Sarcoidosis in a Patient with Metastatic Melanoma Sequentially Treated with Anti-CTLA-4 Monoclonal Antibody and Selective BRAF Inhibitor

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Abstract. *A female patient with stage IV-M1c (distant lymph node and breast metastases), chemotherapy-refractory melanoma was treated with the cytotoxic T-lymphocyte antigen 4 (CTLA-4)-inhibitory monoclonal antibody ipilimumab. At first evaluation following induction treatment, there was marked increase in the volume of the lymphadenopathies (including new adenopathies) and strong uptake of ^{18}Fluorodeoxy-D-glucose (^{18}FDG); marked enlargement of the spleen and interstitial lung infiltrates were also observed. Non-necrotising granulomas were discovered on transbronchial mucosal biopsy and cytology on bronchoalveolar lavage established the diagnosis of sarcoidosis. There was a marked clinical and ^{18}FDG-positron emission tomography/computed tomography (^{18}FDG-PET/CT) documented response following six weeks of corticotherapy. At follow-up, progression of subdiaphragmatic melanoma lymph node metastases was documented. Regression of these metastatic sites was observed during treatment with the selective v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor vemurafenib. The patient died due to progressive disease after three months of vemurafenib treatment. Our case report illustrates the need to take into consideration exacerbation of sarcoidosis as a potential confounder in the assessment of tumor response in a melanoma patient treated with the anti-CTLA-4 mononclonal antibody ipilimumab.*

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Patients with advanced melanoma have had a dismal prognosis for decades, especially once distant metastases have developed beyond the limits for surgical resection. Ipilimumab (Yervoy; Bristol-Myers Squibb), a fully human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), was the first agent to show improved survival of patients with metastatic melanoma in a phase 3 trial (1). In this study, in patients with pretreated metastatic melanoma, ipilimumab monotherapy (3 mg/kg every 3 weeks for 4 doses) significantly improved median OS (Hazard ratio: 0.66, p=0.003) from 6.4 months, in patients treated with the gp100 vaccine control, to 10.1 months. Based on these results, ipilimumab 3 mg/kg received marketing authorization from both the Food and Drug Administration and European Commission, and is therefore available for clinical use in the USA (for all patients with metastatic melanoma) and Europe (for pretreated patients only). Ipilimumab binds the CTLA-4 receptor, a cell surface molecule expressed by T-cells (activated $CD4^+$ or $CD8^+$ T-cells and constitutively by $CD4^+$ regulatory T-cells). The CTLA-4 co-stimulatory receptor on T-lymphocytes acts as a negative regulator of T-cell activation that competes with CD28 for binding to B7-1 (CD80) and B7-2 (CD86) surface molecules found on antigen-presenting cells. Such expression of CTLA-4 on activated T-cells is a negative physiological regulator and effectively induces T-cell anergy (2-5). Therapeutic anti-CTLA-4 monoclonal antibodies, such as ipilimumab and tremelimumab, inhibit this inhibitory signal and thus promote T-cell activation. Ipilimumab has been demonstrated to enforce immune-mediated tumor rejection in animal models and to improve the survival of patients with pretreated melanoma (1). However, ipilimumab can also reduce self-tolerance to normal tissues and is associated with potentially severe immune-related adverse events. The most common adverse events are colitis and diarrhea, rash, pruritus, endocrine deficiency syndromes related to auto-

