JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2020, VOL. 10, NO. 4, 371–376
https://doi.org/10.1080/20009666.2020.1787809

Taylor & Francis
Taylor & Francis Group

CASE REPORT

A Rare Case of Primary Anorectal Melanoma and a Review of the Current Landscape of Therapy

Ho-Man Yeung[a], Brinda Gupta[a] and Bhishak Kamat[b]

[a]Department of Medicine, Temple University Hospital, Philadelphia, PA, USA; [b]Department of Radiology, Temple University Hospital, Philadelphia, PA, USA

ABSTRACT

Introduction: Anorectal mucosal melanoma (ARMM) is an uncommon and highly aggressive malignancy. Given its rarity, there is insufficient evidence on the optimal medical management which presents as a clinical challenge to its diagnosis and treatment. Treatment of ARMM typically involves a multimodal approach including surgical resection, chemotherapy, targeted therapy and/or immunotherapy.

Case Presentation: Here, we present a case of a 78-year-old female who presented with a four-month history of rectal bleeding and bowel incontinence. Ultimately, colonoscopy revealed a mass at the anal verge, and biopsy of the mass showed malignant cells that stained positive for S100, Melan-A and HMB-45, consistent with the diagnosis of malignant melanoma. Molecular testing revealed no *BRAF, KIT* or *NRAS* gene mutations. PD-L1 immunohistochemistry showed tumor proportion score of 1%. She underwent abdominoperineal resection with a plan to initiate immunotherapy with an anti-PD-1 checkpoint inhibitor. This case highlights a rare aggressive malignancy and reviews its treatment option, which are mostly extrapolated from its cutaneous counterpart and some derived from a few case reports. Due to its rarity, there is no consensus guideline for the treatment of ARMM.

ARTICLE HISTORY
Received 27 February 2020
Accepted 23 June 2020

KEYWORDS
Anorectal melanoma; muscosal melanoma; immunotherapy; gastrointestinal cancer

1. Introduction

Primary ARMM is a rare entity, comprising only 1% of all melanomas and 0.05% of all colorectal malignancies [1]. The annual incidence of ARMM in the USA is ~0.3 per million [2] and the prevalence has been increasing from 6.99% in 2004 to 10.53% in 2015 [3]. ARMM most commonly presents with a rectal mass, anorectal pain, rectal bleeding or a change in bowel habits. Due to its nonspecific presentation and its rarity, ARMM is difficult to diagnose in its early stages and is commonly misdiagnosed as hemorrhoids, polyps or rectal cancer in about two-thirds of patients [4]. The pathogenesis of ARMM is currently unknown. Mucosal melanocytes play a role in immune modulation and antimicrobial defense [5], as well as promote the mucosal barrier in conjunction with goblet cells and Paneth cells [6]. Unlike cutaneous melanoma which is known to be associated with UV light exposure, there are no known risk factors associated with ARMM [7]. Current mainstay of treatment typically involves surgical excision, either by wide local excision (WLE) or abdominoperineal resection (APR) for large tumors or those not amenable to wide local excision [7]. Despite surgery, prognosis remains poor and patients often progress to metastatic disease. The overall 5-year survival rate is 6–22% [8], and its annual incidence continues to rise [9]. There remains limited efficacy with adjuvant therapy, but more recent evidence suggests promising results for the use of checkpoint inhibitors [10–12].

2. Case presentation

A 78-year-old Hispanic female, active cigarette smoker of 45 pack-years, with a past medical history of asthma/emphysematous chronic obstructive pulmonary disease overlap syndrome, hypertension, and gastroesophageal reflux disease presented to her outpatient gastroenterologist with a complaint of rectal bleeding and bowel incontinence for 4 months. She endorsed a ten-pound weight loss during this period, as well as, chronic diarrhea for which she used loperamide as needed. She had never undergone colonoscopy for routine screening, nor esophagogastroduodenoscopy (EGD) in the past. Her past surgical history was significant for cholecystectomy, two cesarean-sections, and a total hysterectomy. No family history of cancer was noted. She lives with her husband at home and has baseline ambulatory dysfunction requiring a cane for assistance. She started smoking at age 35 and drank alcohol socially.

