Sarcoidosis complicating anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody biotherapy

To the Editor:

In August 2009, a 57-yr-old male smoker (30 pack-yrs) without medical history was diagnosed as having a melanoma of the left shoulder. A complete surgical excision was performed. The lesion was ulcerated. Breslow's thickness was 1.034 mm and Clark's level was III. As the axillary sentinel lymph node was positive for tumour cells, an additional lymphadenectomy was performed. The disease was finally staged at IIIb (pT2b N2a M0), in agreement with the American Joint Committee on Cancer Classification. In December 2009, the patient was included in a placebo-controlled trial to evaluate ipilimumab (a monoclonal antibody anti-cytotoxic T-lymphocyte-associated antigen (CTLA)-4 antibody), after complete resection of a high-risk stage III melanoma. Ipilimumab was administered by intravenously at 10 $mg \cdot kg^{-1}$, every 3 weeks for four doses (induction) followed by 10 $mg \cdot kg^{-1}$ every 12 weeks (maintenance). After two infusions of the maintenance phase, in July 2010, subcutaneous nodules appeared on his left arm and elbow. A concomitant computed tomography (CT) scan showed multiple micronodular, reticulonodular lesions of the lung and bilateral hilar lymph nodes. Positron emission tomography–CT showed an intense fluorodeoxyglucose binding of lung nodules and mediastinal lymph nodes (fig. 1). The skin lesions were biopsied and a pathological study revealed the presence of noncaseating granulomas. Bronchoalveolar lavage showed a mild lymphocytic alveolitis (11%, with a predominance of CD4+ T-cells). Bronchial biopsies were not informative. An additional mediastinoscopy was performed and pathological study demonstrated the presence of epithelioid and gigantocellular granulomas without caseating necrosis or microorganisms. A diagnosis of sarcoidosis was proposed. Pulmonary function tests, ECG and echocardiography were normal. The patient was asymptomatic and he decided to stop the ipilimumab trial. The patient was carefully followed up and 5 months after treatment discontinuation, the skin and nodular pulmonary lesions had disappeared, and the mediastinal lymph nodes had decreased in size.

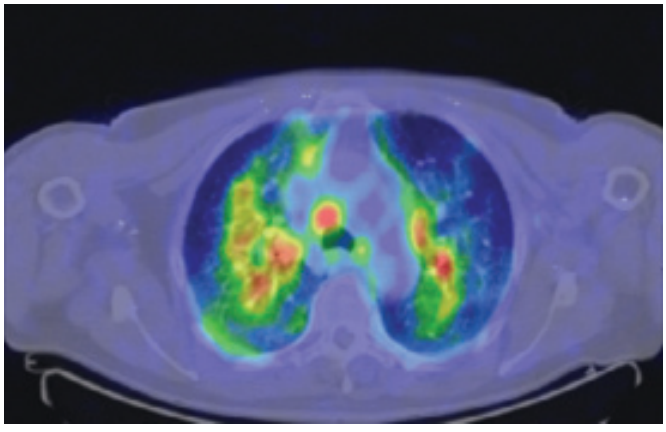

FIGURE 1. Positron emission tomography–computed tomgoraphy fusion image at thoracic level showing diffuse increased fluorodeoxyglucose uptake in the bilateral perihilar opacities and mediastinal lymph nodes.

Sarcoidosis is a multisystemic inflammatory disease of unknown origin that is characterised by the formation of diffuse noncaseating granulomas in affected organs, with a predominant involvement of the lung and mediastinum. The physiopathology of sarcoidosis remains unclear but it has been established that granulomas result from a predominately T-helper cell (Th) type 1 immune response mediated by a complex network of lymphocytes, macrophages and cytokines. In context, the introduction of the Th1 cytokine interferon (IFN), as antiviral therapy to treat chronic hepatitis C virus infection, has been shown to promote sarcoidosis development [1]. Numerous speculative hypotheses have been made implicating the presentation of an unknown antigen to a T-cell, leading to an infiltration of CD4+ activating T-cells of the T-cell type 1 paradigm (interleukin (IL)-2 and INF-γ) and responsible for T-cell expansion, macrophage activation and, finally, granuloma formation [2, 3].

