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Case Report
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Long Term Metastasis-Free Survival in Stage IV anal Melanoma Cured by Repetitive Surgery and Short Cycle of Adjuvant Ipilimubab

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Abstract

Anal melanoma is often advanced at time of diagnosis and despite curative surgery no 5 year disease-specific survival has been observed when distant metastasis have been developed. In June 2011 at 69 years old male affected by anal melanoma was submitted to local excision of the neoplasia. At the follow-up no local recurrence was observed in the anal canal, but iterative metastases occurad at the right retroperitoneum (January 2014), at the left adrenal gland (October 2014), at the left gluteal region (September 2015), and at the first jejunal loop (March 2016) that every time were removed by surgery. On May 2016 the patient began ipilimubab at a dose of 10 mg per kg every 3 weeks for a total of 4 doses. To date (May 2020, 9 years after the diagnosis) the patient is free from disease. This experience confirms the important role of surgical resection of metastases from anal melanoma and the value of adjuvant treatment with immunotherapy for maintaining the result achieved by radical surgery.

Introduction

Anal melanoma arises from melanocytes present in the squamous anal epithelium. It is an extremely rare neoplasia having a prevalence of around 2/1,000,000 person/year [1]. According to a recent review of 22 publications covering 533 melanoma patients the median age of onset is 66 years and the predominant sex is male [2]. This tumor is often locally advanced or metastatic at time of diagnosis. Therefore, prognosis is very poor, with a median overall survival between 8 and 19 months, despite curative surgery, and no 5 year disease-specific survival when distant metastasis have been developed [3,4]. The prognosis is much worse than that observed for cutaneous melanoma, but it is controversial whether the adverse prognosis is due to a more advanced stage at time of the diagnosis or to a biologically more aggressive tumor [5]. The therapeutic strategies have recently changed due to advent of targeted systemic therapies and immunotherapy as adjuvant therapy to surgery and chemotherapy. A case of anal melanoma with distant metastases is described which has been treated with surgical removal of metastases, adjuvant chemotherapy and a short cycle of immunotherapy without evidence of recurrence of metastases after more than 5 years of follow-up.

Case Presentation

In June 2011, at the age of 69, the patient, strong smoker, notices the presence of a swelling of the anal canal. He was subjected to local excision with the diagnosis of hemorrhoids. The histological diagnosis was melanoma of the anal canal. Epithelioid cells with widespread aspects of angioinvasion were observed at histological examen. The margins of the surgical excision were positive. The patient underwent a total body CT scan and an ultrasound of the anal canal that appeared negative. In September 2011 the anal scar of the previous surgery was largely excised. Histological examination does not show residual melanoma. The patient underwent a regular follow-up which in January 2014 shows a mass of about 6 cm × 5 cm at the level of the right retroperitoneal fat. It was removed with a diagnosis of recurrent melanoma. In the following months the patient was submitted to chemotherapeutic treatment based on six cycles of temozolomide. Subsequent controls showed the onset of a left adrenal swelling of the size of 8 cm × 6.5 cm. In October 2014 the patient was subjected to left adrenalectomy and the histological examen confirmed the presence of metastatic melanoma. Subsequent controls show a nodule about 3 cm × 2.5 cm in diameter placed in the fat of the left gluteal region which is removed in September 2015 once again resulting in metastatic melanoma. In March 2016 the patient experienced abdominal pain, vomiting and melena. A relapse at the level of the first jejunal loops is highlighted. At surgery, an ulcerated mass of the size of 6 cm × 5 cm

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which infiltrates the first jejunal loop and the mesosigma was found. A radical resection was performed followed by the reconstruction of intestinal continuity with end to end duodenal-jejunal anastomosis. Histological examination confirms the diagnosis of melanoma. No mutation of BRAF was found. In consideration of the IV (M1c) stage of the melanoma, the good clinical conditions and the absence of BRAF mutation, it was decided to subject the patient to adjuvant immunotherapy. On May 2016 the patient began ipilimubab at a dose of 10 mg per kilogram every 3 weeks which continues until July 2016, for a total of 4 doses. The treatment was well tolerated. In the following months the patient continues the clinical and instrumental checks that were normal. To date (May 2020, 9 years after the diagnosis) the patient is free from disease.