On digital rectal exam, she was found to have a firm mass palpable at 1 cm above the anal verge. The colonoscopy revealed a 6 cm x 4 mm non-

CONTACT Ho-Man Yeung ho-man.yeung@tuhs.temple.edu Department of Medicine, Temple University Hospital, Philadelphia, PA 19140, USA

obstructing mass at the posterior bowel wall at the anal verge (Figure 1). Histopathological review of the biopsied specimen was remarkable for tumor cells staining positive for S100, Melan-A and HMB-45 while being negative for CK7, CK20, CK5/6, CDX2, and PAX8, consistent with malignant melanoma. She was subsequently referred to medical oncology and colorectal surgery. CT of her abdomen and pelvis with intravenous contrast revealed eccentric right lateral rectal wall thickening without findings of perirectal tumor infiltration (Figure 2), but showed an enlarged left pelvic lymph node concerning for nodal metastasis. Staging MRI of the abdomen and pelvis showed a T3 tumor with a depth of invasion of 3 mm involving the puborectalis muscle, with suspicious left internal iliac and presacral lymph nodes. Staging PET/CT scan showed a rectal mass (SUV 43), nonspecific uptake in the left internal iliac lymph node (SUV 7), small focus of the right hepatic lobe (SUV 3), as well as multistation mediastinal and bilateral hilar lymph nodes (SUV 4.2) and multiple lung nodules (Figure 3 and Table 1). She subsequently underwent APR with end colostomy. The surgical specimen showed a 4.1 cm mass of the right posterolateral wall invading into the longitudinal muscular layer with negative surgical margins and five lymph nodes negative for melanoma. She was diagnosed with primary ARMM, with possible lung metastasis or primary lung cancer. Genomic testing by FoundationOne CDx® revealed no mutations of the *BRAF, KIT*, or *NRAS* genes, but found alterations in the NF1, PTEN, RICTOR, and CDKN2A/B genes. Additionally, the tumor had intermediate tumor mutational burden with six mutations per Mb and microsatellite stable status. PD-L1 immunohistochemistry showed tumor proportion score of 1% (Table 2).

3. Follow up

She was seen 3 months after her surgery. She recovered well overall with good ostomy output. She had no abdominal pain, and denied nausea, vomiting, or bloody output. She had good appetite and maintained her weight. Her ECOG (Eastern Cooperative Oncology Group) functional performance status at this time was 2. However, she now complained of shortness of breath, persistent cough with sputum production, occasional hemoptysis, as well as dyspnea on exertion for the past 3 weeks. She was referred to pulmonology for evaluation. Six months after the initial diagnosis, a repeat positron emission tomography/computed tomography (PET/CT) was performed which showed new left upper lobe lung nodule and higher uptake of previously noted left iliac lymph node (SUV 23.8). At this time, it was still unclear whether she had a second primary tumor of the lungs or metastatic melanoma. A high-resolution CT chest showed right upper and middle lobe calcified granulomas, one irregular posterior left upper lobe solid nodule measuring 1.0 × 0.3 cm, and one partially solid pseudocystic

