Abstract. Background: Although the resection of solitary visceral melanoma metastases is indicated when possible, further progression of metastatic disease is seen in the vast majority of patients. New modalities of immunotherapy can offer durable disease control in a significant proportion of melanoma patients. Case Report: A 28-year-old man was diagnosed with stage III melanoma in 2003 and was treated with autologous dendritic cells in the adjuvant setting. Five years later melanoma metastases causing small bowel obstruction were surgically removed and he was retreated with dendritic cells. Following 5 months without disease manifestations, the patient presented with intermittent abdominal discomfort. Following the visualization of a hot spot at the level of the jejunum on 18F-fluorodeoxyglucose position-emission tomography, the patient underwent a laparotomy, during which a solitary melanoma metastasis of the small bowel causing intussusception was resected. The patient has so far remained disease-free, more than one year after the latest surgical intervention. Conclusion: Combined modality treatment with surgery and immunotherapy may result in an improved long-term outcome for patients with metastatic melanoma.

Case Report

Our patient was diagnosed at the age of 22 years with a nodular melanoma of the right shoulder that was resected in March 2003 (AJCC stage IIIA). In September 2003, he underwent a right axillary dissection for a macroscopic lymph node recurrence. As an adjuvant treatment, he was offered cellular immunotherapy with human leukocyte antigen (HLA) class I and II peptide-loaded autologous dendritic cells (at the Hautklinik Universitätsklinikum Erlangen, Professor G. Schuler). The evolution of the patient’s disease had been uneventful until August 2008. During a laparotomy performed for an acute gastrointestinal (GI) obstruction, two small bowel metastases were resected. The patient was subsequently treated at our institution with autologous dendritic cells electroporated with synthetic messenger RNA (TriMix-DC) encoding CD40 ligand, constitutively activated toll-like receptor 4, CD70 and a fusion protein between DC.LAMP and one of four melanoma associated antigens (MAGE-A3, MAGE-C2, tyrosinase, or GP100) (1). Four administrations were performed on a bi-weekly schedule, followed by maintenance administrations every 8 weeks (at each administration a total of 50×10^6 viable dendritic cells were injected intradermally).

Five months following the initiation of retreatment with DC, in October 2009, he was admitted to the Department of Abdominal Surgery for investigation of a 3-week history of intermittent abdominal pain and nausea. Physical examination revealed moderate tenderness during palpation of the upper left abdomen. Routine laboratory tests showed no abnormalities. A contrast-enhanced computed tomography (CT) of the abdomen revealed multiple nonpathological subcentimetre retroperitoneal and mesenteric lymph nodes. A subsequent 18F-fluorodeoxyglucose positron-emission tomography-computed tomography (18F-FDG PET-CT) revealed a focal 18F-FDG hot spot within the left hypochondrium at the level of the proximal jejunum without a corresponding anatomical lesion on CT. This finding was
interpreted to potentially represent physiological $^{18}\text{F}$-FDG uptake by the small bowel. Because of the patient’s persisting symptoms and former medical history, the decision was made to perform an exploratory laparotomy, which revealed an intussusception of the proximal jejunum. Reduction of the intussusception via small bowel manipulation revealed the underlying tumor (Figure 1). A segmental small bowel resection with involved mesentery was performed and continuity was restored by a termino-terminal anastomosis. Further exploration of the abdominal cavity did not reveal any other metastatic lesions.

Histopathological analysis of the surgical specimen revealed a round, pink (non pigmented) tumor, 1.5 cm in diameter with a hard consistency. It predominantly involved the submucosa, with focal extension into the muscularis propria. Tumor cells stained positively on immunohistochemistry for HMB45, S100 and Melan A, characteristic of melanoma (Figures 2 and 3). Reverse transcription-polymerase chain reaction (RT-PCR) indicated expression of Na.17, and tyrosinase but not of MAGE-A3 or MAGE-C2.

Following recovery from surgery, the patient was treated with additional administrations of TriMix-DC that were loaded with antigens matched to the melanoma metastasis antigen expression profile (synthetic mRNA encoding fusion proteins DC.LAMP-tyrosinase and DC.LAMP-Na.17). A video endoscopy performed 3 months after the intervention did not reveal any endoluminal abnormality. Neither did repeated follow-up examination (including $^{18}\text{F}$-FDG PET-CT) reveal any sign of melanoma recurrence. The patient was still recurrence-free at the latest follow-up (19 months after the latest surgical intervention).

Discussion

Cutaneous melanoma is a malignant tumor originating from melanocytes of the skin. Less common are melanomas originating from the mucosa, or the uvea of the eye (2, 3). Melanoma is renowned for its tendency to metastasize to regional lymph nodes and distant sites at an early stage of the tumor. The GI tract is one of the most common sites to which metastatic melanoma spreads (4). Within the digestive tract, the jejunum and ileum are the most commonly involved sites, followed by the colon, rectum and stomach (3, 5). The most common cause of small bowel metastasis is malignant melanoma (4, 6).

