CHEST

Nivolumab-Induced Sarcoid-Like Granulomatous Reaction in a Patient With Advanced Melanoma

François-Xavier Danlos, MD; Cécile Pagès, MD; Barouyr Baroudjian, MD; Laetitia Vercellino, MD; Maxime Battistella, MD, PhD; Maurice Mimoun, MD, PhD; Majdi Jebali, MS; Martine Bagot, MD, PhD; Abdellatif Tazi, MD, PhD; and Céleste Lebbé, MD, PhD

To our knowledge, we report the first case of sarcoid-like granulomatous reaction induced by nivolumab, a fully human IgG4 anti-programmed death 1 (PD-1) immune checkpoint inhibitor antibody. A 57-year-old man was treated with nivolumab 3 mg/kg for 2 weeks for a desmoplastic melanoma stage III American Joint Commission on Cancer, with no *BRAF*, *NRAS*, and *cKit* mutations. At 10 months, although melanoma complete response was achieved, he developed sarcoid-like granulomatous reaction in the mediastinal lymph node and skin, which resumed after nivolumab arrest. Melanoma did not relapse after 12 months of follow-up. Considering the recently demonstrated role of activated PD-1/PDL-1 axis in sarcoidosis, granulomatous reaction in the patient seems to be a paradoxical reaction, but similar observations have been reported with ipilimumab, another immune checkpoint inhibitor. Sarcoid-like granulomatous reaction during immunotherapy treatment could be a manifestation of cell-mediated immunity induced by these drugs. Impact of granulomatous reaction induced by immune checkpoint inhibitor on melanoma progression is not known and requires further study. Melanoma patients treated by immunotherapy (anti-cytotoxic T-lymphocyte-associated protein-4/anti-PD-1) should be considered for developing sarcoid-like granulomatous reaction that must not be confused with tumor progression.

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We report a case of sarcoid-like granulomatous reaction induced by nivolumab, a fully human IgG4 anti-programmed death 1 (PD-1) immune checkpoint inhibitor antibody, in a man with melanoma.

Case Report

A 57-year-old patient was diagnosed in 2011 with an invasive desmoplastic melanoma of the right nasolabial fold (Breslow thickness, 4.0 mm; Clark level, 5), for which he underwent wide local resection.

In May 2013, he developed an unresectable relapse involving on the right nasolabial fold. MRI showed a 27 × 43 mm necrotic tumor, expanding to the outer canthus, lower eyelid region, and lacrimal sac, with a deep

ABBREVIATIONS: CTLA = cytotoxic T-lymphocyte-associated protein; PD-1 = anti-programmed death 1; Th1 = T helper 1

AFFILIATIONS: From the Dermatology Department (Drs Danlos, Pagès, Baroudjian, Bagot, Lebbé; and Mr Jebali), Clinical Investigation Department (Drs Pagès, Baroudjian, Lebbé; and Mr Jebali), Nuclear Medicine Department (Dr Vercellino), Pathology Department (Dr Battistella), Plastic Surgery Department (Dr Mimoun), and Pneumology Department (Dr Tazi), Assistance Publique – Hôpitaux de Paris, Saint Louis Hospital, Paris, France; and Onco-Dermatology, Immunology and Cutaneous Stem Cells (Drs Bagot and Lebbé) and Biostatistics and Clinical Epidemiology research team (Dr Tazi), Université Paris Diderot, Sorbonne Paris Cité, Paris, France.

CORRESPONDENCE TO: François-Xavier Danlos, MD, Dermatology Department, Saint Louis Hospital, Assistance Publique – Hôpitaux de Paris, 1 avenue Claude Vellefaux, 75475 Paris Cedex 10, France; e-mail: danloscrh@gmail.com