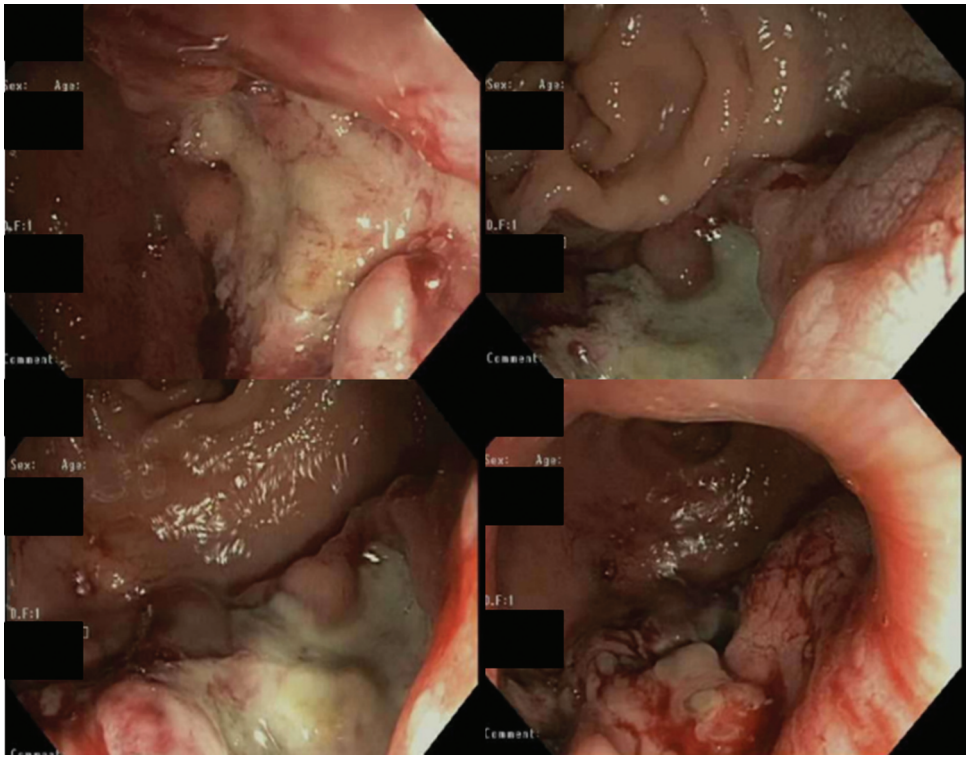

Figure 1. Infiltrative non-obstructive large 6 cm x 4 mm mass found at the anus 0–1 cm from the anal verge with blood oozing present.

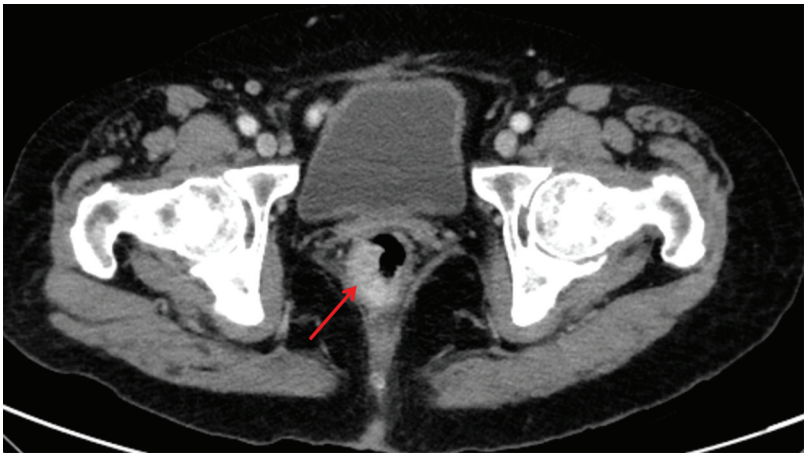

Figure 2. CT pelvis showing eccentric, right lateral rectal wall thickening representing the melanoma, without any findings to suggest perirectal tumor infiltration.

