Graft-Versus-Host Disease Following Autologous Transplantation

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K.T., a 76-year-old woman, was diagnosed with stage IIA multiple myeloma in 2007 when she presented with severe back pain. K.T. underwent kyphoplasty, a minimally invasive surgery to relieve compression fractures, followed by eight cycles of lenalidomide with a good response. Peripheral blood stem cells were collected after mobilization with filgrastim and plerixafor. She was admitted to the hospital and conditioned for an autologous hematopoietic cell transplantation (HCT) with melphalan followed by reinfusion of peripheral blood stem cells, receiving a cell dose of 4.26 x 10^6 CD_{34} cells/kg. K.T. developed neutropenic fever on day 8 that responded to broad spectrum antimicrobials. She achieved a prompt hematologic recovery, reaching an absolute neutrophil count greater than 500 mm^3 by day 11 after transplantation. On day 9, however, K.T. developed diarrhea, negative for *Clostridium difficile*, which was managed with antimotility agents. She was discharged 17 days following transplantation with blood counts within normal limits, except for mild anemia.

On day 19, K.T. presented for follow-up with a pruritic, erythematous skin rash covering 45% of her body surface area, involving her upper extremities, anterior, and posterior torso. She also experienced gastrointestinal (GI) symptoms of nausea, abdominal cramping, weight loss, and anorexia. Tapered methylprednisolone dosing was prescribed for a suspected diagnosis of autologous graft-versus-host disease (GVHD). Skin rash resolved in response to corticosteroids and pruritis was managed with topical triamcinolone. GI symptoms initially improved, but recurred following completion of the methylprednisolone taper.

On day 32, K.T. presented with progressive diarrhea and diffuse skin rash involving 100% of her body surface area. Medication review did not reveal a likely source for drug reaction. A skin biopsy was taken and showed foci of basal cell vacuolization with apoptosis consistent with acute GVHD. K.T. received a dose of IV methylprednisolone followed by prednisone 2 mg/kg per day in divided doses. With initiation of corticosteroids, skin rash and pruritis abated, but K.T. continued to have diarrhea and anorexia. Her stool tested positive for *C. difficile*, and metronidiazole was prescribed. With a maturing skin rash, confirmed *C. difficile*, and the development of steroid myopathy, a rapid prednisone taper was initiated.

On day 44, K.T. was readmitted after presenting with a pruritic, erythematous rash, 8–10 liquid bowel movements per day, abdominal cramping, pain with defecation, and maroon-colored stool (hematochezia). Symptom onset coincided with a taper of prednisone. Her stool tested positive for *C. difficile*, despite the completion of a two-week course of oral vancomycin and metronidiazole. A clinical diagnosis of autologous GVHD was suspected, given the presence of GVHD identified on skin biopsy and symptoms that persisted despite receiving metronidiazole and vancomycin. Resistant *C. difficile* infection or an opportunistic infection could not be excluded without histologic confirmation. Upper endoscopy and flexible sigmoidoscopy at day 58 revealed severe pseudomembraneous colitis with severe gastritis in the antrum and body of the stomach. K.T.'s duodenum appeared normal and no apoptosis was identified. At that time, findings did not support a diagnosis of GVHD. No viral inclusions were seen and immunohistochemical stain for cytomegalovirus was negative. With an excess of 10 loose bowel movements daily, K.T. required a short course of total parenteral nutrition for adequate caloric intake. GI symptoms failed to respond to treatment with vancomycin and metronidiazole; therefore, prednisone was restarted for a two-week period followed by a successful taper. Total parenteral nutrition was discontinued and K.T. was discharged on day 77 receiving prednisone 10 mg every other day, antimicrobial prophylaxis, and vancomycin.

On day 103 (three days after discontinuation of steroids), K.T. was readmitted with complaints of progressive diarrhea while receiving vancomycin. Subsequent colonoscopy showed thick mucus covering the colonic mucosa and a severely inflamed colon. Pathology showed acute pseudomonas colitis with foci of acute cryptitis and crypt dropout. Biopsies did not reveal apoptosis, but detachment of fibrinopurulent exudates was noted, consistent with a diagnosis of acute GVHD. Laboratory examination revealed mild anemia, thrombocytopenia, mild elevation in leukocyte count, normal liver function tests, and a negative cytomegalovirus test by polymerase chain reaction analysis. Stool assay tested positive for *C. difficile* on multiple occasions. High-dose prednisone was reinstituted and vancomycin was increased to 500 mg four times daily for 10 days. This was followed by a rapid steroid taper given the marked improvement in symptoms. On completion of taper, intestinal symptoms recurred, prompting readmission for correction of fluid loss. At the time of this writing, K.T. was being considered for alternative therapy in the treatment of recurrent acute GVHD and complicated *C. difficile* following autologous transplantation for multiple myeloma.

