a favorable prognostic marker in patients treated with nivolumab. Concerning serum LDH levels, while the median survival in MM patients with elevated serum levels of LDH (>240Ul) was only 5 months, that in MM patients with normal se-

rum LDH was 16 months.[3] In another study, patients who were treated with anti-PD-1 therapy against metastatic MM had significantly longer OS when their LDH was not elevated than when it was elevated.[4] Therefore, low serum LDH level is an another favorable prognostic marker. Indeed, the PFS of our cases (12 months for case 1 and 6 months for case 2) were longer than the median PFS in patients treated with nivolumab (5.1 months).[10] Regrettably, intestinal metastases appeared despite the favorable prognostic markers of normal LDH level and vitiligo in both cases. Although the immune tolerance of the intestinal tract might be associated with MM metastases, this is not obvious from previous clinical and experimental studies.

Conclusion

We reported two patients who developed intestinal metastasis despite other metastatic sites responding to nivolumab and despite favorable findings of vitiligo and normal LDH. The cases suggest that we should pay attention to intestinal metastasis through fecal occult blood and body weight loss, since intestinal metastasis is difficult to detect through routine examinations, including CT.

References

1 Yun S, Vincelette ND, Green MR, Wahner Hendrickson AE, Abraham I. Targeting immune checkpoints in unresectable metastatic cutaneous melanoma: a systematic review and meta-analysis of anti-CTLA-4 and anti-PD-1 agents trials. *Cancer Med* 2016; 5: 1481-91.

2 Teulings HE, Limpens J, Jansen SN *et al.* Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J Clin Oncol* 2015; 33: 773-81.

3 Franzke A1, Probst-Kepper M, Buer J *et al.* Elevated pretreatment serum levels of soluble vascular cell adhesion molecule 1 and lactate dehydrogenase as predictors of survival in cutaneous metastatic malignant melanoma. *Br J Cancer* 1998; 78: 40-45.

4 Diem S, Kasenda B, Spain L *et al.* Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *Br J Cancer* 2016; 114: 256-61.

5 Dasgupta T, Brasfield R. METASTATIC MELANOMA. A CLINICOPATHOLOGICAL STUDY. *Cancer* 1964; 17: 1323-39.

6 Asad-Ur-Rahman F, Abbass A, Majeed U, Navaneethan U. Melanoma Metastasizing to the Small Intestine: A Case Report Illustrating Symptomatic and Asymptomatic Involvement. *Cureus* 2016; 8: e608.

7 Koelzer VH, Rothschild SI, Zihler D *et al.* Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. *J Immunother Cancer* 2016; 4: 13.

8 Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.

9 Faut M, Bisschop K, Jalving M *et al.* Diagnosis and Treatment of Intestinal Melanoma Metastases in the Era of Effective Systemic Treatment *Ann Surg* 2015.

10 Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; 372: 320-30.

11 Hwang SJ, Carlos G, Wakade D *et al.* Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort. *J Am Acad Dermatol* 2016; 74: 455-61.

Figure legends

Figure 1

(a) The line graph shows the change in body weight. The X-axis indicates the time elapsed initial from nivolumab therapy (months). The Y-axis indicates body weight (kilograms).

(b) In-transit metastasis in the left thigh at the 4th course of nivolumab therapy.

(c) In-transit metastasis in the left thigh at the 22nd course of nivolumab therapy.

(d) CT imaging shows lung metastasis at the 4th course of nivolumab therapy (red circle).

(e) CT imaging shows lung metastasis at the 22nd course of nivolumab therapy (red circle).

(f) CT imaging shows intussusception on the ileocecal valve (yellow arrowheads).

(g) Colonoscopy shows colon metastasis.

Figure 2

(a) The line graph shows the change in body weight. The X-axis indicates the time elapsed from initial nivolumab therapy (months). The Y-axis indicates body weight (kilograms).

(b) CT shows lymphadenopathy of the neck at the initiation of nivolumab therapy (yellow arrowheads).

(c) CT shows lymphadenopathy of the neck at the 10th course of nivolumab therapy (yellow arrowheads).

(d) Small bowel capsule endoscopy shows small intestinal metastases (yellow arrowheads).