Discussion

Anal melanoma is manifested by the onset of an anal swelling which causes ulceration and bleeding. It can be confused with hemorrhoids and therefore any atypical anal lesion should be biopsied [6]. The surgical option is between wide local excision or abdominoperineal amputation. The choice is guided by preoperative staging (transanal ecography, MRI and 18F-FDG-PET/CT) [7,8]. If the tumor does not infiltrate the deep structures local excision can be performed, but if the deep planes are involved and/or metastases are present in the mesorectally lymph nodes Abdominoperineal Resection (APR) is preferred. Although local recurrence is higher after wide local excision than after APR, long-term survival is very similar [9,10]. Prognosis of anal melanoma is very poor. Negative prognostic factors are considered the age >60 yrs, the male gender, the perineural invasion and overall the stage according to TNM evaluation [11,12]. Since the year 2000, the revised TNM staging has classified three categories for M: M1a (metastases to distant skin, subcutaneous tissue), M1b (metastases to lung) and M1c (metastases to all other viscera). The last group has the worst prognosis [13]. Metastases from anal melanoma are detected in up to one-third of the patients at time of diagnosis. They arise both by lymphatic spread in mesorectal or inguinal nodes or by hematogenous way to liver, lung, brain and bones as preferred sites. The present case has a peculiar hematogenous metastatic diffusion occurred progressively in the two years following the excision of the primitive tumor and capriciously both in the soft tissues and in the adrenal and small intestine. Frequent recurrences, widespread metastases and abdominal localization of the metastases are accompanied by a poor prognosis, as in the present case. The possible advantage of a surgical approach to distant metastases for anal melanoma can be mediated by the analysis of the follow-up of the patients affected by cutaneous melanoma. The data of cutaneous melanomas enrolled in the first Multicenter Selective Lymphadenectomy Trial (MSLT-I) show that the patients submitted to surgery ± systemic medical therapy have a significative survival advantage in confront of the patients submitted only to systemic medical therapy [14]. This survival advantage is found even in patients with high-risk visceral metastases (M1B oc) or multiple and recurrent metastases that may require several operations for complete resection. This result is probably due to the interruption of the metastatic cascade due to hematogenous diffusion of melanoma from the metastatic site to other sites. But another potential advantage could be the drastic reduction of tumor burden with a consequent reduction of tumor-induced immune suppression. However, the survival after complete resection of the distant metastases is very poor in absence of adjuvant systemic therapy. Until 2015, the adjuvant therapy for melanoma surgery approved by FDA and EMA consisted only of IFNα-2b or pegylated IFNα-2b that had shown a benefit in relapse-free survival interval, but any advantage in the overall survival [15,16]. Afterwards, selective kinase inhibitors and immune checkpoint inhibitors were approved for the treatment of melanoma and tested also for adjuvant treatment. Vemurafenib or dabrafenib, selective BRAF inhibitors, and trametinib blocking MAPK kinase are able to significantly improve progression-free survival in comparison with placebo in patients affected by cutaneous melanoma when the BRAF oncogene or MEK (a constituent of the RAS/MEK pathway) are found mutated [17,18]. Mutation of these genes are present in at least 50% of patients with cutaneous melanoma, but much less in mucosal or anal melanoma [11,19,20]. They activate the MAPK signaling and are responsible of increased cell proliferation and reduced apoptosis. In the present patient wild type BRAF of the metastases did not indicate use of adjuvant target therapy. The targeted therapies can have serious side effects, challenging to resolve, and could also determine the growth of new tumors. Starting in 2015, checkpoint inhibitor immunotherapies were studied as adjuvant therapy in stage III or stage IV cutaneous melanomas after complete surgical resection. Ipilimumab, a fully human IgG1 monoclonal antibody against the immune check point receptor CTL4, modulates the host's immune system recognition of neoplastic cells by the cytotoxic T-lymphocites. The results of a clinical trial with ipilimumab administered after radical surgery for a long period (up to 3 years) had shown a significant higher rate of durable clinical benefit (concerning both the recurrence-free survival and the overall survival) compared to placebo [21]. However, serious side effects had been frequently observed causing the suspension of the treatment in the majority of the patients. Nivolumab, a human IgG4 monoclonal antibody against PD1, had been approved for the treatment of patients with metastatic melanoma after the positive result of a clinical trial [22]. A randomized double-blind, phase 3 trial had evaluated nivolumab versus ipilimumab as adjuvant therapy in patients with complete resection of stage IIIb, IIIc and IV melanoma. The treatment was administered for up 1 year. The nivolumab group has shown longer recurrence-free survival and less adverse effects [23]. The rarity of the primary anal melanoma does not allow to perform clinical trials in this type of melanoma biologically different from the cutaneous counterpart. However, the data of more than 150 patients with advanced mucosal melanoma enrolled in clinical trials of immunotherapy (with ipilimumab, nivolumab and the association of these two drugs) were recently published [24]. Improvement of progression-free-survival and overall survival was observed overall for the association of nivolumab with ipilimumab. This analysis confirms the efficacy of the immunotherapy also in the mucosal melanoma and suggests the employment of immune antibodies against programmed CTL4 or PD-1 as adjuvant therapy for the anal melanoma. However, the need to perform an adjuvant immunotherapeutic treatment must be carefully evaluated. Despite the positive effects observed and the increase in survival that is likely to occur, the risk of rapid progression of the tumor while using immunotherapy is possible especially in old people. The immunological mechanism underlying this hyper progression disease is currently unknown [25,26].

Conclusion

Surgical resection of metastases from anal melanoma plays an important role and gives the chance of a prolonged survival. The aim of surgery must be to perform a complete resection. Therefore, patients must be appropriately selected on the basis of the site of distant metastasis, their number and the interval of time elapsed between their appearance and the removal of the primary tumor.

Removal of metastasis occurring synchronously or within one year from the primary melanoma resection is accompanied by a poor result. Actually, immunotherapy seems the better adjuvant treatment for maintaining the result achieved by a radical surgery.

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