Autologous Graft-Versus-Host Disease

Historically, GVHD has been a complication of allogeneic HCT and a major cause of morbidity and mortality (Drobyski, Hari, Keever-Taylor, Komoroski, & Grossman, 2009; Holmberg et al., 2006). An estimated 50%–70% of patients develop acute GVHD following allogeneic HCT (Kline, Van Besien, Nathanson, Noffsinger, & Artz, 2006). Holmberg et al. (2006) reported a similar syndrome that exists in the autologous setting after HCT, one that arises as a result of immunologic manipulation (immunosuppression administration and withdrawal to stimulate a graft-versus-tumor effect) or spontaneously without immunosuppressant stimulation. Spontaneous-onset autologous GVHD

Table 1. Organ Staging of Acute Graft-Versus-Host Disease

Stage	Skin	Liver	Gastrointestinal Tract
0	No rash from graft-versus-host disease	Bilirubin less than 2 mg per 100 ml	None (less than 280 ml/m^2)
I	Maculopapular rash less than 25% of body surface area without associated symptoms	Bilirubin from 2 mg to less than 3 mg per 100 ml	Diarrhea more than 500–1,000 ml per day Nausea and emesis
II	Maculopapular rash or erythema with pruritis or other associated symptoms greater than 25% of body surface area or localized desquamation	Bilirubin from 3 mg to less than 6 mg per 100 ml	Diarrhea more than 1,000–1,500 ml per day Nausea and emesis
III	Generalized erythroderma Symptomatic macular, papular, or vesicular eruption with bullous formation or desquamation covering more than 50% of body surface area	Bilirubin 6 mg to less than 15 mg per 100 ml	Diarrhea more than 1,500 ml per day Nausea and emesis
IV	Generalized exfoliative dermatitis or bullous eruption	Bilirubin greater than 15 mg per 100 ml	Diarrhea more than 1,500 ml per day Nausea and emesis Abdominal pain or ileus

Note. From "1994 Consensus Conference on Acute GVHD Grading," by D. Prezpiorka, D. Weisdorf, P. Martin, H.G. Klingemann, P. Beatty, J. Hows, and E.D. Thomas, 1995, *Bone Marrow Transplantation, 15,* p. 826. Copyright 1995 by Stockton Press. Adapted with permission.

affects 5%–20% of patients following HCT (Holmberg et al., 2006; Hood, Vogelsang, Black, Farmer, & Santos, 1987). Autologous GVHD develops in response to an inappropriate recognition of self-antigens (Hess & Jones, 2004; Tokime, Isoda, Yamanaka, & Mizutani, 2000). First reported in 1987, autologous GVHD is described as a self-limited syndrome with a more mild course than acute GVHD in the allogeneic setting (Hood et al., 1987; Kline et al., 2006). The incidence of autologous GVHD is higher in patients who undergo HCT for multiple myeloma compared to patients who develop GVHD following autologous HCT for acute myelogenous leukemia, non-Hodgkin lymphoma, or Hodgkin disease. The risk for developing autologous GVHD among patients who participate in tandem transplantation (12%) for multiple myeloma is higher compared to single HCT (0.9%) (Drobyski et al., 2009; Goddard et al., 2009; Holmberg et al., 2006; Lazarus et al., 2009). Patients with multiple myeloma who develop autologous GVHD after tandem HCT are more likely to have steroid refractory GVHD requiring salvage therapy or prolonged use of corticosteroids (Goddard et al., 2009; Holmberg et al., 2006).