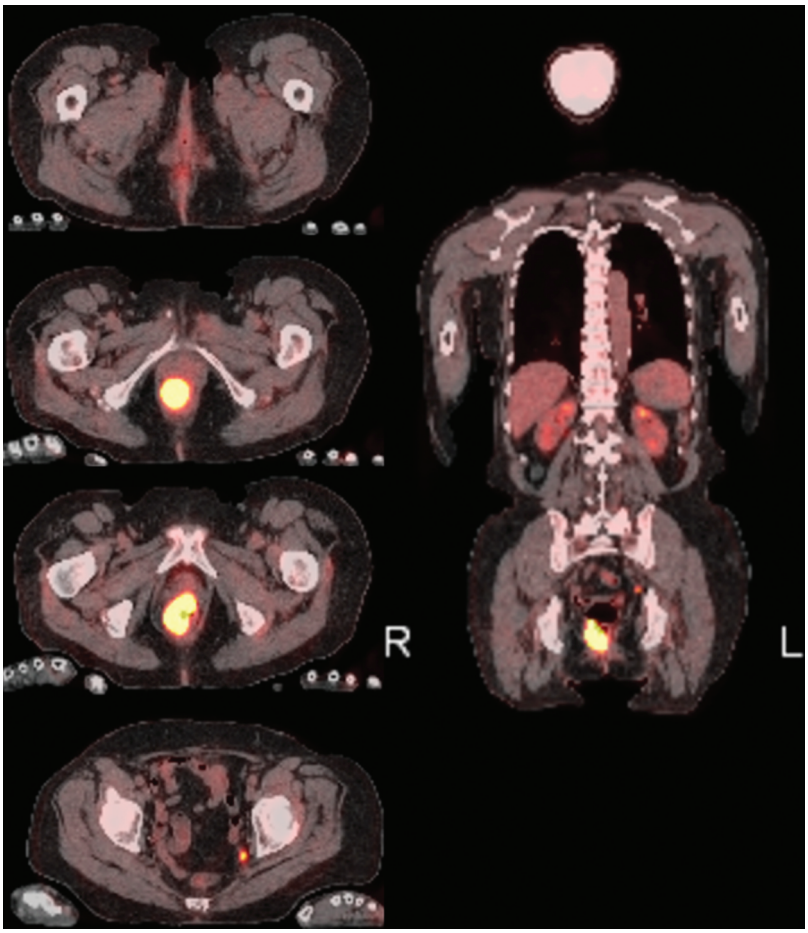

Figure 3. Staging PET/SPECT confirming an atypically high metabolically active rectal mass consistent with malignant melanoma, and a moderately active left internal iliac lymph node concerning for metastasis.

nodule also within the posterior left upper lobe measuring 1.6 cm x 1.5 cm.

Given these new findings and concern for new primary lung cancer, she underwent a navigational bronchoscopy for a left lung nodule biopsy. Brush sampling of the left upper lobe did not reveal any malignant cells on cytology; however, transbronchial biopsy of the left upper lobe was non-diagnostic for malignancy. Surprisingly, 3 weeks later, acid-fast bacilli culture grew mycobacterium tuberculosis and mycobacterium avium complex. She continued to have hemoptysis and was started on rifampin, isoniazid, pyrazinamide, and ethambutol. Further questioning revealed that both her father and mother deceased from tuberculosis. One month later, she returned to the emergency department with daily persistent

Table 1. Changes in metabolic activity detected on PET of notable lesions.

Lesions	1 month after diagnosis (SUV max)	6 months after diagnosis (SUV max)
Right sided rectal mass	43	Non visible
Left internal iliac lymph node	7.0 (10 mm x 8 mm)	23.8 (1.5 cm x 1.1 cm)
Anterior segment R hepatic lobe	3.0	Non visible
Bilateral hilar and mediastinal lymph nodes	4.2	4.6
LUL pulmonary nodule	Non visible	8.7 (1.1 cm x 0.8 cm)
Apicoposterior segment LUL subpleural nodule	3.8 (17 mm x 15 mm)	2.1 (8 mm)
Apical segment RUL nodule	1.3 (6 mm)	1.1 (5 mm)

Table 2. Results of genomic testing and tumor characteristics.

Tumor Features	
Biomarker Findings	
PD-L1 expression	1% Tumor Proportion Score
Microsatellite status	MS-Stable
Tumor Mutational Burden	6 Muts/Mb (Intermediate)
Genomic Findings	
Genes	Alteration
NF1	E1334*
PTEN	V166fs*14
RICTOR	Amplification
CDKN2A/B	p16INK4a loss and p14ARF loss exons 2-3

headaches, and underwent lumbar puncture to evaluate for meningeal tuberculosis. She was ultimately lost to follow up with her oncologist and did not initiate any systemic therapy for her melanoma.

4. Discussion

We present a case of an elderly woman with chronic diarrhea who complained of rectal bleeding and weight loss, and was found to have an anal mass which was diagnosed by biopsy as malignant melanoma. It may be that the chronic diarrhea was an early sign of her malignancy, but it is unclear whether the melanoma was present as she had never undergone routine screening colonoscopy. Her case was then complicated by persistent cough and later hemoptysis, which was concerning for metastatic melanoma with lung involvement versus primary lung cancer from ongoing cigarette use versus pulmonary infection/inflammation. It was not until after the bronchoscopy that she was diagnosed with tuberculosis by AFB culture. Molecular testing revealed no mutations of the *BRAF, KIT*, or *NRAS* genes, which excluded her from any potential benefit of targeted therapy. PD-1 testing was positive, which suggests potential response to anti-PD-1 inhibitors; however, she was lost to follow up and did not initiate any systemic treatment.