Fig. 1

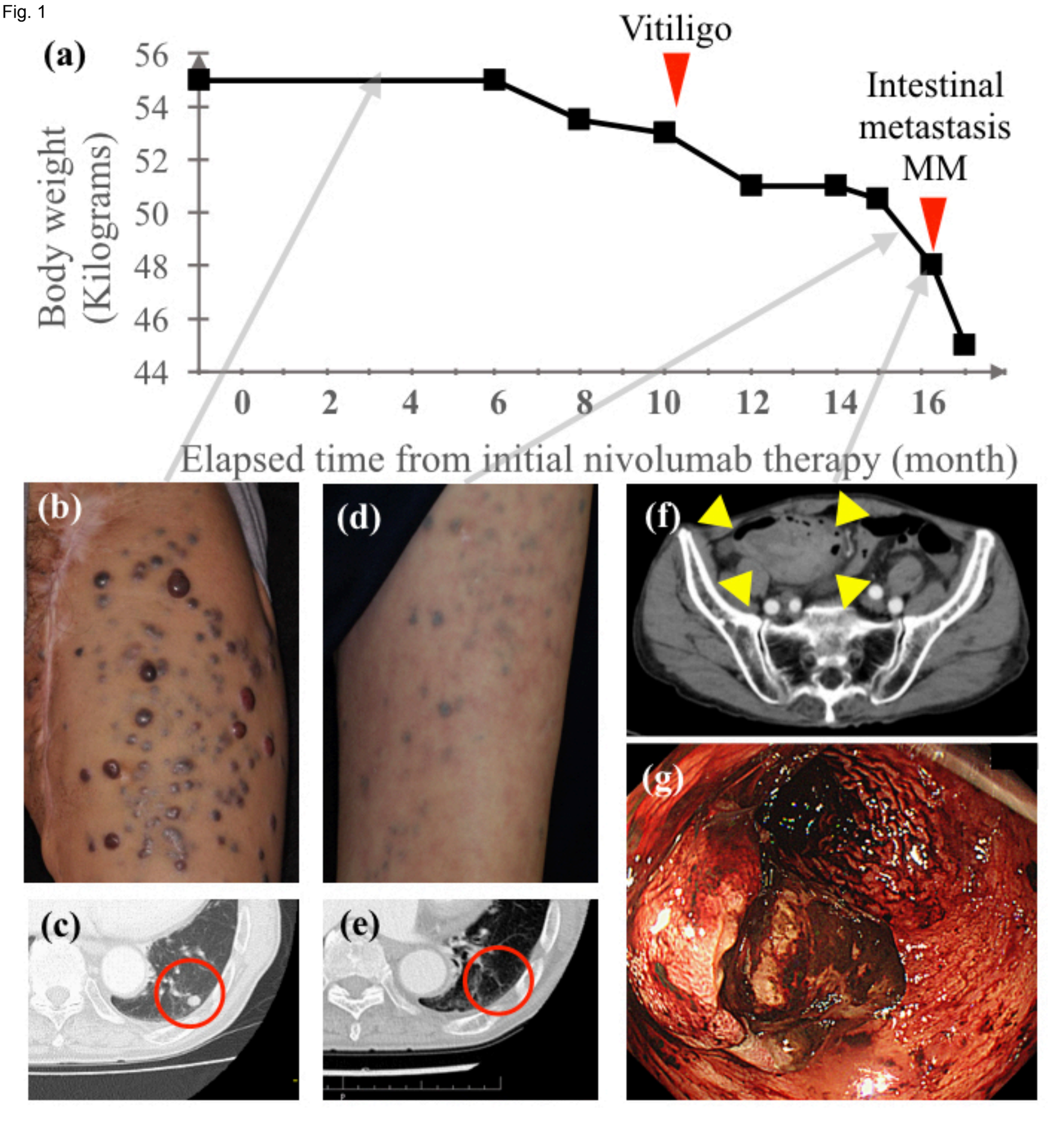
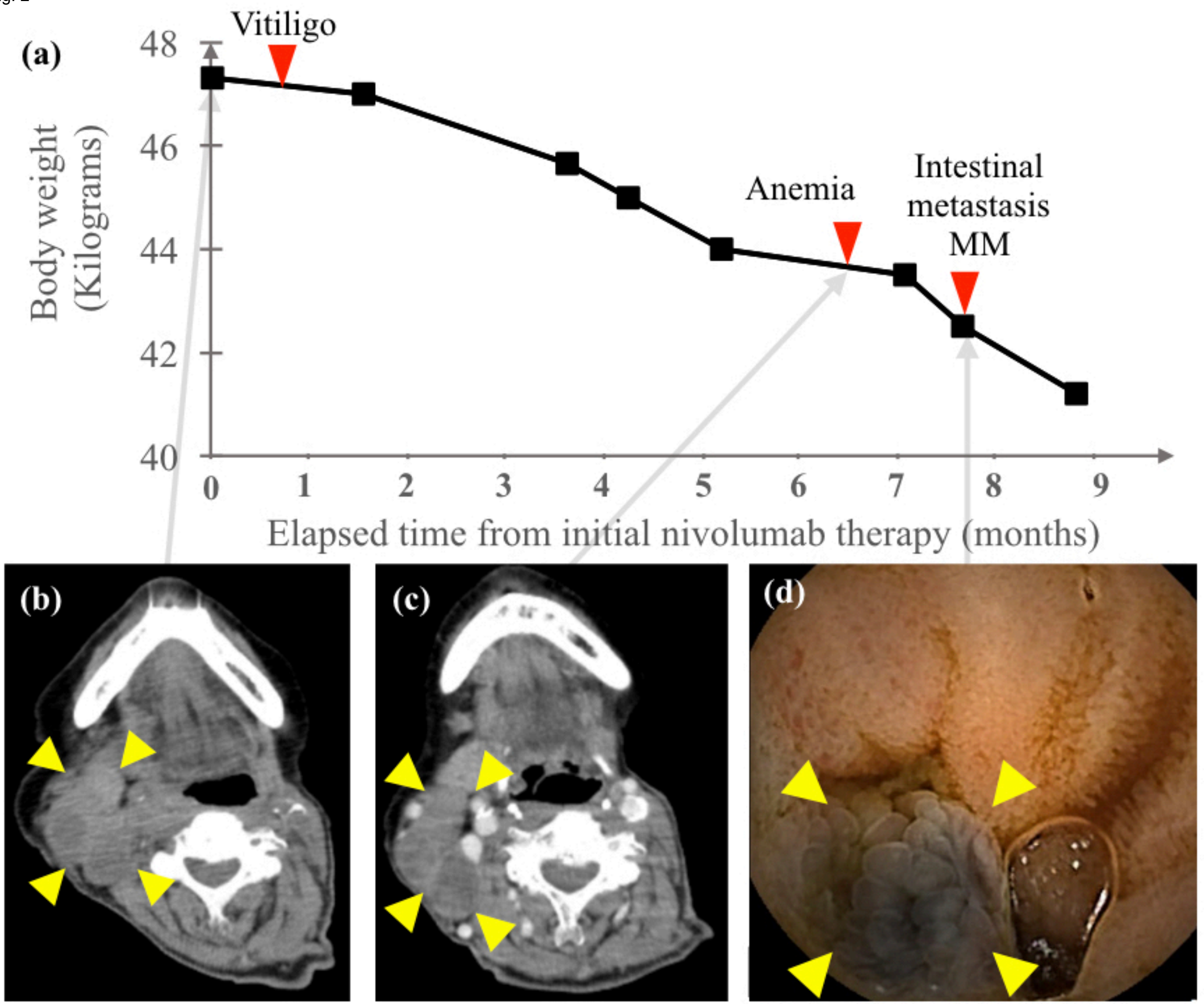

(a)
Vitiligo
Intestinal metastasis MM
Body weight (Kilograms)
56
54
52
50
48
46
44
0
2
4
6
8
10
12
14
16
Elapsed time from initial nivolumab therapy (month)
(b)
(d)
(f)
(g)
(c)
(e)

Fig. 2


(a)
Vitiligo
Anemia
Intestinal metastasis MM
Body weight (Kilograms)
48
46
44
42
40
0
1
2
3
4
5
6
7
8
9
Elapsed time from initial nivolumab therapy (months)
(b)
(c)
(d)