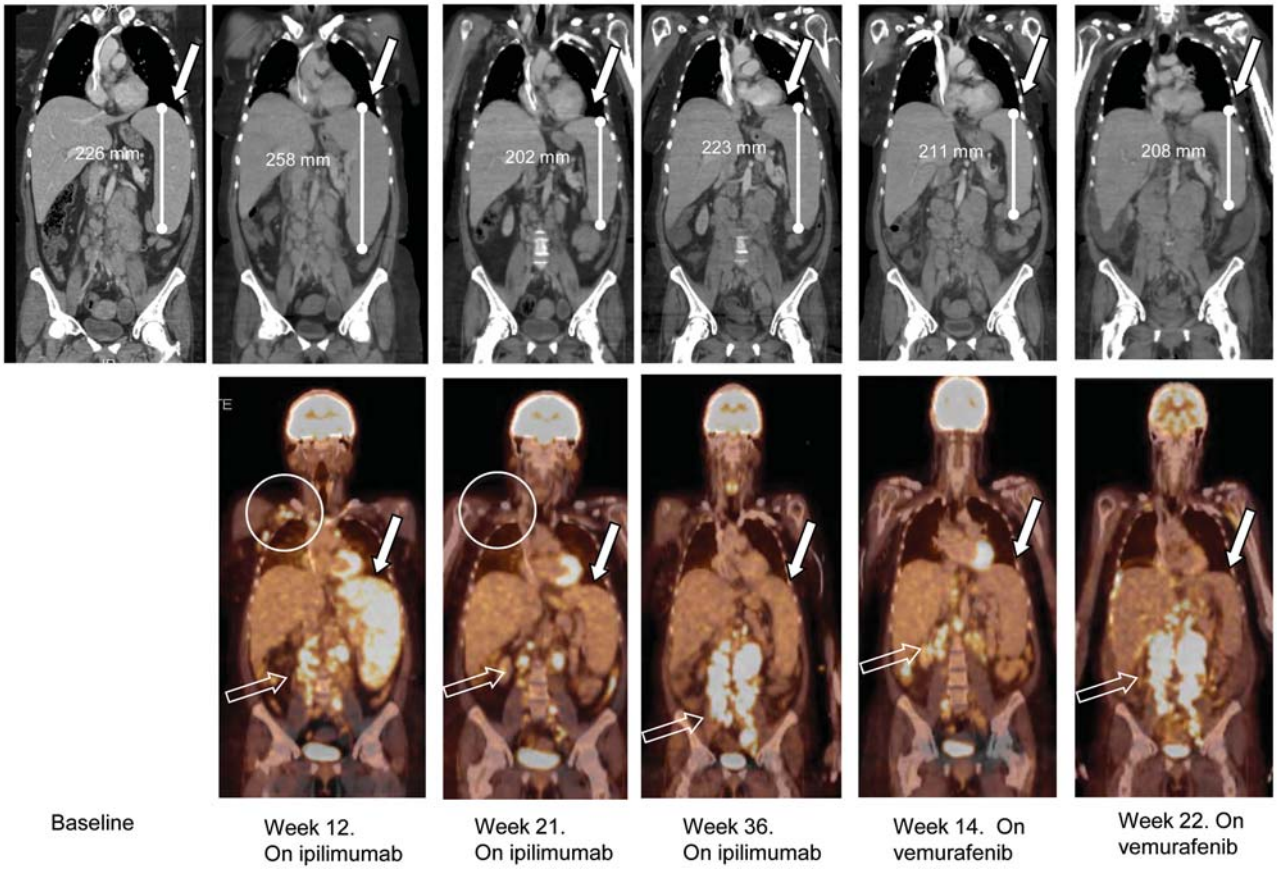

Figure 1. *Coronal sections by computed tomography (CT) (upper panel), and ^{18}Fluorodeoxy-D-glucose positron emission tomography/CT imaging (lower panel).*

immune damage to endocrine organs (pituitary, adrenal or thyroid), hepatitis and uveitis (6-8). Therefore, ipilimumab should not be used to treat melanoma in patients with a known clinically relevant auto-immune disease.

Case Report

Following the resection of a suspicious nevus on the left knee, a 48-year-old female patient was diagnosed with a primary malignant melanoma (Breslow 3.46 mm, Clark IV, superficial spreading type) in June 2002. Four years later (at the age of 52 years), bilateral sub-centimeter lung nodules and right-sided axillary adenopathies were detected during radiological follow-up. Histopathological examination of a transthoracic biopsy and excision of a right-sided axillary adenopathy was unable to confirm the diagnosis of melanoma metastasis. Two years later, biopsy of a newly detected breast nodule established the diagnosis of melanoma metastasis (AJCC stage IV-M1c). First-line therapy was initiated with a combination chemotherapy regimen (dacarbazine/cisplatinum). Chemotherapy was discontinued after two cycles because of disease progression (progressive mediastinal and retroperitoneal lymph node metastases).