Approximately 8% of patients with stage IV melanoma are diagnosed with GI tract metastases, and 1-5% of these patients will have metastasis to the small bowel (3, 5, 7-11). The incidence is close to 60% in post-mortem studies (5, 9, 12). Small bowel metastases are infrequent in other
Figure 2. Microscopic section of the small bowel tumor showed a non-pigmented melanoma metastasis located in the submucosa. The tumor cells had an eosinophilic cytoplasm and irregular nuclei with prominent nucleoli. The tumor had a high mitotic activity. Cytoplasmic melanin pigment was not observed. Hematoxylin-eosin staining, magnification ×25 and ×630 (inset).

Figure 3. Immunohistochemical staining for HMB45 was strongly positive in tumor cells. Magnification ×400.
metastatic malignancies (3, 7). Besides melanoma, metastasis to the intestines has also been reported in patients with lung, renal cell, and breast cancer (13).

Symptoms of small bowel metastases of melanoma are non-specific and consist of abdominal pain, nausea, vomiting, weight loss, GI bleeding and obstruction (3, 4). Anemia due to GI bleeding is sometimes the only clinical manifestation (5, 9, 10, 14). Despite the non-specific GI symptoms, metastatic melanoma should be suspected in patients with a history of melanoma and unexplained GI symptoms or anemia (3, 5-8).

Radiological diagnosis of small bowel metastases is difficult and diagnosis is thus often delayed until complications occur (5, 7). Computed tomography with intravenous contrast can detect intussusception, as well as mesenteric and omental implants (3, 7, 8). Intussusception classically presents as a target-shaped lesion caused by an intraluminal mass with an eccentric fat density resulting from the drawing in of the adjacent mesentery in association with the invaginated bowel. A target sign is a diagnostic feature of all intussusceptions whether they are symptomatic, asymptomatic or transient, and may be present with or without an associated mass (11, 14). Lesions longer than 3.5 cm should probably be followed by enteroclysis or CT-enteroclysis to find a lead point, most commonly a tumor lead point (14).

$^{18}$F-FDG PET-CT is a highly sensitive method for the detection of melanoma metastases and it appears to be superior to other conventional imaging methods including PET (9). Remarkable is the focality of staining (FDG-uptake) in PET-CT fusion images (9). FDG-PET imaging has a sensitivity of nearly 100% for lesions greater than 1 cm (12). PET-CT fusion technology combines structural information of CT with physiologic information of $^{18}$F-FDG-PET in one set of images (12). In addition, magnetic resonance enteroclysis has been described as a sensitive method for the detection of melanoma of the small bowel (2). Biopsy of masses during surgery is essential for histopathological examination. Immunohistochemical stains, including HMB-45 and S100, are useful in the confirmation of the diagnosis (4, 6).

Surgical resection for GI tract melanoma metastases, whenever possible, should be attempted as the primary treatment as it provides the most efficient treatment option with low operative morbidity and mortality (10). Extensive surgical resection, including wide resection of the tumor with wedge resection of the mesentery to remove the regional lymph nodes, is recommended, especially if the disease is not widely disseminated within the abdomen (2, 8). However, the prognosis of melanoma patients with visceral metastasis remains, on average, very poor, with an average 5-year survival rate of 10-20% (4, 7, 8). Series of selected patients that present with few metastases and can undergo complete surgical resection indicate that such patients have a better prognosis (with 5-year survival rates of between 20% and 41%). In rare patients, even long-term survival or cure has been reported after complete surgical resection of solitary metastases (7).

New immunotherapies have become available with activity against melanoma. Ipilimumab, a monoclonal antibody directed against the cytokotoxic T-lymphocyte antigen-4 (CTLA-4) receptor has recently been demonstrated to improve the survival of patients with pretreated melanoma (15, 16). Improved survival with ipilimumab was obtained despite a relatively low objective response rate (4.2-10.9%). In addition to the antitumor activity captured by conventional tumor response criteria such as the mWHO criteria, immunotherapy can be associated with atypical patterns of response (17, 18). Furthermore, in individual cases, response to immunotherapy can be heterogeneous among individual metastases (19). Following the development of small bowel metastases, our patient was treated with autologous dendritic cell therapy (TriMix-DC) (1). Although speculative, this experimental cellular therapy may have contributed to the immune-elimination of micrometastases through the induction of protective antitumor immunity directed against the melanoma-associated antigens MAGE-A3, MAGE-C2, tyrosinase and GP100 that were loaded onto the DC. Expression analysis of melanoma metastasis that was resected at the second recurrence indicated loss of expression of three out of the four antigens present in the TriMix-DC. Selection of metastatic melanoma cells could be presumed. Following adaptation of the TriMix-DC to match the antigens expressed by the metastasis (Na.17 and tyrosinase), our patient may have developed immune protection against further evolution of melanoma metastases expressing these antigens.

Because of the increasing incidence of melanoma, and potentially also because of mixed tumor responses to immunotherapy, a higher number of patients presenting with isolated recurrences, including metastasis in the GI tract can be expected in the future. Adjuvant immunotherapy, as suggested by the history of our case, may also alter the classical course of this disease and increase the frequency of unusual presentations of late and isolated recurrences. It is, therefore, of importance for physicians dealing with melanoma patients and abdominal surgeons in general to be aware of the potential manifestations of recurrence of metastatic melanoma so that they may provide appropriate patient treatment, thus optimizing the chance for durable survival of these patients (5).

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References


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