Key Features of Autologous Graft-Versus-Host Disease

Acute GVHD in the allogeneic and autologous setting involves one or more of the three target organ systems: skin, GI tract, or liver (Goddard et al., 2009; Kline, Subbiah, Lazarus, & Van Besien, 2008). Clinical findings of acute cutaneous GVHD may appear as a maculopapular or pruritic skin rash. Hepatic involvement is manifested by an elevation in bilirubin, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase. Acute GVHD involving the GI tract is characterized by profuse, watery diarrhea; nausea; vomiting; abdominal cramping; or bleeding (Drobyski et al., 2009; Goddard et al., 2009; Sica et al., 2000). Using the staging criteria adapted from Prezpiorka et al. (1995), a single grade (see Table 1) is assigned to determine the extent of GVHD involvement (see Table 2). Although acute GVHD is a clinical diagnosis, histologic confirmation is used to corroborate an impression of acute GVHD (Jacobsohn & Vogelsang, 2007). Histologic findings from skin biopsy show perivascular infiltrates, epidermal lymphocyte infiltration, dyskeratosis, and apoptosis or basal cell necrosis (Chao, 2009; Jacobsohn & Vogelsang, 2007). Endoscopy of the GI tract shows edema, mucosal sloughing, or bleeding. Histopathologic diagnosis is characterized by apoptosis, crypt cell necrosis, and dropout with crypt abscess (Chao, 2009; Jacobsohn & Vogelsang, 2007; Shidham et al., 2003). Histologic confirmation of hepatic GVHD is manifested by bile duct damage, epithelial cell dropout, loss of bile ducts, and lymphocyte infiltration (Heymer, Bunjes, & Friedrich, 2002; Jacobsohn & Vogelsang, 2007). The use of biopsy to support clinical findings is appropriate because other conditions often exhibit similar symptoms. Skin rash following autologous HCT may be explained by acute GVHD, drug eruption (particularly from antimicrobials), viral infection, engraftment syndrome (ES), or an eruption of lymphocyte recovery (Inaba et al., 2006; Nellen, Van Marion, Frank, Poblete-Gutierrez, & Steijlen, 2008). The histology of skin rash secondary to acute GVHD is identical to histologic findings of ES.

Table 2. Acute Graft-Versus-Host Disease Grading Using Modified Keystone Criteria

Grade	Skin	Liver	Gut
0	None	None	None
1	Stages 1–2	None	None
2	Stage 3	Stage 1	Stage 1
3	–	Stages 2–3	Stages 2–4
4[a]	Stage 4	Stage 4	–

[a] Grade IV may include lesser organ involvement coupled with extreme decrease in performance status.

Note. From "1994 Consensus Conference on Acute GVHD Grading," by D. Prezpiorka, D. Weisdorf, P. Martin, H.G. Klingemann, P. Beatty, J. Hows, and E.D. Thomas, 1995, *Bone Marrow Transplantation, 15,* p. 826. Copyright 1995 by Stockton Press. Adapted with permission.

Differential Diagnoses

Spitzer (2001) proposed a set of criterion to diagnose ES, allowing for differentiation between the two complications of HCT. These include the presence of skin rash independent of medications, noninfectious fever, and histologic evidence of skin GVHD. The presence of dyspnea or pulmonary infiltrate excludes the diagnosis of acute GVHD but correlates with findings of ES (Gorak et al., 2005; Maiolino et al., 2003; Spitzer, 2001). Eruption of lymphocyte recovery is limited to cutaneous involvement, unlike acute GVHD, which may present as multiorgan involvement. GI symptoms often require biopsy to distinguish between cytomegalovirus colitis and acute GVHD because the symptomatology may be identical (Chao, 2009; Kline et al., 2006; Shidham et al., 2003) (see Table 3). Incorporating histologic findings, an accurate review of symptoms (including timing of symptom onset), laboratory testing, and medication review decreases inaccurate diagnoses, delayed treatment, and poorer outcomes (Kline et al., 2006; Shidham et al., 2003).

