

CLINICAL CHALLENGES

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Chronic Graft-Versus-Host Disease

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Case Study

Mr. F is a 62-year-old Caucasian man who was diagnosed with acute myelogenous leukemia (AML) 15 months prior. Following two cycles of induction chemotherapy, his AML was in remission. Four months ago, after a reduced-intensity conditioning regimen, Mr. F received an allogeneic peripheral blood stem cell transplant from his human leukocyte antigen-identical 56-year-old sister. Mr. F received a regimen of the calcineurin inhibitor tacrolimus and antimetabolite methotrexate for graft-versus-host disease (GVHD) prophylaxis. Mr. F was diagnosed with biopsy-proven stage 1 acute GVHD of the skin on his arms and the palms of his hands 43 days following his transplant. At the time, he was receiving tacrolimus 8 mg per day for GVHD prophylaxis, and that was continued. In addition, the GVHD was treated with topical steroid cream and resolved promptly. Mr. F had no other signs of acute GVHD.

Mr. F arrives at the blood and marrow transplantation (BMT) outpatient clinic for a routine follow-up visit. He complains of pain and dryness in the mouth, with occasional bleeding after brushing his teeth, and skin redness and irritation on his arms. He states that he has an increased visual sensitivity to sunlight with frequent feelings of dryness and irritation in his eyes. Mr. F denies nausea, vomiting, and diarrhea but has lost eight pounds since his last visit to the clinic one month prior. He reports pain in his wrists and elbows that slightly limits his movements and interferes with his daily strength-training regimen. He is being tapered off of his immunosuppressive prophylaxis and currently is taking tacrolimus 2 mg per day.

Physical examination reveals small, patchy, firm, erythematous maculopapular eruptions on his neck, shoulders, and arms, with dry desquamation and mild pigmentation changes. Mr. F states that he has a pain level of 2 (on a scale of 1–10) in the skin on his arms. Evaluation of his oral cavity reveals ulcers in the oral mucosa and inflammation of the gums.

Mr. F's temperature is 97.9°F, blood pressure is 145/95 mmHg, pulse is 80 beats per minute, and respirations are 18 breaths per minute. His oxygen saturation, measured by pulse oximeter at rest, is 98%. He has a white blood cell count of 3.5 K/UL with 42% neutrophils, 40% lymphocytes, and 12% eosinophils. His hemoglobin is 11.1 G/dl, hematocrit is 31%, and his platelet count is 85,000 K/UL. Serum liver function tests show a total bilirubin of 0.9 mg/dl, alanine aminotransferase of 17 IU/L, aspartate aminotransferase of 21 IU/L, and alkaline phosphatase of 94 IU/L. The advanced nurse practitioner who initially evaluates Mr. F suspects that he has developed chronic GVHD.

Clinical Problem Solving

What is chronic GVHD?

Chronic GVHD is an autoimmune-like reaction, occurring months to years following allogeneic BMT, that damages tissues and organs and causes pronounced immunodeficiency. It can affect almost any organ of the body, but common sites are the skin, liver, mouth, and eyes (Bhushan & Collins, 2003). Chronic GVHD also is associated with constitutional symptoms of fatigue, weight loss, and muscle wasting. Approximately 38%–77% of patients receiving allogeneic BMTs are reported to develop chronic GVHD, depending on patient, donor, and cell product characteristics (Akpek, 2002). The effects of chronic GVHD can be extremely debilitating and devastating to patients who often have been cured of underlying malignancies.

What are the risk factors for the development of chronic GVHD?

Risk factors that are consistently associated with the development of chronic GVHD include patient factors of older age, a diagnosis of chronic myeloid leukemia or aplastic anemia, and a history of acute GVHD (Bhushan & Collins, 2003; Lee, Vogelsang, & Flowers, 2003; Socie, 2004). Donor factors consistently associated with the development of chronic GVHD include

a female donor for a male patient and a mismatched or unrelated donor (Bhushan & Collins; Lee et al.). Cell product characteristics consistently associated with chronic GVHD include a cell source of peripheral blood stem cells versus bone marrow (Cutler et al., 2001) and a cell product that is not T-cell depleted (Bhushan & Collins; Cutler et al.; Lee et al.; Socie). In addition, use of donor lymphocyte infusions following BMT is associated consistently with the development of chronic GVHD (Lee et al.; Socie). Risk factors that are more controversial or less established include patients who are seropositive for cytomegalovirus (CMV) or have a reactivation of CMV infection, patients who have had a splenectomy, ethnic disparity between donors and patients, use of corticosteroids or not using methotrexate for acute GVHD prophylaxis, and a high number of CD34+ cells in the cell product (Bhushan & Collins; Lee et al.; Socie). Mr. F's risk factors for the development of chronic GVHD included his age and receiving a BMT from a female donor. His most significant risk factor was a prior episode of acute GVHD (Bhushan & Collins; Cutler et al.; Socie).