Following ligand–receptor interactions, multiple signals are generated in the immune synapse between T-cells and antigen-presenting cells. The balance of activating and inhibitory signals is thought to be crucial in the physiopathology of sarcoidosis [4]. Cytotoxic T-lymphocyte associated antigen (CTLA)-4 is one of the modulatory receptors expressed on the surface of most activated T-cells. It shares homology with CD38 and members of the B7 family. Following interaction with B7 receptors on antigen-presenting cells, CTLA-4 down-regulates T-cell activation and is involved in self-antigen tolerance. CTLA-4 antagonises T-cell activation, interferes with cell-cycle regulation, and inhibits IL-2 production and IL-2 receptor expression [5].

Ipilimumab is a fully human monoclonal antibody that blocks CTLA-4 and so inhibits CTLA-4-dependent T-cell down-regulation. CTLA-4 blockade enhances the immune response against tumours and it has been shown that ipilimumab improved survival in patients with metastatic melanoma. The impact of anti-CTLA-4 monoclonal antibody in the adjuvant setting of high-risk stage III/IV melanoma patients is also under active investigation [6]. Overall, this explains why anti-CTLA-4 monoclonal antibodies such as ipilimumab represent a promising strategy to induce tumour regression or stabilisation and to prolong survival [5, 7].

However, this treatment is causative of immune-related adverse events (IRAEs). Enterocolitis, hypophysitis, dermatitis, uveitis, vitiligo, arthritis and hepatitis have been described, suggesting that immune tolerance is compromised [8, 9]. These IRAEs are thought to be mediated by the emergence of autoreactive T-cells, which are consecutive to the abolishment of the CTLA-4 immune brake on T-cell proliferation [8, 9]. Previous cases of anti-CTLA-4

monoclonal antibody-related sarcoidosis have been reported. In these cases, granuloma lesions were revealed during anti-CTLA-4 treatment [10, 11]. We have shown a similar pattern, with emergence and progression of the sarcoidosis lesions during biotherapy employment, followed by their disappearance following drug discontinuation. In sarcoidosis, as well as IRAEs, the absence of blockade of T-cell proliferation might be responsible for the granulomatous lesions and autoreactive T-cell development, respectively; these are the keystones of development for both diseases. Our description of a decrease in the size of the mediastinal lymph nodes and disappearance of both pulmonary and skin lesions of sarcoidosis after assay discontinuation add weight to the potential responsibility of anti-CTLA-4 treatment in the pathogenesis of granulomatous lesions.

This case report contributes to improving our knowledge of sarcoidosis, the physiopathology of which remains largely debated and misunderstood. Interestingly, an impact of the immune synapse has been suggested in sarcoidosis. Butyrophilin-like molecule (BTNL)2, a co-stimulatory molecule, has been described as a downregulator of T-cells [12]. Polymorphisms of BTNL2 have been shown to induce a dysfunction of this negative signal, capable of promoting T-cell activation and, finally, sarcoidosis development [13]. As announced by a recent editorial in the *European Respiratory Journal* [14], these aspects of immunopathogenesis will soon be discussed in a new series on sarcoidosis.

In the initial case report of sarcoidosis related to ipilimumab treatment [7], diagnosis was performed using bronchial biopsy. Our case report underlines how it may be much more difficult to diagnose pulmonary lesions and mediastinal lymph nodes in this context of ipilimumab treatment for melanoma. Both lesions mimicked either melanoma metastasis or lesions of sarcoidosis and a mediastinoscopy was required. Because CTLA-4 blockade appears to be a promising strategy for cancer immunotherapy, the occurrence of adverse effects, such as sarcoidosis, might be more frequent and have to be well-known by physicians.

In summary, our case report highlights that in the follow-up of melanoma patients treated with ipilimumab, physicians have to consider the hypothesis of biotherapy-induced sarcoidosis. Furthermore, this case report argues for the role of new pathophysiological mechanisms in sarcoidosis, involving additional co-stimulatory molecules of the immune synapse.

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