In June 2009, the patient consulted our melanoma clinic for the first time and was recruited in a prospective phase II trial investigating sunitinib malate in patients with chemotherapy-refractory melanoma (9). Treatment with sunitinib malate [an oral vascular endothelial growth factor receptor (VEGFR), v-kit Hardy Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) and platelet-derived growth factor receptor (PDGFR) small molecule tyrosine kinase inhibitor; Sutent, Pfizer] was initiated in July 2009 and the disease remained stable for 12 months. In July 2010, progressive disease was documented, with an increase in volume of the pre-existing subdiaphragmatic adenopathies, as well as the development of new retrocrural adenopathies. The mediastinal lymphadenopathies and pulmonary micronodules remained stable. In August 2010, treatment with ipilimumab was initiated in an expanded access program for ipilimumab (Yervoy; Bristol-Myers Squibb), a fully humanized monoclonal antibody (mAb) of the IgG1 class, directed against the CTLA-4 receptor, administered intravenously at a dose of 3 mg/kg every three weeks for a total

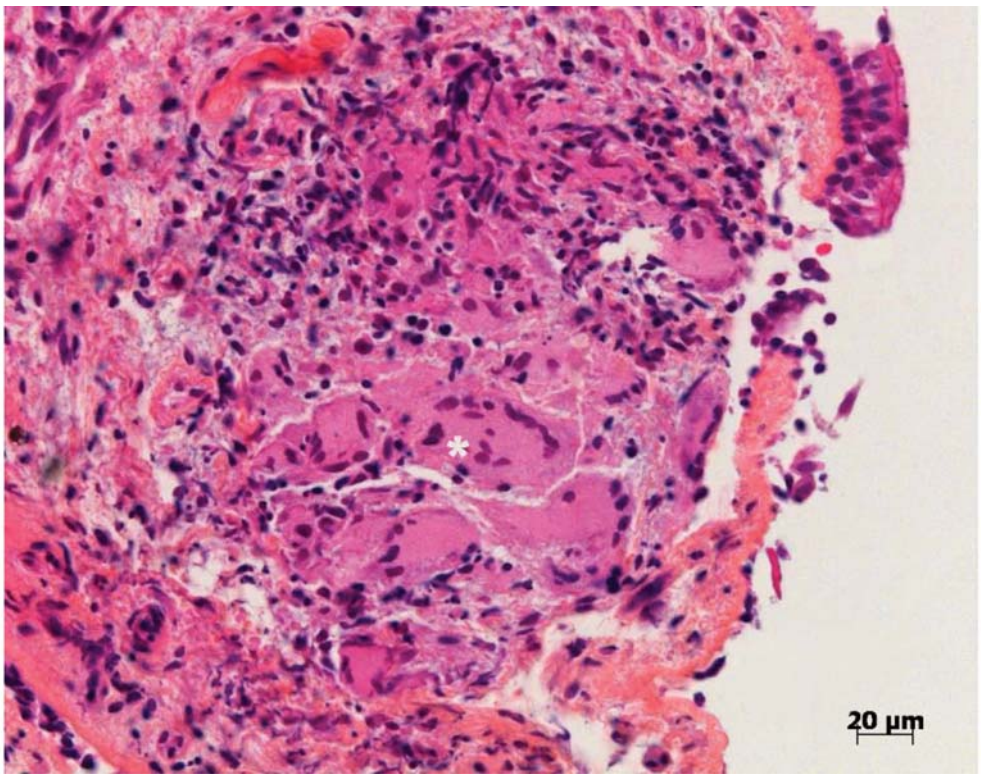

Figure 2. *Microscopic view of a transbronchial biopsy revealing chronic inflammation and the presence of non-necrotizing epithelioid granulomas (indicated by an asterisk).*