Given the relatively few number of cases of ARMM compared to its cutaneous counterpart, large randomized trials are lacking with no consensus treatment guidelines available. ARMM frequently responds poorly to radiation and chemotherapy, making surgery the current mainstay of treatment. Available treatment options are described next in the discussion.

4.1. Surgical therapy

Surgical approaches include WLE and APR. It still remains controversial as to which approach is preferred. Though APR is a more extensive procedure with higher morbidity, it has not been shown to improve overall survival in comparison to WLE [13–15]. The advantage of WLE is quicker recovery time and preservation of the sphincter, hence eliminating the need for a stoma, which may be a reasonable palliative treatment [16,17]. On the other hand, with local recurrence rates as high as 65% with WLE alone [18], APR has been thought to give better local disease control and lymphatic spread [19,20] and has been recommended when local margins are positive or in recurrent disease. Regardless of whether patients underwent APR or WLE, achieving an R0 resection with microscopically negative margins has been shown to significantly predict long-term advantage [18]. Despite surgery, many patients will progress to metastatic disease, as neither resection method can control lymphatic spread.

4.2. Adjuvant chemotherapy

Only one phase II randomized trial has demonstrated a benefit for adjuvant chemotherapy in mucosal melanoma [21]. This trial showed a prolonged progression-free survival with six cycles of temozolomide plus cisplatin compared to observation (20.8 months versus 5.4 months, respectively) after surgical resection. However, this was studied within a Chinese population and further study would be necessary before considering it for a Western population.

In the metastatic setting, systemic therapies are largely extrapolated from the treatment of cutaneous melanoma, which include cytotoxic chemotherapy, targeted therapy, and checkpoint inhibitor immunotherapy. Because most of the literature discussing metastatic ARMM comprises case reports given the limited number of patients with the disease, there is currently no standard systemic therapeutic regimen [22].

4.3. Cytotoxic chemotherapy

A retrospective single-institution study reported a modest response in metastatic melanoma of

mucosal primary [23]. Of the 81 patients included in this study, 38% had primary anorectal melanoma. The main result is that the response rate to first-line cytotoxic chemotherapy single agent was similar to combined therapy with alkylation agent (10% versus 8%, respectively), both with an overall survival of 10.3 months.

4.4. Targeted therapy

As our understanding of the molecular pathogenesis of metastatic melanoma evolves, targeted therapies continued to develop for a subset of patients. Approximately 25% of mucosal melanomas exhibit amplification of the *KIT* gene while 10% contain activating mutations of the *BRAF* gene. *KIT*-mutated melanomas are more commonly located at acral and mucosal sites, while *BRAF* and *NRAS*-mutated melanomas are mostly located at sunlight-exposed sites [24]. Several randomized trials of *KIT*-mutated melanoma have reported positive results when treated with tyrosine kinase inhibitors such as imatinib [25], nilotinib [26], sorafenib [27], and dasatinib [28]. The response rates varied from 23% to 54%, but all responders interestingly had exon 11 or exon 13 *KIT* mutations.

