

Acquisition of Vernal and Atopic Keratoconjunctivitis After Bone Marrow Transplantation

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- **PURPOSE:** Vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) result from genetic and environmental factors. We present patients who had no history of atopic disorders before bone marrow transplantation (BMT) and who seem to have acquired VKC or AKC from their donors, who had atopic disorders.
- **DESIGN:** Observational case series.
- **METHODS:** The patients in this study were part of a cohort of patients who had undergone allogeneic hematopoietic stem cell transplantation (HSCT) from January 1997 through December 2007. Of 621 HSCT recipients, four recipients who were free of allergic disorders acquired VKC or AKC from their afflicted donors after HSCT. Each patient underwent complete ophthalmologic examination, determination of the total serum immunoglobulin (Ig) E, and conjunctival scrapings.
- **RESULTS:** Four (0.64%) of 621 patients who had undergone HSCT acquired VKC or AKC after BMT. The donors had VKC or atopic dermatitis. In addition, in two of these four patients, asthma developed. One patient had elevated total serum IgE. Conjunctival scrapings of all four patients revealed the presence of eosinophils. One patient had concurrent graft-versus-host disease.
- **CONCLUSIONS:** VKC and AKC are systemic allergic disorders characterized by local ocular manifestations. This report suggests the possibility of the acquisition of VKC or AKC after BMT by adoptive transfer. (Am J Ophthalmol 2008;xx:xxx. © 2008 by Elsevier Inc. All rights reserved.)

VERNAL KERATOCONJUNCTIVITIS (VKC) AND ATOPIC keratoconjunctivitis (AKC) result from genetic and environmental factors. A unique opportunity to understand the development of atopic ocular disorders occurs during bone marrow transplantation (BMT). Previous studies have shown that recipients undergoing BMT from

donors with allergic disorders have a high risk of acquisition of donor allergen-specific immunoglobulin E (IgE) in the first year of transplantation.¹⁻³ This is consistent with the fact that donor transfer of B- and T-cell clones with allergen-specific memory cells occurs after BMT.

Allergic rhinitis or asthma can complicate BMT, albeit rarely, with allergic manifestations in recipients long after BMT.³ Allergen-specific IgE hypersensitivity can be transferred by BMT. The main objective of this article is to present patients who acquired VKC or AKC by adoptive transfer of immune cells through BMT.

METHODS

THE PATIENTS IN THIS STUDY WERE PART OF A COHORT OF patients who were followed up after allogeneic hematopoietic stem cell transplantation (HSCT) from January 1997 through December 2007. A total of 621 patients underwent allogeneic HSCT from 1997 through 2007. There were 469 bone marrow transplantation patients, 142 peripheral blood transplantations, and 10 cord blood transplantation recipients. All patients with ocular symptoms underwent an ophthalmologic evaluation. Patients with evidence of VKC or AKC were identified. Each patient underwent a complete ophthalmologic examination, determination of total serum IgE, and conjunctival scrapings.

RESULTS

NONE OF THE PATIENTS WHO UNDERWENT PERIPHERAL blood transplantation or cord blood transplantation had allergic disorders. Four of 469 bone marrow transplantation recipients had VKC or AKC. None of the patients had allergic disorders before BMT. The Table summarizes the findings among four cases with VKC or AKC.

- **CASE 1:** A 17-year-old male had severe aplastic anemia. The patient gave no history of allergic disorders and had no ocular symptoms. His 7-year-old donor brother had VKC. He was admitted electively and underwent allogeneic BMT from his human leukocyte antigen (HLA)-identical brother (6/6 major HLA antigen match using low-resolution molecular typing for class I antigens and high-resolution molecular typing for the DR antigen). The

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TABLE. Summary of Cases with Acquired Vernal and Atopic Keratoconjunctivitis after Bone Marrow Transplantation

Case No.	Age (yrs)	Gender	Follow-up after BMT (mos)	Initial Diagnosis	Ocular Findings after BMT	Onset of Symptoms after BMT (mos)	Other Disorders	Donor's Original Disorder
1	17	M	24	Aplastic anemia	VKC	18	Asthma	VKC
2	37	M	31	Multiple myeloma	AKC	12	Atopic dermatitis	Atopic dermatitis and keratoconjunctivitis
3	29	M	36	ALL	AKC	14	Asthma	Atopic dermatitis and asthma
4	41	F	30	AML	AKC	12	GVHD	Atopic dermatitis

AKC = atopic keratoconjunctivitis; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BMT = bone marrow transplantation; F = female; GVHD = graft-versus-host disease; M = male; mos = months; VKC = vernal keratoconjunctivitis; yrs = years.

patient received standard posttransplantation immunosuppression therapy using cyclosporine and a short course of methotrexate and had no history of acute or chronic graft-versus-host disease (GVHD). Six months after the discontinuation of immunosuppressive drugs, he began to report redness, itching, and sensitivity to light.

On eye examination, he was found to have a visual acuity (VA) of 20/20 in both eyes. The right eye showed diffuse papillary hypertrophy with conjunctival edema. The bulbar conjunctiva was hyperemic, and there was evidence of perilimbal infiltration. The left eye showed similar palpebral conjunctival hypertrophy and edema. The bulbar conjunctiva was hyperemic, and there was evidence of 360 degrees of perilimbal infiltration with eight to 10 Trantas dots. The left cornea showed superficial punctate keratitis. The anterior chambers (AC) were deep. The pupils were regular and reactive, and the lens in each eye was clear. The fundus in each eye was normal. Total serum IgE was 1076 kU/l.

