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LETTERS

Sarcoidosis in donor-derived tissues after haematopoietic stem cell transplantation

To the Editor:

This is the first case of sarcoidosis in donor-derived tissues, confirmed by fluorescence *in situ* hybridisation (FISH), after haematopoietic stem cell transplantation (HSCT).

A 64-year-old Japanese female was diagnosed to have adult T-cell leukaemia in December 2009. She had neither any past history nor a family history of sarcoidosis. She underwent HSCT (unrelated bone marrow transplantation) in May 2010, after receiving treatment with fludarabine, busulfan, and total body irradiation, from a human leukocyte antigen (HLA)-matched male donor who had no history of sarcoidosis. Although no lung involvement was seen in the early phase after HSCT, she was complicated by cytomegalovirus viraemia and acute graft *versus* host disease (GVHD), which required ganciclovir, systemic steroids and tacrolimus hydrate. She had achieved a negative proviral load of human T-cell lymphocytic virus (HTLV)-1 in her peripheral blood, 3 months after the transplant. At that time, the patient did not show any skin or eye symptoms or liver dysfunction, which are symptoms that are often seen in patients with chronic GVHD.

A subcutaneous mass developed on her left upper arm in September 2011 (16 months after the transplant), although the proviral load of HTLV-1 remained negative. Fluorodeoxyglucose positron emission tomography (FDG-PET) or computed tomography (CT) imaging showed FDG accumulations in the mediastinal and hilar lymphadenopathy, in addition to the mass lesion located on the left upper arm. Although there were no findings of uveitis, gallium-67 scintigraphy did show an increased uptake in the lacrimal glands. The patient was administered prophylactic therapy: 200 mg per day of itraconazole, 400 mg per day of aciclovir, and 320 mg/1600 mg per day (twice a week) of a combination of trimethoprim and sulfamethoxazole. Laboratory findings from routine haematology and biochemistry tests were normal, and the serum level of angiotensin converting enzyme concentration was also normal (22.6 $IU \cdot L^{-1}$, normal range: 7–25 $IU \cdot L^{-1}$), but the serum level of soluble interleukin-2 receptor was elevated (1814 $IU \cdot L^{-1}$, normal range: 145–519 $IU \cdot L^{-1}$). The findings of tuberculin testing were negative. A biopsy specimen obtained from the mass in her arm did not show any neoplasms, but non-caseating granulomas without any fungus or acid-fast bacilli were observed. Bronchoalveolar lavage fluid (BALF) showed a total cell count of 2.8×10^5 $cells \cdot mL^{-1}$, of which 86.4% were macrophages and 12.5% were lymphocytes, and the CD4/CD8 ratio was 4.3. There were neither any lymphocytes with nuclear atypia nor pathogenic microbes in the BALF. Both the biopsy specimens from the lung and the mediastinal lymph node showed non-caseating granulomas, similar to those seen in the mass found in her arm. Specific PCR products for HTLV-1 proviral DNA were not amplified from these biopsy samples. In addition, a FISH analysis with the DXZ1 and DYZ1 probes using the tissue of her mediastinal lymph node demonstrated the 100% presence of XY donor-derived cells. We diagnosed her to have systemic sarcoidosis which developed in donor-derived tissues, based on these clinico-radiological findings in addition to the evidence of non-caseating epithelioid cell granulomas in three organs [1, 2]. The patient has remained asymptomatic, and decreased mediastinal lymphadenopathy and the decreased mass in her left arm have been observed without any treatment for over a year.

