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Graft-vs-host disease

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Case Presentation

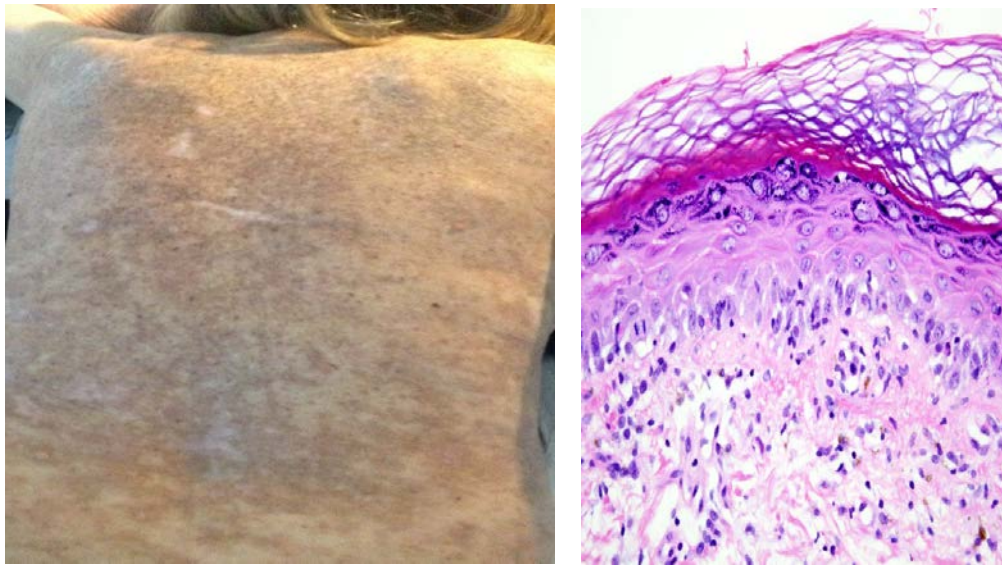
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Abstract

We present a case of chronic graft-versus-host disease in a 61-year-old woman with a history of B-cell chronic lymphocytic leukemia that was treated with an allogeneic bone marrow transplant from an unrelated donor. The patient initially presented with erythematous patches on the trunk and extremities that evolved into reticulated, hyperpigmented patches and lichenified plaques.



History: A 61-year-old woman presented to New York University Dermatologic Associates in November, 2010, for evaluation of a two-week history of a diffuse, erythematous, non-pruritic, macular eruption on her trunk, and arm. She experienced flu-like symptoms, intermittent mild diarrhea, and intra-oral ulcerations as well as chronically dry, irritated eyes. She was initially treated with fluocinonide ointment twice daily. Over the next several months the eruption evolved into reticulated, hyperpigmented patches overlying her trunk, arms, and legs.

Ten years prior to presentation a diagnosis of a B-cell chronic lymphocytic leukemia had been made and she had been treated with multiple chemotherapeutic agents, which included fludarabine, rituximab, and bendamustine. She also had a splenectomy. The patient ultimately received an allogeneic bone marrow transplant from an unrelated donor eighteen months prior to presentation.

Physical Examination: Reticulated, hyperpigmented patches and lichenified plaques were distributed symmetrically on both the anterior and posterior aspects of the trunk, arms, and legs. Hair density on the scalp was diffusely decreased. The oral mucosa showed no ulcers.

Laboratory Data: A complete blood count showed a white-cell count of $15.5 \times 10^9/L$, hemoglobin 10.8 g/dL, and a platelet count of $209 \times 10^9/L$. A basic metabolic panel was normal. Liver function tests showed an elevated alkaline phosphatase of 190 U/L, elevated total bilirubin at 3.0mg/dL, and elevated direct bilirubin of 1.4mg/dL. Alanine aminotransferase and aspartate aminotransferase levels were normal.

Histopathology: There is a superficial, perivascular infiltrate that is comprised of lymphocytes and melanophages. Lymphocytes extend to the overlying dermoepidermal junction where there are vacuolar changes with necrotic keratinocytes and slight regenerative atypia. There is mild hypergranulosis and early orthokeratosis.

Diagnosis: Chronic graft-versus-host disease, non-sclerotic variant

Discussion: Graft-versus-host disease (GVHD) is a multisystem disorder that results when mature T-cells from a donor organ recognize host antigens as foreign and precipitate immune-mediated tissue damage. GVHD is the most common cause of non-relapse related mortality after allogeneic hematopoietic cell transplantation (HCT) [1]. Although the gastrointestinal tract, liver, lungs, and lymphoid tissue may be affected, the skin is the most commonly affected organ in GVHD, which makes dermatologists essential in the recognition and treatment of the disease [2].

GVHD has traditionally been divided into acute and chronic categories based on the time of onset after the transplant. Acute GVHD was formerly defined by its onset within the first 100 days after the transplant, with chronic GVHD occurring after the first 100 days. However, the artificial nature of the 100-day benchmark has become increasingly recognized and a comprehensive effort to standardize clinical and pathologic criteria for GVHD recently resulted in a reclassification of GVHD [3]. Using the newer criteria, late acute GVHD is defined by acute features of GVHD that manifest after 100 days after the transplant; this category is then further subdivided into persistent late acute GVHD, which represents the continuation of previously-diagnosed acute GVHD past the 100-day mark, and late-onset acute GVHD, which represents disease that manifests after the withdrawal of immunosuppressants.