4.5. Immunotherapy

Cell cycle blockade immunotherapy has been revolutionary to the current landscape of oncology. Melanomas are highly immunogenic and have been shown to respond well to immunotherapies targeting cytototoxic T-lymphocyte associated antigen (CTLA-4) and programmed cell death protein 1 (PD-1). Ipilimumab, an anti-CTLA4 monoclonal antibody, has been shown to significantly improve the survival of patients with cutaneous melanoma; however, the same has not been shown in mucosal melanoma. One retrospective study of 33 patients found that only 2 patients had responded at week 12 [29]. Another study conducted in Italy consisted of 71 patients with mucosal melanoma. Only 12% of those patients responded, while 9% suffered from immune-related adverse events of grade 3 or 4 [30]. Nivolumab and pembrolizumab are anti-PD-1 monoclonal antibodies that were shown in cutaneous melanoma to have significantly increased survival. Although there are no randomized clinical trials of using anti-PD-1 inhibitors specifically for mucosal melanoma, some efficacy has been demonstrated by post-hoc analysis and retrospective studies. Hamid and colleagues assessed the efficacy of pembrolizumab in mucosal melanoma in three clinical trials (KEYNOTE 001, 002, and 006), resulting in 84 patients with a response rate of 19% and median overall survival of 11.3 months [31]. A retrospective study assessed the efficacy of anti-PD-1 blockade by either pembrolizumab or nivolumab in 35 patients with mucosal melanoma and found an overall response rate of 23% [32]. Compiled subset data among clinical trials seem to suggest a decreased response in mucosal melanoma compared to cutaneous melanoma, prompting further studies in combination therapies. A pooled analysis of six studies by D'Angelo et al. identified 86 patients with advanced mucosal melanoma treated with single-agent nivolumab (anti-PD-1) and 35 patients treated with a combination of nivolumab/ipilimumab (anti-PD-1/anti-CTLA-4). They demonstrated a 23% response rate for those who received nivolumab monotherapy compared to 37% for those who received combination therapy with ipilimumab. The analysis also included patients with cutaneous melanoma and showed that patients with cutaneous melanoma, on average, respond better than its mucosal melanoma counterpart when treated both with nivolumab monotherapy or nivolumab/ipilimumab combination [33]. This striking result suggests that cutaneous and mucosal melanoma behave and respond differently to immunotherapy, prompting further investigations and randomized control trials specific to mucosal melanoma.

5. Conclusion

ARMM is a rare entity with a very poor prognosis. We presented a case of a 78 year old Hispanic female found to have primary ARMM. This case demonstrates the need to have early detection as this malignancy is aggressive, as well as early surgical referral as surgery remains the mainstay of treatment. The treatment of mucosal melanoma remains controversial and randomized clinical trials are limited. Current systemic treatment options include cytotoxic chemotherapy, targeted therapy, and single agent or combination immunotherapy, which are extrapolated from cutaneous melanoma. Further studies and clinical trials of mucosal melanoma are needed as it may behave and respond differently from cutaneous melanoma.

Acknowledgement

Publication of this article was funded in part by the Temple University Libraries Open Access Publishing Fund.