Treatment of Autologous Graft-Versus-Host Disease

Corticosteroids are the mainstay of treatment for allogeneic and autologous acute GVHD. In contrast to the allogeneic setting, GVHD prophylaxis with immunosuppressant therapy usually is not indicated following autologous transplantation. The exception is the use of immunosuppression as a modulator to induce GVHD in an attempt to gain a graft-versus-tumor effect (Couriel, Caldera, Champlin, & Komanduri, 2004; Kline et al., 2008; Nakamura et al., 1999). Additional research to gain a better understanding on the graft-versus-tumor effect following autologous HCT is warranted. Among patients who develop GVHD following allogeneic HCT, both single-drug and multimodality regimens have proved successful (Busca et al., 2005; Deeg, 2007). GVHD treatment may include the use of high-dose prednisone (1–2 mg/kg per day), tacrolimus, cyclosporine, cellcept, rapamune, extracorporeal photopheresis, pentostatin, rabbit antithymocyte globulin, or topical therapy (Deeg, 2007; Franchimont, 2004). Autologous GVHD has been described as a self-limited syndrome, with favorable results to corticosteroids alone (Deeg, 2007; Hess & Jones, 2004; Kline et al., 2006). Contradictory to previous studies, Drobyski et al. (2009) reported that patients with autologous GVHD with unsuccessful treatment responses to initial course of corticosteroids are at higher risk for being steroid refractory, therefore necessitating prolonged steroid use or need for salvage therapy (Goddard et al., 2009; Holmberg et al., 2006). These findings suggest poorer outcomes from GVHD in autologous patients than previously described by Hood et al. (1987).

Unresolved Questions

Drobyski et al. (2009) reported an increased incidence of autologous GVHD in patients who underwent HCT for multiple myeloma compared to other hematologic malignancies. These findings suggest a higher incidence of autologous GVHD in patients who underwent tandem HCT for multiple myeloma within one year from the first transplantation (Drobyski et al., 2009; Goddard et al., 2009). Patients who develop GVHD following tandem HCT may have an altered regulatory network, increasing the autoimmunity potentiating GVHD or increasing the incidence of steroid refractory GVHD (Drobyski et al., 2009). Future studies should focus on the affect of autologous GVHD incidence secondary to repetitive exposure of high-dose melphalan and the effect of chemotherapeutics (i.e., bortezomib) used in the treatment of multiple myeloma.

Nursing Implications

The oncology nurse plays a pivotal role in caring for patients with GVHD. Conducting a thorough review of systems and physical assessment promotes symptom identification, which correlates with

Table 3. Differential Diagnosis for Diarrhea Following Myeloablative Chemotherapy and Autologous Hematopoietic Cell Transplantation

Etiology	Essential Workup
Cytotoxicity as a result of chemotherapy	Stool electrolytes
Neutropenic enterocolitis	Imaging studies, endoscopy, and biopsy
Infections *Clostridium difficile* infection (most common infection) Viral infections, including herpes simplex, cytomegalovirus, adenovirus, and enteric viruses (coxsackie, echovirus, and rotavirus) Fungal colonization Other bacterial infections, such as *Salmonella, Escherichia coli,* and *Campylobacter* Reactivation of parasitic infections (strongyloidiasis and cryptosporidiosis)	*C. difficile* stool toxin assay Endoscopy and biopsy Stool ova and parasites Small bowel aspirate Stool *Giardia* antigen Viral polymerase chain reaction studies
Engraftment syndrome	Endoscopy and biopsy
Autologous graft-versus-host disease	Endoscopy and biopsy
Gastrointestinal amyloidosis (in patients with primary amyloidosis and multiple myeloma)	Endoscopy and biopsy
Lactose intolerance (secondary to mucosal injury)	Stool electrolytes (differentiate osmolar versus secretory diarrhea), oral breath test, and trial of a lactose-free diet
Radiation enteritis	Endoscopy and biopsy
Irritable bowel syndrome	Diagnosis of exclusion
Hormonal disturbances	Thyroid-stimulating hormone, cortisol
Worsening of preexisting diseases, including inflammatory bowel disease, celiac disease, and microscopic colitis	Endoscopy and biopsy, serum markers

Note. From "Recurrent Spontaneous Gastrointestinal Graft-Versus-Host Disease in Autologous Hematopoietic Stem Cell Transplantation," by S.G. Krishna, B. Barlogie, L.W. Lamps, K. Krishna, F. Aduli, and E. Anaissie, 2010, *Clinical Lymphoma, Myeloma and Leukemia, 10,* p. E20. Copyright 2010 by CIG Media Group, LP. Adapted with permission.

early access to care and reduced delays in medical intervention. Components of competent care include maintaining open communication between the patient and the transplantation facility, ensuring medication adherence, and initiating infection control practices (i.e., hand hygiene, mucosal membrane and skin care, and aseptic catheter care). Patient advocacy and communication among the multidisciplinary team facilitates access to physical therapy, nutritional attention, and social support services (Nellen et al., 2008; Wingard, Vogelsang, & Deeg, 2002). Evaluating for the presence of steroid-induced hyperglycemia, steroid myopathy or atrophy, muscle wasting, or reactivation of viral illnesses such as cytomegalovirus promote improved patient care (Ringden, 2005). Among patients with intestinal GVHD, oncology nurses should assess for fluid loss, protein-losing enteropathy, or arrhythmias secondary to electrolyte imbalance (Mattson, 2007; Nellen et al., 2008).

