More immune dysregulation: Sarcoidosis and chronic graft-versus-host disease after allogeneic stem cell transplant

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Key words: allogeneic hematopoietic stem cell transplant; chronic graft-versus-host disease; cutaneous manifestations of systemic disease; cutaneous sarcoidosis; graft-versus-host-disease; granulomatous dermatitis; human leukocyte antigen; noncaseating granulomas; sarcoidosis.

INTRODUCTION

Approximately 25,000 allogeneic hematopoietic stem cell transplants (HSCTs) are performed annually. Cutaneous complications are common and include a spectrum of acute and chronic graft-versus-host disease (GVHD). Mechanisms implicated in the rare development of sarcoidosis after HSCT include specific pretransplant conditioning regimens, possible donor-to-recipient transmission, genetic predisposition of sarcoidosis, and post-HSCT immune dysregulation.

Abbreviations used:

GVHD: graft-versus-host disease
HLA: human leukocyte antigen
HSCTs: hematopoietic stem cell transplants

REPORT OF A CASE

A 58-year-old woman with a history of polymyalgia rheumatica, myelofibrosis (27 months postallogeneic HSCT from her human leukocyte antigen [HLA]-matched brother), hypothyroidism, GVHD of the gut, and noncaseating granulomas on lung biopsy, presented with the following new skin findings: white, firm lesions under her breasts (Fig 1) and an increasing number of asymptomatic red scaly bumps on her bilateral forearms and trunk (Fig 2). The lesions persisted despite use of triamcinolone 0.1% ointment. She denied family history of skin or lung disease. Her medications included omeprazole, vitamin D, calcium, duloxetine, levothyroxine, and alprazolam as needed. Importantly, she had not received any immunosuppressive therapy for almost 1 year.

Physical examination found bilateral inframammary white atrophic plaques and erythematous-to-

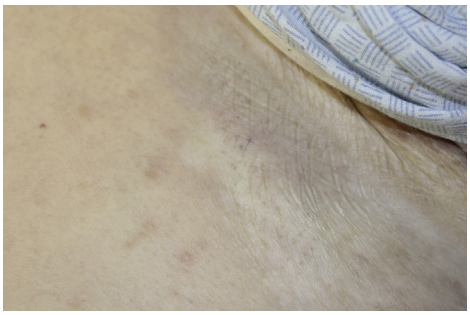

Fig 1. White firm atrophic plaques of the inframammary skin.

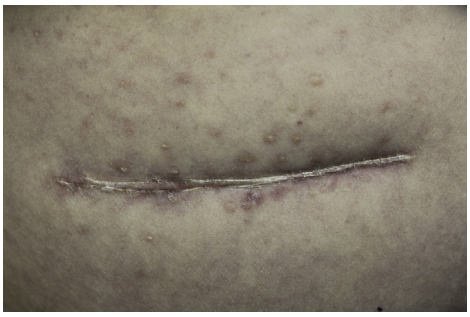

Fig 2. Erythematous-to-violaceous papules with minimal scale centered around an old, well-healed abdominal scar.

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Funding sources: None.
Conflicts of interest: None declared.
This work has been presented previously at the 60th Annual Georgia Society of Dermatology and Dermatologic Surgery Meeting, Amelia Island, Florida, June 5-7, 2015.
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JAAD Case Reports 2016;2:138-40.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2016.01.008

Table I. Characteristics of patients reported to have sarcoidosis after allogeneic HSCT