Chronic GVHD typically manifests after 100 days after the transplant and is defined by characteristic clinical features. Chronic GVHD is usually not preceded by acute GVHD although preceding acute GVHD confers an increased risk of developing the chronic form of the disease [4]. Other risk factors for chronic GVHD include older age, a history of chronic myelogenous leukemia, higher degree of human leukocyte antigen (HLA) mismatch between donor and recipient, a history of splenectomy, and cytomegalovirus seropositivity in either the donor or recipient [5].

Approximately 60 to 70% of patients who have received an allogeneic HCT will eventually develop chronic GVHD [6]. At the time of initial presentation, the skin is the most commonly involved organ in chronic GVHD, followed by the oral mucosa, liver, and eye [7]. Cutaneous manifestations of chronic GVHD are polymorphous and include sclerotic and non-sclerotic presentations [2]. Sclerotic chronic GVHD can be very debilitating and difficult to treat. This form of the disease may manifest as hypopigmented, guttate papules and plaques that resemble lichen sclerosus [8] or as indurated plaques that resemble morphea. Sclerosis overlying joints may impair range of motion and lead to joint contractures. Sclerosis of subcutaneous tissues also can result in a rippled appearance of the overlying epidermis as well as the groove sign between fascial bundles; both features usually are associated with eosinophilic fasciitis [8,9]. Additional manifestations of sclerotic GVHD include edema of the affected limbs, weakness, and painful cramps [10].

Cutaneous findings in non-sclerotic chronic GVHD include xerosis, perifollicular erythema, or papules that resemble keratosis pilaris. In addition, purple or hyperpigmented papules that resemble lichen planus, scaly patches and plaques that resemble eczematous dermatitis or psoriasis, dyspigmentation that resembles vitiligo, and poikiloderma are typical manifestations [2]. Scarring and non-scarring alopecia may develop and may be difficult to distinguish from drug-induced alopecia and persistent hair loss after the recovery from chemotherapy.

Mucosal chronic GVHD may lead to dry xerostomia and dental caries, Wickham's striae and erosions that resemble lichen planus, gingivitis, mucocelles, and formation of pseudo-membranes [2]. Patients also may complain of intermittent oral ulcers that are non-infectious in etiology. Genital involvement may lead to fibrosis and scars and may impair sexual function.

Histopathologic findings in chronic GVHD reflect the protean nature of its clinical presentation. Biopsy specimens may resemble acute GVHD with the findings of keratinocyte necrosis, basal layer vacuolar degeneration, and a lymphohistiocytic infiltrate in the upper dermis [11]. Sclerotic chronic GVHD may or may not exhibit these epidermal features in addition to fibrosis of the underlying dermis, subcutaneous tissue, and fascia. Panniculitis with thickening of subcutaneous fat septae may be observed.

Owing to its polymorphous nature, the differential diagnosis of chronic GVHD is broad and includes lichenoid drug eruptions, lichen sclerosis, autoimmune connective tissue diseases, such as morphea and systemic sclerosis, and papulosquamous disorders, such as psoriasis. When in doubt, histopathologic confirmation of the diagnosis is of paramount importance. Patients diagnosed with chronic GVHD must be monitored for the systemic manifestations, which include esophageal webs and strictures, bronchiolitis obliterans, and, more rarely, cardiac, renal, and other organ system disease [3].

The pathogenesis of GVHD is complex and only partially understood. Although alloreactive donor T-cells are thought to be central to the development of chronic GVHD as well as acute GVHD, the process by which these T-cells and other immune mediators lead to the clinical findings observed in chronic GVHD has yet to be fully elucidated [12]. A central role for B-cells also has been suggested [13] since many of the presentations of chronic GVHD resemble autoimmune disease. This role has been supported by evidence that the use of rituximab, which is a monoclonal anti-CD20 antibody, has resulted in complete clearance of chronic GVHD in some patients [14]. Other studies have found that circulating levels of B-cell activating factor (BAFF), which is a marker of B-cell activation, remain persistently high in patients with chronic GVHD [15,16]. Patients with chronic GVHD often have multiple autoantibodies that include antinuclear and anti-dsDNA antibodies, although these antibodies have not been demonstrated to correspond to specific disease manifestations [17,18].

The treatment of chronic GVHD is challenging. First-line topical therapies include mid- to high-potency glucocorticoids and calcineurin inhibitors. For chronic GVHD limited to the skin, phototherapy with psoralen plus ultraviolet A (PUVA) photochemotherapy, ultraviolet B phototherapy, and ultraviolet A-1 phototherapy have shown efficacy in small series. However, the potential for increased skin malignant conditions related to the frequency of concurrent immunosuppressive therapy must be considered [19]. Many patients with GVHD also may be taking photosensitizing medications. For instance, voriconazole, which is a drug that commonly is used as prophylaxis against fungal infections in HCT recipients, is associated with phototoxicity and can predispose patients to cutaneous malignant conditions [20]. All patients with chronic GVHD should receive regular screening examinations for skin cancer.

First-line systemic therapy for chronic GVHD consists of systemic glucocorticoids, with or without oral tacrolimus or cyclosporine [21]. However, 50% of patients do not respond to glucocorticoid therapy. For steroid-refractory patients, no standard treatment regimen has demonstrated definitive superiority over others. Treatment options that have shown efficacy in small case series include imatinib mesylate [22,23], rituximab [14], and most recently, the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus [24]. Extracorporeal photopheresis, which is a process of leukopheresis followed by *ex vivo* photoactivation with psoralen plus UVA photochemotherapy, has shown particular promise, with one study reporting a positive response in 59% of patients treated [25,26]. All systemic treatments for chronic GVHD require close collaboration with the patient's oncologist and an understanding of the complex multi-organ involvement the disease entails.

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