What treatments might be prescribed for Mr. F to treat his chronic GVHD, and what would be the expected side effects?

Mr. F's current dosage of tacrolimus 2 mg per day most likely would be increased, and his physician also may prescribe a topical corticosteroid to treat the skin and oral manifestations (Bhushan & Collins, 2003). The side effects of tacrolimus include tremor, headache, nausea, constipation, nausea, vomiting, renal

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dysfunction, and leukopenia (Karch, 2005). Topical steroids may be used without systemic steroids for mild chronic GVHD of the skin, and they have few side effects. A lower dose of topical steroids must be used on facial skin to avoid thinning. Lee et al. (2003) recommended that patients receiving topical steroids for oral chronic GVHD be given topical antifungal therapy to prevent oral candidiasis.

What symptoms should Mr. F be instructed to report that would indicate progression of his chronic GVHD?

Mr. F should be instructed to report worsening of any of his current symptoms. Continued and more extensive irritation, redness, or desquamation of the skin, oral mucous membranes, and eyes; ongoing weight loss; hemotypsis; and progressive worsening or loss of movement in his extremities all would indicate progression of his chronic GVHD and must be addressed promptly (Bhushan & Collins, 2003; Cutler et al., 2001; Socie, 2004). In

addition, Mr. F should be instructed to report the development of new symptoms such as mild shortness of breath with exertion, nausea, vomiting, dysphagia, indigestion, diarrhea, yellowing of his sclera or skin, fever, easy bruising or bleeding, stiffness of his joints, or muscle pains. Any of those symptoms could indicate involvement of other organ systems (Higman & Vogelsang, 2004; Stewart et al., 2004). See Figure 1 for a list of symptoms according to organ system.

If Mr. F's chronic GVHD progresses, what other treatments might be used, and what would be the expected side effects?

Progression of the disease necessitates institution of additional immunosuppressive medications, such as systemic corticosteroids. Systemic corticosteroids have numerous side effects, including difficulty sleeping, increased appetite, gastrointestinal bleeding, glucose intolerance, fluid retention, risk of opportunistic infections, muscle weakness,

bone loss, cataracts, rounding of the face, and psychological effects such as psychosis (Lee et al., 2003). If Mr. F is started on systemic steroids, he and his caregiver will need education about the side effects, how to monitor for them, and ways to prevent further complications.

What may be the long-term consequences of chronic GVHD?

Fifty percent of patients with chronic GVHD have limited disease and a good prognosis. Of those with more extensive disease processes, 60% will respond to treatment and eventually be weaned off immunosuppressive therapy. Unfortunately, the remainder will either die from opportunistic infections or need prolonged immunosuppressive therapy (Bhushan & Collins, 2003).

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Skin

The most common findings of chronic graft-versus-host disease (GVHD) of the skin are sclerodermatous and lichenoid changes. The skin may start out with redness, plaques, and desquamation, which can lead to hypo- or hyperpigmentation, tightening, atrophy, or telangiectasia. The manifestations can occur diffusely throughout the skin or be limited to certain areas. Damage or loss of nails and skin ulcerations also can occur. Premature graying of the hair, including the eyelashes and eyebrows, may occur, even in children (Vogelsang, 2004).

Liver

Physical manifestations of chronic GVHD of the liver usually are not apparent until advanced stages. Consequently, liver dysfunction frequently is assessed through blood hepatic enzyme levels, which can show moderate elevation in bilirubin, alkaline phosphatase, or transaminases. The laboratory findings also can mimic acute viral hepatitis or drug toxicity; therefore, a biopsy is used as the definitive method of confirmation of chronic GVHD of the liver (Vogelsang, 2004). Portal hypertension, cirrhosis, and hepatic failure are rare (Horwitz & Sullivan, 2006).