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extension to the nasal cavity. Whole-body tomodensitometry and cerebral MRI did not show any distant metastases. No *BRAF*, *NRAS*, or *cKit* gene mutations were detected. The patient was enrolled in the CA209-066 randomized clinical trial (evaluating previously untreated patients with metastatic, unresectable, wild-type *BRAF* melanoma, to receive either nivolumab 3 mg/kg every 2 weeks, or dacarbazine). The first nivolumab infusion was administered on August 6, 2013. In June 2014, complete clinical and radiological tumor response was noted. However, whole-body CT showed supra-centimetric bilateral hilar and mediastinal lymph nodes, without pulmonary parenchymal involvement. PET showed hypermetabolism of the upper lip (maximum standardized uptake value, 5.3), appendectomy scars, and moderate hypermetabolism (maximum standardized uptake value, 2.5) of the bilateral hilar-mediastinal lymph nodes (Fig 1A). Biological examinations showed mild lymphopenia (1,430/mm^3), normal levels of angiotensin-converting enzyme, and normal serum protein electrophoresis (gamma-globulin 12 g/L). The biopsy sample of a subcutaneous nodule of the appendectomy scar revealed giant-cell epithelioid granulomas without necrosis, surrounded by few lymphocytes (Fig 1B). Some birefringent foreign bodies were seen under polarized light. Ziehl-Neelsen and periodic acid–Schiff stainings were negative.

Sarcoid-like granulomatous reaction was diagnosed, probably induced by nivolumab. The patient did not require steroids. He stopped his treatment in August 2014. In August 2015, the melanoma was still in complete remission, and granulomatous lesions had regressed on PET.

Discussion

To our knowledge, this is the first report of nivolumab-induced sarcoid-like granulomatous reaction. Nivolumab improves overall survival of patients with advanced melanoma in first-line treatment in *BRAF* wild-type melanoma patients.[1] Nivolumab is a fully human IgG4 anti-PD-1 immune checkpoint inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2, disrupting the negative signal that regulates T-cell activation and proliferation.

Sarcoidosis is a granulomatous disease of unknown etiology characterized by compartmentalization of CD4 T helper 1 (Th1) cells and activated monocyte/macrophages in the organs involved.[2] In 2009, Sève et al[3] described 20 patients with sarcoidosis associated with melanoma. Among them, six occurred after interferon treatment and one after ipilimumab, an antibody directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Since then, others cases of sarcoidosis and sarcoid-like granulomatous reaction occurring in patients treated with ipilimumab for melanoma have been reported (Table 1).[3-11] Among these case reports, no sarcoidosis was refractory to treatment, and 44.4% (4/9) of the patients required systemic steroids. The blockade of immune checkpoints in cancer immunotherapy turns ratio between cytotoxic

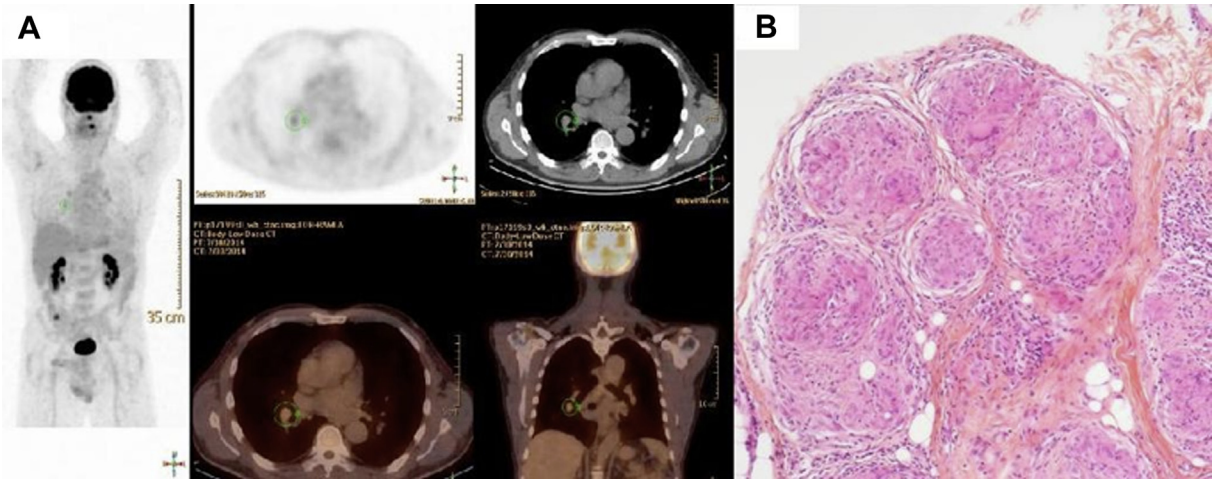

Figure 1 – *(A) PET scan showing a moderate hypermetabolism (maximum standardized uptake value, 2.5) of bilateral hilar-mediastinal lymph nodes. (B) Epithelioid granulomatous infiltrate in the form of rounded granulomas, small to medium in size, surrounded by a thin lymphocytic halo, with some giant cells without necrosis.*