Cutaneous Hodgkin's disease

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Cutaneous Hodgkin's disease is a rare condition that usually occurs late in the course of Hodgkin's lymphoma. This rare condition is thought to have decreased in incidence in recent decades, likely owing to improved treatment of patients with Hodgkin's disease, who are receiving improved chemotherapy and radiation therapy, and the advent of peripheral blood stem cell transplantation. We present the case of a man who developed specific cutaneous Hodgkin's lymphoma 6 months after nonmyeloablative allogenic stem cell transplantation for his recurrent systemic disease. The patient's manifestation of relapse was cutaneous dissemination of the tumor, manifested by erythematous papules and ulcerated nodules. At the time of the cutaneous relapse he had minimal systemic disease. This case illustrates an example of this complication of Hodgkin's disease and stresses the importance of a timely diagnosis to direct appropriate therapy. A review of the literature demonstrates that the patient's lesion morphology and distribution are typical of specific manifestations of cutaneous Hodgkin's disease. (J Am Acad Dermatol 2008;58:295-8.)

CASE REPORT

A 39-year-old man with a history of relapsing nodular sclerosing Hodgkin's disease presented in October 2004 with a new erythematous, nodular rash over his chest 6 months after an allogenic stem cell transplantation.

In 2001, the patient presented for the first time with stage IIA (Ann Arbor classification) nodular sclerosing Hodgkin's disease. After initiation and consolidation chemotherapy and radiation, the patient had an autologous stem cell transplantation in January 2003, but relapsed 8 months later with widespread lymphadenopathy. In April 2004, the patient underwent a nonmyeloablative conditioned allogenic HLA identical matched unrelated stem cell transplantation with resolution of all of his mediastinal and cervical lymphadenopathy.

In August 2004, approximately 4.5 months after the transplantation, the patient presented with a 5- × 6-cm asymptomatic, indurated, erythematous plaque on the right portion of the upper aspect of his chest. The patient refused cutaneous biopsy at that time. A chest radiograph at that time was normal, and the induration resolved during the next 4 weeks without intervention. In October 2004, the patient presented with a new skin symptom: multiple, firm, fixed, asymptomatic and erythematous nodules coalescing around his xiphoid process and radiating across his right and left chest to the midclavicular line, with a central area of ulceration (Fig 1). Each individual nodule was firm, nonmobile, and not painful or tender. The patient denied other skin or mucosal lesions, fevers, chills, weight loss, chest pain, shortness of breath, arthralgias or arthritis, abdominal pain, nausea, vomiting, or diarrhea. His medications at that time included a taper of cyclosporine, trimethoprim/sulfamethoxazole, acyclovir, magnesium, and voriconazole. Other than Hodgkin's disease, the patient had no significant medical or surgical history. At the time of this presentation, his physical examination was unremarkable other than his cutaneous lesions. His white blood cell, hemoglobin, and platelet counts were within normal limits. The most recent engraftment assays from August 2004 showed mixed donor chimerism after successful allogeneic stem cell transplantation with 53% donor hematopoesis.

A punch biopsy specimen from a representative nodule showed a nearly pandermal interstital, perivascular, and adnexal infiltrate of markedly atypical and pleomorphic lymphocytes with minimal involvement of the subcutaneous tissue (Fig 2). The lymphocytes were large with vesicular nuclei and prominent nucleoli. Reed-Sternberg cells were identified, and aggregates of eosinophils were present. Immunohistochemical stains demonstrated that the atypical cells were positive for CD30 and Leu 15

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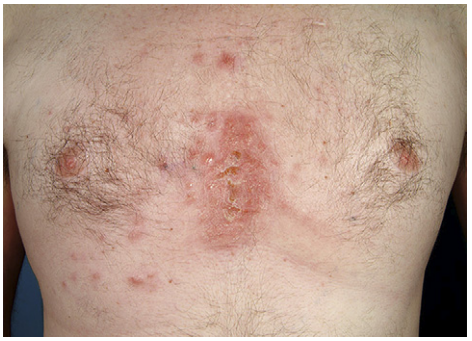

Fig 1. Photograph of patient's chest showing multiple discrete erythematous papules and nodules with central area of coalescing nodules with central ulceration. Lesions developed after several weeks of slightly erythematous induration over right chest.

(Fig 2) and negative for epithelial membrane antigen, CD20, and CD3, consistent with cutaneous Hodgkin's disease. The lesions did not respond to localized radiation therapy, and, at the time of manuscript preparation, the patient was undergoing therapy with donor lymphocyte infusions in an attempt to stimulate a graft-versus-Hodgkin's disease reaction.[1]

DISCUSSION

First described by the German physician Grosz in 1906, specific cutaneous Hodgkin's disease occurs when the malignant cells, now identified by immunohistochemical techniques, invade areas of the skin.[2] There have been 5 major studies of patients with Hodgkin's disease looking at the incidence of specific cutaneous Hodgkin's disease during the past century (Table I). Between the 1940s and 1990s, the incidence of cutaneous Hodgkin's disease was estimated to be between 0.5% and 3.4%; fewer cases than that were seen in the early part of the 20th century.[2-5] This decrease in incidence is thought to be caused in part by improved therapy, particularly the use of stem cell transplantation, leading to decreased mortality of patients with Hodgkin's disease.[2,6] The patient described here is unique in that he is, to our knowledge, the only patient presenting with cutaneous Hodgkin's disease after autologous or allogeneic stem cell transplantation for systemic Hodgkin's lymphoma.