Gastrointestinal System

The most common gastrointestinal symptoms of chronic GVHD are malabsorption, nausea, vomiting, cramping, diarrhea, dysphagia, early satiety, and esophagitis. Chronic GVHD results in desquamation and web formation in the inner lining of the digestive tract, and fibrosis and strictures may develop (Vogelsang, 2004). The esophagus is the area most often affected, with intestinal involvement being rare (Horwitz & Sullivan, 2006). Weight loss is common and is attributed to decreased intake and poor absorption (Vogelsang).

Lungs

Respiratory symptoms are similar to obstructive lung disease. Patients present with dyspnea, coughing, and wheezing. Bronchiolitis obliterans, a fatal obstructive lung disease, is a late manifestation but classic hallmark of chronic GVHD of the lungs. In bronchiolitis obliterans, peribronchiolar tissues proliferate, causing obstruction of the bronchioles (Lee et al., 2003).

Eyes and Mouth

Ocular chronic GVHD presents with burning and irritation of the eyes, xerophthalmia, photophobia, and excessive tearing. The symptoms are a result of the destruction of the lacrimal glands (Socie, 2004). The inflammation and irritation can progress to corneal lesions. Xerostomia and extra sensitivity to acidic or spicy food often are the first symptoms of the onset of oral chronic GVHD. Erythema with white plaques similar to that seen with thrush occurs in mild cases of the disease, whereas lichenoid changes occur in advanced disease (Socie). Manifestations of chronic GVHD appear to mimic the autoimmune disorder Sjogren syndrome. Typical Sjogren symptoms include xerostomia and xerophthalmia (Janin-Mercier et al., 1987).

Other

Patients with chronic GVHD may experience weakness, joint contractures, and muscle cramps caused by fasciitis. Fasciitis usually is associated with skin changes and often affects the forearms and legs, thus causing limited movement (Lee et al., 2003). Children with chronic GVHD may experience growth retardation but may achieve normal growth once chronic GVHD has been controlled and immunosuppression has been tapered if their growth plates remain open (Vogelsang, 2004).

Figure 1. Clinical Findings of Chronic Graft-Versus-Host Disease

Clinical Highlights: Chronic Graft-Versus-Host Disease

Definition: Chronic graft-versus-host disease (GVHD) is an autoimmune-like reaction, occurring months to years following allogeneic bone or marrow transplantation (BMT), that damages tissues and organs and causes pronounced immunodeficiency. Chronic GVHD can affect almost any organ of the body, but common sites are the skin, liver, mouth, and eyes (Bhushan & Collins, 2003). Although it frequently occurs more than 100 days after BMT, it can occur at any time following BMT (Filipovich et al., 2005). Chronic GVHD is a serious late complication of allogeneic BMT and is the leading cause of nonrelapse deaths more than two years after BMT (Socie et al., 1999). Approximately 38%–77% of patients receiving allogeneic BMT develop chronic GVHD, depending on patient, donor, and cell product characteristics (Akpek, 2002).

Pathophysiology: The pathophysiology of chronic GVHD is not completely understood and is most likely multifactorial. T-lymphocyte imbalances have been implicated in the pathophysiology of chronic GVHD. The imbalances may occur from an overabundance of alloreactive T cells or loss of regulation of autoreactive T cells. Alloreactive T cells attack specific organs based on antigens expressed on the surfaces of cells (Cutler & Antin, 2006). Autoreactive T cells also are thought to play a role in the development of chronic GVHD. Populations of autoreactive T cells may arise in patients following allogeneic BMT because of thymic injury from acute GVHD, immunosuppressive medications such as cyclosporine, or other causes. Thymic injury prevents the deletion of autoreactive clones (Weinberg et al., 2001). Autoreactive T cells interact with interferon to produce increased collagen deposition in tissues, as is seen in chronic GVHD (Parkman, 1998). Cytokine dysregulation also plays a role in the pathogenesis. Higher levels of proinflammatory cytokines interleukin-1 and -6, interferon, and tumor necrosis factor are associated with more severe chronic GVHD (Barak, Levi-Schaffer, Nisman, & Nagler, 1995), whereas low levels of the anti-inflammatory cytokine interleukin-10 have been found in patients with chronic GVHD (Korholz et al., 1997).