Study	Heyll[2]	Sundar[3]	Tauro[4]	Morita[5]	Bhagat[6]	Gooneratne[7]		Pukiat[8]	Kushima[9]	Current case
Age (y) & Sex	34 M	37 F	36 F	55 F	51 F	45 F	51 M	47 M	64 F	58 F
Type of HSCT, donor	Allo, sibling	Allo, sibling	Allo, sibling	Allo, UD	Allo	Allo, UD	Allo, UD	Allo, UD	Allo, UD	Allo, sibling
Family history of sarcoidosis	+Donor	+Donor	+Donor & +Patient	None	None	None	None	None	None	None
Donor diagnosed with sarcoid before or after the HSCT? (at the time of case publication)	Yes, before the HSCT	Yes after the HSCT (Lymph node biopsies with noncaseating granulomas)	Yes, before the HSCT (sarcoidosis of the liver)	Unknown	Unknown	No	No	No	Unknown	No signs or symptoms of sarcoidosis to date (31 months posttransplant)
Underlying disease	NHL	B cell lymphoma	CML	FL	CML	MDS	MDS	CMML	ATL	MF
HLA	A1, A2, B8, B51, DR4, DR4	A(1,26), B(8,49), Cw(7,-), DRb1*03011, DRb1*1302	A-24(9), B-8 52(5), C-7 16; DR-17(3) 18(3) DQ-2 4 DP-	Donor had one locus mismatch HLA phenotype & genotype (DRB1 locus)	Unknown	Unknown	Unknown	A*0101, A*2501, B*0801, B*1801, DRB1*0301, DRB1*1501, DQB1*0201, DQB1*0602	Unknown	A*0301, B*0702, B*5501, C*0702, C*0304, DRB1* 1301, DRB1* 1501, DQB1*0602
Post-HSCT period (mo)	3	18	21	6	6	12	20	22	16	27
Organs confirmed to have non-caseating granulomatous changes on biopsy	Lung & liver	Lung, (skin biopsy not done)	Bone marrow	Mediastinal lymph nodes, pleura, and a piece of lung	Lung	Liver, Skin: non-caseating granulomas	Liver	Lymph nodes, Skin: poorly defined granulomatous inflammation in the deep dermis	Lung, mediastinal lymph nodes, Subcutaneous mass in left upper arm: noncaseating granulomas	Lung, skin: noncaseating granulomas
Clinically evident cutaneous lesions reported	No	Petechial rash owing to chronic GVHD over lower extremities; skin bx not done	No	No	No	Purple-brown firm skin lesions on limbs, upper back, right cheek	No	Papular rash (cutaneous chronic GVHD), indurated erythematous plaque (granulomatous)	Subcutaneous mass in left upper arm	Red papules with minimal scale on forearms and trunk; White firm atrophic patches inferior to bilateral breasts

Allo, Allogeneic; *ATL*, adult T-cell leukemia; *CML*, chronic myeloid leukemia; *CMML*, chronic myelomonocytic leukemia; *FL*, follicular lymphoma; MDS, myelodysplastic syndrome; *MF*, myelofibrosis; *NHL*, non-Hodgkin's lymphoma; *UD*, unrelated donor.

violaceous guttatelike papules with minimal scale on her bilateral dorsal forearms and lower back. The papules were also becoming confluent around an old scar on her abdomen. Biopsy of an inframammary atrophic plaque found epidermal thinning and atrophy, papillary dermal hyalinization and sclerosis, telangiectasias, and sparse interstitial lymphocytic infiltrate. Biopsies of the abdominal scar and forearm found numerous epithelioid histiocytes and multinucleated giant cells forming noncaseating granulomas without polarizable material; special stains were negative for organisms.

She received a diagnosis of cutaneous chronic GVHD, manifested as lichen sclerosus, and cutaneous and pulmonary sarcoidosis. Thirty-one months after transplantation, her donor HLA-matched brother did not have any signs or symptoms of sarcoidosis.

DISCUSSION

In 2014, the National Institutes of Health proposed updated diagnostic requirements for chronic GVHD, none of which include granulomatous phenomenon.[1] Thorough literature review found 9 cases of sarcoidosis after allogeneic HSCT, all reported in nondermatologic literature (Table I).[2-9] Five of the 9 cases describe cutaneous findings, 4 of which had cutaneous biopsies showing noncaseating granulomas. An additional 5 cases of sarcoidosis have been reported after autologous HSCT.[10]

Immune dysregulation, both donor derived and de novo, after allogeneic HSCT is postulated to provide the immunologic environment necessary for the development of sarcoidosis. Additionally, 2 reported cases have confirmed donor-derived sarcoidosis with chimerism analysis of sarcoidal lesions.[5,9] Genetic predisposition to sarcoidosis is well established and frequently associated with HLA types A1, B8, and DR3. Acute disease with good prognosis is associated with HLA types DRB1*0301 and DQB1*0201, whereas prolonged disease course with poor prognosis is associated with DRB1*1501 and DRB1*0602.[11] Our patient and her healthy donor possess these 2 poor-prognostic HLA types. One of the donors in the 9 previously reported cases had sarcoidosis after the marrow donation, whereas 2 of the 9 had sarcoidosis diagnosed before the donation. Based on these findings, our patient's donor may be at an increased risk for sarcoidosis.

Immune dysregulation after HSCT is well known to manifest as a variety of forms of GVHD. Because sarcoidosis is also attributed to immune dysregulation, it is not surprising that this common granulomatous dermatitis may be seen with increased frequency after HSCT. Our case shows the simultaneous presentation of chronic GVHD in the form of lichen sclerosus and new-onset sarcoidosis after HSCT. Dermatologists should add sarcoidosis to the list of possible posttransplant cutaneous eruptions, especially in patients with susceptible HLA types. Further research including analysis of specific HLA types, information always available in the transplant population, may lead to a better understanding of the risk factors and pathogenesis of this granulomatous conundrum.

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