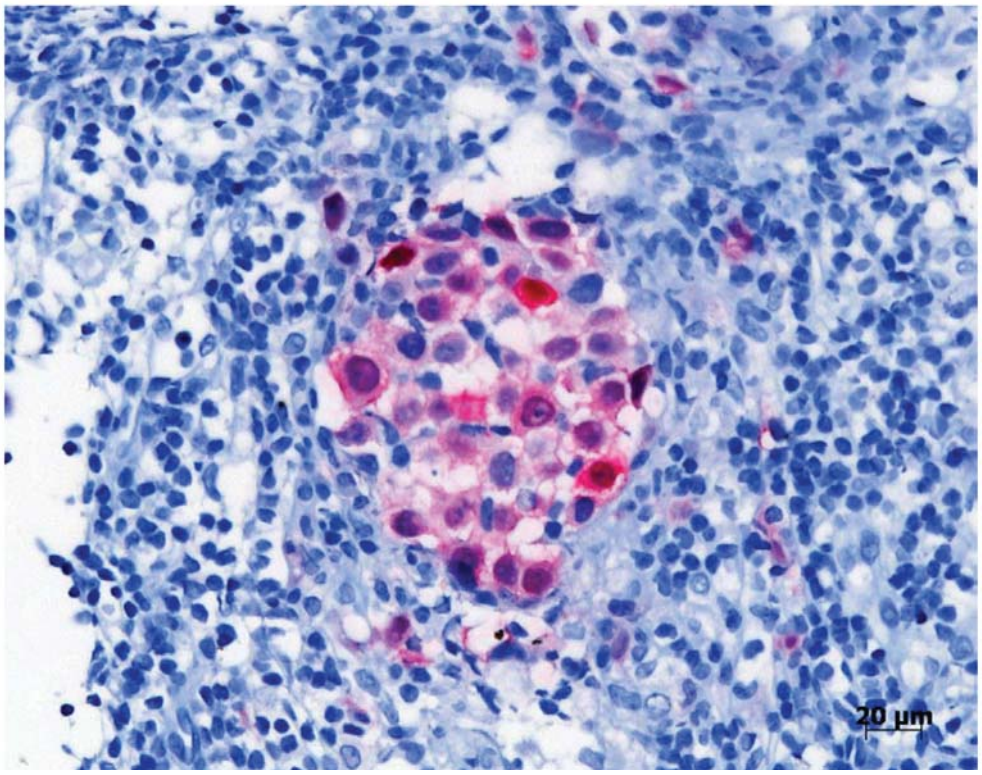

Figure 3. *Microscopic view of a melanoma metastasis in a biopsy from an illiaco-femoral adenopathy.*

of four administrations. One week after the second administration of ipilimumab, she reported a persistent dry cough, with increasing shortness of breath and fatigue. Clinical examination revealed the patient to be apyretic, with a stable weight (99 kg). A high serum C-reactive protein (CRP) level (23.5 mg/l; upper limit of normal (ULN)=5 mg/l), as well as decreased serum potassium (3.3 mEq/l; laboratory normal=3.6 to 5 mEq/l), elevated serum lactate dehydrogenase (LDH) (750 U/l; ULN=502 U/l), and a normal angiotensin-converting enzyme (ACE) level (42 U/l, normal=<56 U/l) were documented in the blood. ^{18}Fluorodeoxy-D-glucose positron emission tomography/computed tomography (^{18}FDG-PET/CT) revealed an increase in the volume of multiple ^{18}FDG-avid adenopathies at the base of the neck, axillae, mediastinum and retroperitoneal space (Figure 1). There was also a marked increase in the size of the pulmonary lesions. A marked increase in the volume of the spleen with a homogenous uptake of ^{18}FDG was also apparent. Magnetic resonance imaging of the brain and spine did not reveal any abnormalities. Suspecting sarcoidosis, further invasive examinations were performed. Bronchoscopy with broncho-alveolar lavage (BAL) indicated a marked lymphocytic predominance (54% lymphocytes), with an elevated CD4/CD8 ratio (3.95). Microbiological cultures of BAL remained negative. Ophthalmological and cardiological investigations excluded ocular or cardiac involvement. The suspected diagnosis of sarcoidosis was confirmed by histopathology of transbronchial biopsies, revealing chronic inflammation and the presence of non-necrotizing epithelioid granulomas (Figure 2). Administration of ipilimumab was stopped following the first four administrations (induction therapy). Cough and dyspnea resolved after six weeks of high-dose corticotherapy (48 mg of methylprednisolone administered per os once daily) and did not recur when tapering the dose of corticosteroids. A first follow-up ^{18}FDG-PET/CT, obtained 21 weeks after the initiation of ipilimumab, revealed a marked decrease of the splenomegaly and supradiaphragmatic lymphadenopathies. Subdiaphragmatic adenopathies had also decreased in volume but to a lesser extent, and remained ^{18}FDG-avid (Figure 2). One week after her re-evaluation, the patient was admitted to a regional hospital with abdominal pain and vomiting. Acute cholecystitis was suspected and a laparoscopic cholecystectomy was performed. Symptoms however persisted and a new ^{18}FDG-PET/CT, performed 36 weeks after the initiation of ipilimumab, revealed a significant increase in the size of subdiaphragmatic adenopathies. A diagnostic biopsy of the progressive illiaco-femoral adenopathies revealed melanoma metastasis (Figure 3). The dimensions of the spleen had slightly increased but without re-appearance of the strong uptake of ^{18}FDG. Mutation analysis of the tumor material demonstrated the presence of a v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation and treatment was initiated with the selective BRAF inhibitor vemurafenib (Zelboraf; Roche) in June 2011. During the first weeks of treatment, the patient experienced rapid symptomatic relief, together with a marked decrease of the elevated serum LDH. At first tumor evaluation in August 2011, regression of the subdiaphragmatic adenopathies was confirmed (Figure 1). Treatment-related adverse events were restricted to photosensitivity and grade 1 arthralgia. Unfortunately, in October 2011, progressive disease with rapidly progressive peritoneal carcinomatosis was diagnosed and the patient died shortly thereafter.