Author contributions

HY and BG drafted and revised the manuscript. BK provided the key clinical images and interpretation. HY created the table. All authors agree on the final version of the submitted manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Khan M, Bucher N, Elhassan A, et al. Primary anorectal melanoma. Case Rep Oncol. 2014;7(1):164–170.
[2] Yang H, Hsiao S, Schaeffer D, et al. Identification of recurrent mutational events in anorectal melanoma. Mod Pathol. 2016;30:286–296.
[3] Taylor J, Stem M, Yu D, et al. Treatment strategies and survival trends for anorectal melanoma: is it time for a change? World J Surg. 2019;43:1809–1819.
[4] Malaguarnera G, Madeddu R, Catania VE, et al. Anorectal mucosal melanoma. Oncotarget. 2018;9(9):8785-8800.
[5] Plonka PM, Passeron T, Brenner M, et al. What are melanocytes really doing all day long … ? Exp Dermatol. 2009;18(9):799–819.
[6] Takeda K, Takahashi NH, Shibahara S. Neuroendocrine functions of melanocytes: beyond the skin-deep melanin maker. Tohoku J Exp Med. 2017;211(3):201–221.
[7] Singer M, Mutch MG. Anal melanoma. Clin Colon Rectal Surg. 2006;19(2):78–87.
[8] Chen H, Cai Y, Liu Y, et al. Incidence, surgical treatment, and prognosis of anorectal melanoma from 1973 to 2011: a population-based SEER analysis. Medicine (Baltimore). 2016;95(7):e2770.
[9] Callahan A, Anderson WF, Patel S, et al. Epidemiology of anorectal melanoma in the USA: 1992 to 2011. Dermatol Surg. 2016;41(1):94–99.
[10] Del Vecchio M, Di Guardo L, Ascierto PA, et al. Efficacy and safety of ipilimumab 3mg/kg in patients with pretreated, metastatic, mucosal melanoma. Eur J Cancer. 2014;50(1):121–127.
[11] Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11(2):155–164.
[12] Thierauf J, Veit JA, Hess J, et al. Checkpoint inhibition for advanced mucosal melanoma. Eur J Dermatol. 2017;27(2):160–165.
[13] Heeney A, Mulsow J, Hyland JMP. Treatment and outcomes of anorectal melanoma. Ann Med Surg. 2017;19:74–77.
[14] Yap LB, Neary P. A comparison of wide local excision with abdominoperineal resection in anorectal melanoma. Melanoma Res. 2004;14(2):147–150.
[15] Matsuda A, Miyashita M, Matsumoto S, et al. Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma. Ann Surg. 2015;261(4):670–677.
[16] Stoidis CN, Spyropoulos BG, Misiakos EP, et al. Diffuse anorectal melanoma; review of the current diagnostic and treatment aspects based on a case report. World J Surg Oncol. 2009;7:64.
[17] Ross M, Pezzi C, Pezzi T, et al. Patterns of failure in anorectal melanoma. A guide to surgical therapy. Arch Surg. 1990;125(3):313–316.
[18] Carcoforo P, Raiji MT, Palini GM, et al. Primary anorectal melanoma: an update. J Cancer. 2012;3:449–453.
[19] Brady MS, Kavolius JP, Quan SH, et al. Anorectal melanoma. A 64-year experience at Memorial sloan-kettering cancer center. Dis Colon Rectum. 1995;38(2):146–151.
[20] Ramalingam G, Gan EY, Kutt-Sing W. Laparoscopic abdominoperineal resection for anorectal melanoma: a case report and review of the literature. Surg Laparosc Endosc Percutan Tech. 2009;19(4):149–151.
[21] Lian B, Si L, Cui C, et al. Phase II randomized trial comparing high-dose IFN-α2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. Clin Cancer Res. 2013;19(16):4488–4498.
[22] Kim KB, Sanguino AM, Hodges C, et al. Biochemotherapy in patients with metastatic anorectal mucosal melanoma. Cancer Interdiscip Int J Am Cancer Soc. 2004;100(7):1478–1483.
[23] Shoushtari AN, Bluth MJ, Goldman DA, et al. Clinical features and response to systemic therapy in a historical cohort of advanced or unresectable mucosal melanoma. Melanoma Res. 2017;27(1):57–64.
[24] Ponti G, Manfredini M, Greco S, et al. BRAF, NRAS and C-KIT advanced melanoma: clinico-pathological features, targeted-therapy strategies and survival. Anticancer Res. 2017;37(12):7043–7048.
[25] Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J clin oncol. 2013;31(26):3182–3190.
[26] Guo J, Carvajal RD, Dummer R, et al. Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol. 2017;28(6):1380–1387.
[27] Quintás-Cardama A, Lazar AJ, Woodman SE, et al. Complete response of stage IV anal mucosal melanoma expressing KIT Val560Asp to the multikinase inhibitor sorafenib. Nature Clin Pract Oncol. 2008;5(12):737–740.
[28] Kalinsky K, Lee S, Rubin KM, et al. A phase 2 trial of dasatinib in patients with locally advanced or stage IV mucosal, acral, or vulvovaginal melanoma: a trial of the ECOG-ACRIN Cancer Research Group (E2607). Cancer. 2017;123(14):2688–2697.
[29] Postow MA, Luke JJ, Bluth MJ, et al. Ipilimumab for patients with advanced mucosal melanoma. Oncologist. 2013;18(6):726–732.
[30] Del Vecchio M, Di Guardo L, Ascierto PA, et al. Efficacy and safety of ipilimumab 3mg/kg in patients with pretreated, metastatic, mucosal melanoma. Eur J Cancer. 2013;50(1):121–127.
[31] Hamid O, Robert C, Ribas A, et al. Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006. Br J Cancer. 2018;119(6):670–674.
[32] Shoushtari AN, Munhoz RR, Kuk D, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. Cancer. 2016;122(21):3354–3362.
[33] D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J clin oncol. 2016;35(2):226–235.