When specific cutaneous disease does develop, it tends to be in the setting of advanced disease and is a poor prognostic sign (Table I).[2,3] Our patient had minimal disease on the basis of disappearance of the lymphadenopathy and the minimal activity seen on positron emission tomography scanning. If his skin disease had not been recognized as specific cutaneous Hodgkin's lymphoma, he would have been

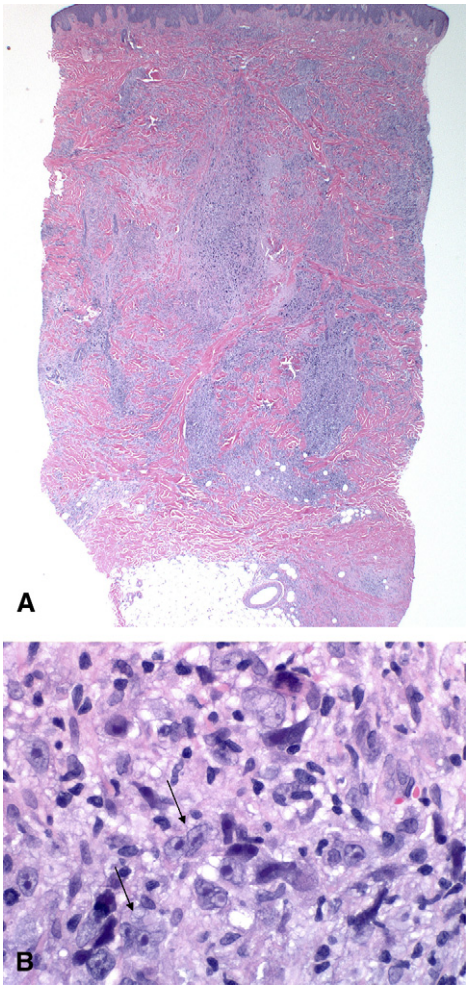

Fig 2. Cutaneous Hodgkin's disease. Punch biopsy specimen from chest. **A**, There is nearly pandermal atypical lymphocytic infiltrate in dermis, which spares epidermis. **B**, High-power view demonstrating markedly atypical lymphocytes with anaplastic morphology. There are cells with binucleate morphology and prominent nucleoli, similar to Reed-Sternberg cells (*arrows*). (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×1.25; **B**, ×40.)

considered to be responding to treatment, when in reality he had progressing, stage IV disease.

The clinical descriptions of specific cutaneous Hodgkin's disease have been remarkably similar across case reports and time, a fact that can assist a physician in making this important diagnosis (Table I). The typical clinical picture of painless, erythematous papules and nodules that frequently become ulcerated was termed the "Grosz-Hirschfeld" type after the physicians who first described it in the early 20th century.[2-5,7-11]

Although specific cutaneous Hodgkin's disease tends to present with distinct lesions, it still must be

Table I. Summary of 5 previous studies of specific cutaneous Hodgkin's disease, including incidence, common lesion morphology, and mortality at 24-month postcutaneous diagnosis

Time period	Location	Incidence	Common lesion morphology	Patients dying within 24 mo of cutaneous disease diagnosis	Reference
1906-1959	United States	NR*	"Multiple nodular and nodulo-ulcerative lesions"	NR	5
1936-1968	United States	10/134 (7.5%)	"Up to 10 ulcerating nodules and swelling"	NR	11
1944-1977	United States	9/1810 (0.5%)	"Reddish papules and nodules . . . becoming ulcerated"	8/9	2
1951-1980	United States	16/465 (3.4%)	"Erythematous papules and nodules that often ulcerated"	12/16	3
1969-1990	Spain	3/349 (0.85%)	"Papules or nodules, . . . ulcerated areas or combinations"	1/3	4

NR, Not reported.
*Forty-five pages of case reports were collected, almost all representing patients presenting before 1940, but the total number of examined patients is not reported.

histologically and immunohistochemically distinguished from infection, graft-versus-host disease, the nonspecific skin conditions that accompany Hodgkin's lymphoma, and other lymphoid proliferations, particularly mycosis fungoides,[12] lymphomatoid papulosis, anaplastic large cell lymphoma, and granulomatous slack skin disease, all of which can be associated with systemic lymphoma. In addition, nonspecific cutaneous manifestations of Hodgkin's disease are common, with between 3% and 50% of patients with Hodgkin's disease experiencing one or more of the following: Addison-like areas of hyperpigmentation, pruritis and associated prurigo, acquired ichthyosis, herpes zoster, and alopecia distinct from that often caused by chemotherapy.[2,7,8] In 1995, Cerroni et al[10] summarized the immunohistochemical features of cutaneous Hodgkin's disease on the basis of 7 patients and concluded that immunohistochemical analysis is helpful for diagnosis and that, in most cases, these aspects are consistent with that of the involved lymph nodes.

Three mechanisms have been proposed to explain the spread of disease from systemic Hodgkin's disease to the skin: hematogenous dissemination, direct extension from involved lymph nodes, and retrograde lymphatogenous spread from proximal involved lymph nodes.[2-5,7-14] The most frequent mode of spread seems to be retrograde from affected nodes, because most of the reported cases occur over areas of skin drained by affected lymph nodes, such as chest and axilla, and pathology does not usually demonstrate direct extension from an adjacent node.[2,3-5] This mode was also likely the case in our patient; his mediastinal nodes were known to have been involved with his lymphoma at one time, and his lesions appeared on his chest.

Although specific cutaneous Hodgkin's disease is unusual in this era of advanced treatment, it still can occur, even in patients who received high-dose therapy and stem cell transplantation, and who have little systemic disease. Discovering cutaneous Hodgkin's disease may result in therapeutic intervention for a patient who otherwise would not receive it, or it may signal the need for more aggressive therapy in a patient with established systemic disease currently undergoing treatment. Pathologic diagnosis using immunohistochemistry often is necessary for diagnosis of cutaneous conditions in patients with Hodgkin's disease.

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