The previous reports of nine patients with sarcoidosis after HSCT (table 1) show that in two patients who underwent allograft transplantations, both were received from a sibling with a diagnosis of sarcoidosis before the transplants (cases 1 and 2) [3, 4]. Three patients underwent autograft transplantation (cases 4–6) [5], and another three patients and the present case received stem cells from unrelated donors [6, 7]. None of

TABLE 1 Characteristics of the patients that developed sarcoidosis following haematopoietic stem cell transplantation (HSCT)

Characteristics	Case 1 [3]	Case 2 [4]	Case 3 [5]	Case 4 [5]	Case 5 [5]	Case 6 [5]	Case 7 [6]	Case 8 [6]	Case 9 [7]	Present case
Age years	34	36	51	50	47	48	45	51	55	64
Sex	Male	Female	Female	Female	Female	Female	Female	Male	Female	Female
Family history of sarcoidosis	With the donor	With the donor	None	None	None	None	None	None	None	None
Underlying disease	NHL	CML	CML	Breast cancer	Breast cancer	Breast cancer	MDS	MDS	FL	ATL
Type of HSCT	Allo, sibling	Allo, sibling	Allo	Auto	Auto	Auto	Allo, UD	Allo, UD	Allo, UD	Allo, UD
Post-HSCT period months	3	21	6	8	3	120	12	20	6	16
Chimerism analysis of lymph nodes	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	STR-PCR	FISH

NHL: non-Hodgkin's lymphoma; CML: chronic myeloid leukaemia; MDS: myelodysplastic syndrome; FL: follicular lymphoma; ATL: adult T-cell leukaemia; Allo: allogeneic; Auto: autologous; UD: unrelated-donor; STR-PCR: short tandem repeat based PCR; FISH: fluorescence *in situ* hybridisation.

the donors in cases 3–9 or the present case had been diagnosed to have sarcoidosis before undergoing transplantation [5–7]. The possibility of a transmissible agent was suggested for the development of sarcoidosis in the recipients in cases 1 and 2 [3, 4]. However, there have been only two cases of donor-derived sarcoidosis, which were confirmed by a chimerism analysis using their sarcoidosis lesions (case 9 [7] and the present case). The period from the HSCT in all of the reported cases, including the present case, was over 3 months (table 1). This means that these patients achieved successful marrow engraftment and thereafter developed sarcoidosis, thus, indicating that a responsive immune system is a prerequisite for the formation of sarcoid granulomas in recipients. The aetiology of sarcoidosis after HSCT may not be due to a transmissible agent from the donor alone. There is also the possibility of an abnormal immunological response caused by donor-derived cells. Therefore, a chromosomal analysis is needed to confirm whether sarcoidosis lesions in recipients contain donor-derived cells, especially in cases that received allografts from unrelated-donors.

Although there have been only nine reported cases of sarcoidosis after HSCT, BHAGAT *et al.* [5] estimated the prevalence of sarcoidosis to be approximately 150 cases per 100 000 HSCT recipients, and that was 10-fold higher than that in the normal population. In the present case and previously reported cases [3–7], the possibility of GVHD or a sarcoid reaction should be considered. Although chronic GVHD usually develops more than 3 months after transplantation, a series of findings suggestive of sarcoidosis in the present case appeared at 16 months after transplantation. At that time, her bone marrow was replaced with the new donor-derived marrow, the proviral load of HTLV-1 remained negative, and no skin, eye or liver complications were seen. In addition, the chronic pulmonary complications which occur as late phase GVHD after HSCT are usually bronchiolitis obliterans [8], but the lung biopsy specimen of the present case showed non-caseating granulomas that were consistent with sarcoidosis, but no findings of bronchiolitis obliterans. The FDG-PET or CT findings were also compatible with systemic sarcoidosis. The findings of the present case, with a complete remission of leukaemia, were also inconsistent with sarcoid reaction, which was hypothesised to be related to the presence of an underlying malignancy [9].

It is difficult to distinguish the recurrence of lymphoma from other diseases from sarcoidosis, by using CT or FDG-PET [10]. Therefore, a biopsy from the lesions of lymphadenopathy is important to confirm the pathological diagnosis and determine the course of treatment. Furthermore, whether the granuloma tissue of sarcoidosis after HSCT contains donor-derived cells or host cells should be determined by a chromosomal analysis.

This is the first report presenting a patient with donor-derived sarcoidosis, in which full donor chimerism of the recipient's lymph nodes was confirmed by FISH. Further evaluation of the pathogenesis, including a chromosomally based analysis, may be helpful to understand the mechanism of onset in patients with sarcoidosis following HSCT.

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