Discussion

At the time that ipilimumab treatment was initiated in our patient, her self-reported medical history did not include the notion of a prior history of sarcoidosis. Moreover, the clinical presentation and histologically confirmed diagnosis of melanoma metastasis to the breast favored progressive melanoma; the atypical lung infiltrates and lymphadenopathy could also have been part of a paraneoplastic sarcoid-like reaction (10). Sarcoidosis is a multisystemic granulomatous disease of unknown etiology, most commonly affecting the respiratory tract. The hypothetical immunological mechanism responsible for sarcoidosis is that the immune system mounts an uncontrolled strong T-helper 1 cell-mediated response to an unknown antigen. The most prominent sites of extrapulmonary disease include the skin, eyes, reticulo-endothelial system, musculoskeletal system, exocrine glands, heart, kidney and central nervous system. Sarcoidosis is characterized by the formation of non-necrotizing epithelioid granulomas (11). These sarcoidal granulomas produce ACE, and ACE levels are elevated in 60% of patients with sarcoidosis (12). Two previous reports described pulmonary and cutaneous sarcoidosis induced by an anti-CTLA-4 antibody in the treatment of metastatic melanoma (13, 14). Sarcoidosis has been associated with malignancy, most often lymphoma and melanoma. Malignancy can also be associated with the occurrence of sarcoid reactions that typically are restricted to the regional lymph nodes or the visceral organ of tumor origin (10). Antineoplastic treatment of either the hematological malignancy or the solid tumor has been reported to either induce the initial onset or lead to a flare in the activity of sarcoidosis (10). Moreover, sarcoidosis has been reported as an adverse event in melanoma patients treated with the immunostimulatory cytokine interferon alfa-2b (15).

Conclusion

We conclude that patients treated with the CTLA-4 mAb ipilimumab should be considered at risk for the exacerbation of sarcoidosis. Active, symptomatic sarcoidosis, or a prior history of clinically relevant sarcoidosis should therefore be considered a relative contraindication for treatment with

ipilimumab. Patients without an established diagnosis but suspected as having sarcoidosis or sarcoid-like paraneoplastic manifestations should be monitored closely following the initiation of ipilimumab therapy. Coincident development of sarcoidosis and metastatic melanoma poses a particular diagnostic challenge as both diseases share common features, such as the development of ^{18}FDG-avid adenopathies. Unusual features such as splenomegaly should draw the attention of the treating physician to the possibility of coexisting sarcoidosis. Our patient responded favorably to corticosteroids and cessation of ipilimumab treatment, consistent with the efficacy of corticosteroid treatment for controlling other immune-related adverse events that may be encountered during ipilimumab treatment.

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