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Clinical Highlights: Autologous Graft-Versus-Host Disease Definition

Traditionally, graft-versus-host disease (GVHD) has been a complication of allogeneic hematopoietic cell transplantation (HCT) that develops in response to the new donor immune system recognizing antigen-presenting cells as foreign and mounting an inflammatory response (Neumann, 2004). First reported by Hood, Vogelsang, Black, Farmer, and Santos (1987), a similar syndrome arises following autologous HCT in response to autoreactivity, a failure of self-tolerance. This syndrome, termed autologous GVHD, develops either as a response to intentional induction by immunosuppressant manipulation or spontaneously without immunosuppressant therapy (Drobyski, Hari, Keever-Taylor, Komoroski, & Grossman, 2009; Kline, Van Besien, Nathanson, Noffsinger, & Artz, 2006). The development of spontaneous autologous GVHD affects 5%–20% of patients following HCT and almost 70% of patients when immunosuppression is used (Drobyski et al., 2009; Kline et al., 2006). GVHD is classified as acute or chronic, depending on the timing of symptoms. Acute GVHD occurs within the first 100 days after transplantation, and chronic GVHD occurs after the first 100 days (Mattson, 2007; Neumann, 2004). The features of autologous GVHD are comparable to findings seen with acute GVHD.

Diagnostic Workup and Differential Diagnoses

Unlike chronic GVHD, which is characterized by multiorgan involvement and immunodeficiency, acute GVHD involves one or more of the three target organ systems: skin, gastrointestinal tract, or liver (Neumann, 2004). Clinical features of acute or autologous GVHD include any of the following symptoms: maculopapular rash, pruritis, nausea, vomiting, tenesmus, watery diarrhea, hyperbilirubinemia, elevated alkaline phosphatase, or elevated liver function tests. Acute GVHD is a clinical diagnosis, but histologic confirmation is used to support clinical findings. Histologic changes of the skin reveal apoptosis, lymphocyte infiltration, or dyskeratosis (Heymer, Bunjes, & Friedrich, 2002; Jacobsohn & Vogelsang, 2007). Similar histologic features are seen in engraftment syndrome, making it difficult to distinguish between the two syndromes. Histopathologic features of gastrointestinal GVHD reveal apoptosis, crypt cell necrosis, or crypt dropout (Heymer et al., 2002; Neumann, 2004). Stool toxin to evaluate for *Clostridium difficile* is included in the diagnostic approach to a patient with diarrhea following HCT. Risk factors for infectious diarrhea (*C. difficile* is the most common infection) include impaired immunity, antimicrobial therapy, chemotherapy, and hospitalization. The relationship and co-existence of *C. difficile* and GVHD is well understood and reported in the scientific literature (Kline et al., 2006). Liver histology show lymphocyte infiltration, epithelial cell dropout, and bile duct loss (Jacobsohn & Vogelsang, 2007). Using histologic evidence and information from clinical findings helps to exclude differential diagnoses such as drug rash, viral infection, or engraftment syndrome (Jacobsohn & Vogelsang, 2007).

Treatment

Corticosteroids are first-line treatment for GVHD in the autologous and allogeneic setting. GVHD in the autologous setting was previously considered a self-limited syndrome with favorable results to corticosteroids alone (Drobyski et al., 2009; Hess & Jones, 2004). Research suggests that autologous GVHD is associated with increased incidence of steroid refractoriness and poorer outcomes in patients who undergo tandem transplantation for multiple myeloma (Drobyski et al., 2009; Jacobsohn & Vogelsang, 2007; Mattson, 2007).

Nursing Implications

Oncology nurses should recognize the signs and symptoms of autologous GVHD and act as liaisons between patients and the transplantation facility. This facilitates accurate communication of information and avoids delays in medical intervention. Strict adherence to infection control measures and medication compliance are of pivotal importance (Jacobsohn & Vogelsang, 2007; Mattson, 2007).

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