Classification and grading: Chronic GVHD is classified by sequence of development and severity. The three categories based on sequence of development are progressive, quiescent, and de novo. Progressive chronic GVHD is an extension of acute GVHD and is the most common presentation. Quiescent onset occurs after resolution of an episode of acute GVHD. De novo onset develops without any prior occurrence of acute GVHD. Progressive chronic GVHD has a poor prognosis, whereas quiescent or de novo chronic GVHD has a better prognosis (Lee, Vogelsang, & Flowers, 2003).

Two widely recognized classification systems for severity of chronic GVHD exist. The traditional classification system categorizes chronic GVHD as either limited or extensive. Limited chronic GVHD involves hepatic dysfunction, localized skin involvement, or both. Extensive chronic GVHD includes generalized skin involvement, hepatic dysfunction, and involvement of other organs, such as the eyes and

salivary glands (Vogelsang, 2004). Recently, a different system of classifying the severity of chronic GVHD was introduced to improve the usefulness of the system for guiding treatment. The system classifies chronic GVHD as mild, moderate, or severe. Mild chronic GVHD involves only one or two organs, excluding the lungs, without any clinically significant functional impairment. Moderate chronic GVHD involves at least one organ with clinically significant functional impairment but no major disability, three or more organs without any clinically significant functional impairment, or the lungs with no clinically significant functional impairment. Severe chronic GVHD involves major disability as a result of chronic GVHD or involvement of the lungs with clinically significant functional impairment. Patients with moderate or severe chronic GVHD should receive systemic treatment for their disease (Filipovich et al., 2005).

Risk factors: A greater risk for chronic GVHD is associated with pretransplant splenectomy, early engraftment, more advanced disease, previous acute GVHD, female donor for a male recipient, unrelated allogeneic BMT, peripheral blood stem cells as the source of the graft rather than bone marrow, increased corticosteroid use, greater histoincompatibility, and older age of the recipient (Bhushan & Collins, 2003). Infusion of donor lymphocytes and lack of T-cell depletion of the cell product are also risk factors. More controversial risk factors for chronic GVHD include cytomegalovirus infection and ethnic differences between donor and recipient (Socie, 2004). The most important risk factor for the development of chronic GVHD is previous significant acute GVHD (Lee et al., 2003).

Prevention and treatment: Systemic immunosuppressive therapies are used to prevent or treat GVHD. They include nonspecific immunosuppressive therapies such as corticosteroids or specific T-cell immunosuppressive drugs such as cyclosporine A. Partial or complete T-cell depletion of the cell product also is used to prevent chronic GVHD (Horwitz & Sullivan, 2006).

Treatment should begin as soon as possible after diagnosis. Systemic or local therapy may be used to treat chronic GVHD depending on the extent of the disease. Corticosteroids and immunosuppressive drugs, such as tacrolimus, are the main line of systemic therapy. Treatment is continued until patients show signs of improvement, then tapering of immunosuppressant drugs is begun, even if all manifestations have not resolved completely. During immunosuppressive treatment and continuing until six months after therapy, antibiotic prophylaxis is given to prevent opportunistic infections (Martin, Carpenter, Sanders, & Flowers, 2003). Other treatments for chronic GVHD include phototherapy, antithymocyte globulin, and topical steroids. Supportive treatment is also important to treat the manifestations of chronic GVHD. The use of synthetic lubricant tears, ophthalmic ointment, eyeglasses, and sunglasses help prevent dryness of the eyes and minimize further damage. Topical steroid creams or treatments can be used for gingivitis and oral ulcers. Physical therapy can help prevent joint contractures. Antacid medications can help alleviate gastrointestinal symptoms (Vogelsang, 2004).

Course and prognosis: Fifty percent of patients with chronic GVHD have limited disease and a good prognosis. Of those with more extensive

disease processes, 60% will respond to treatment and be weaned off immunosuppressive therapy. Unfortunately, the remainder will either die from opportunistic infections or need prolonged immunosuppressive medications (Bhushan & Collins, 2003). Uncontrolled GVHD is associated with a delay in immune recovery, causing increased risk for opportunistic infection and subsequent death in patients following allogeneic BMT (Martin et al., 2003). However, chronic GVHD also is associated with a lower rate of relapse of leukemia following allogeneic BMT (Vogelsang, 2004).

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