• **CASE 2:** A 37-year-old patient was diagnosed with multiple myeloma (immunoglobulin G κ , stage IIIA). He had received five cycles of vincristine (Mayne Pharma Inc, Paramus, New Jersey, USA), adriamycin (EBEWE Pharmaceuticals, Unterach, Austria), and dexamethasone chemotherapy and was maintained on thalidomide and prednisone. He had undergone allogeneic BMT from his fully HLA-matched brother, who had atopic dermatitis and AKC.

The patient was kept on standard posttransplantation immunosuppression and had no history of acute or chronic GVHD. One year after transplantation, he started having redness and itching of both eyes, and well-defined cutaneous skin patches developed over the arms, cheek, and dorsal surface of the toes. He also reported of redness, itching, and tearing of both eyes.

On eye examination, he was found to have a VA of 20/20 in both eyes. The right eye showed papillary hypertrophy with conjunctival edema. The bulbar conjunctiva was hyperemic with perilimbal edema. There was superficial punctate keratitis of the cornea. The left eye showed

conjunctival perilimbal infiltration and a superficial punctate keratitis. The ACs were deep, the pupils were regular and reactive, and the lens in each eye was clear. The fundus examination showed no abnormalities. Giemsa-stained conjunctival scrapings revealed many eosinophils with normal epithelial cells. Assessment of total serum IgE was 45.7 kU/l.

• **CASE 3:** A 29-year-old man had acute lymphoblastic leukemia. He had no history of atopic disorders or any allergic condition. He was started on an induction chemotherapy protocol and achieved complete remission. Subsequently, he underwent allogeneic BMT from his HLA-identical brother, who had atopic dermatitis and asthma. He received standard posttransplantation immunosuppression therapy and had no history of acute or chronic GVHD.

Fourteen months after the BMT, the patient began to report redness, itching, and mucoid stringy discharge from both eyes. The ocular findings began after discontinuation of his immunosuppressive therapy. On eye examination, the patient was found to have bilateral conjunctival hyperemia with papillary hypertrophy of the conjunctiva (P3). The cornea was clear, the AC was deep, and the lens was clear. In addition to the ocular findings, patient also was found to have asthma and was treated with inhalation therapy.

The clinical findings were consistent with AKC, and the patient had lesions on the skin consistent with atopic dermatitis. Serum total IgE was 23.1 kU/l. Giemsa-stained conjunctival scrapings revealed many eosinophils.

• **CASE 4:** A 41-year-old woman was diagnosed with acute myeloid leukemia. She received an induction course of chemotherapy and showed evidence of continued complete remission. The patient gave no history of allergic disorders and no history of atopy.

The patient underwent uneventful BMT from her HLA-identical sister, who had atopic dermatitis. She received standard posttransplantation immunosuppression. Twelve months after BMT, she began to report redness, itching, and mucoid discharge. On eye examination, the patient

was found to have VA of 20/20 in both eyes. Tension by applanation was 16 mm Hg in the right eye and 17 mm Hg in the left eye. Schirmer test results were 6 mm in the right eye and 9 mm in the left eye. The patient had poliosis of the eyelashes and areas of pigmentation and depigmentations of the skin of the eyelids. The patient had similar lesions over the face. The findings were clinically consistent with chronic GVHD.

Biomicroscopy of both eyes revealed conjunctival hyperemia. There was evidence of papillary hypertrophy. The cornea showed superficial punctate keratitis in both eyes involving the lower quadrants. The AC was deep, the pupil was regular and reactive, and the lens was clear. Ophthalmoscopy of both eyes revealed normal optic nerve heads, blood vessels, and maculae.

The serum total IgE level was 50.5 kU/l. Giemsa-stained conjunctival scrapings revealed many eosinophils. The patient was diagnosed to have GVHD, VKC or AKC, and atopic dermatitis.

DISCUSSION

THE CASES DESCRIBED HERewith DEMONSTRATE THAT atopic disorders subsequently were diagnosed in recipients after HSCT. VKC and AKC appeared in all four patients whose recipients had atopic disorders. These events were associated with significant elevation in the total IgE in one patient and the development of VKC and AKC. Two cases of asthma were documented six weeks and 17 months after BMT in previously nonasthmatic recipients of HLA-identical donors with asthma.

Our cases demonstrate the fact that bone marrow-derived progenitors of immune cells from allergic donors can be transferred to recipients and can predispose these patients to VKC or AKC. The passive transfer of bone marrow memory cells and the suppression of T regulatory cells by immunosuppression are possible contributing factors.

One patient had no signs or symptoms of VKC before BMT. After BMT from his donor sibling who had VKC, the patient demonstrated signs and symptoms of VKC. It seems that VKC represents a systemic disease with local ocular manifestations. Because hematopoietic progenitor bone marrow cells are transferred through BMT, this is a unique opportunity to understand the development of VKC during BMT. Although common in younger children, VKC seldom presents with an onset at the age of 17 years.

The acquisition of VKC is consistent with the adoptive transfer of the B- and T-helper-cell clones with allergen-specific memory. Adoptive transfer of allergen-specific IgE occurs in the first year after BMT from atopic donors.¹ Previous reports have shown that allergen-specific IgE and oral and cutaneous allergy can be transferred adoptively from atopic donors to nonatopic

recipients early after BMT.⁴⁻⁶ In our patients, the signs and symptoms of VKC or AKC occurred 12 to 18 months after BMT. This is consistent with the adoptive transfer of mature B-cell clones with allergen-specific memory after BMT. Acquisition of increased total IgE with new allergen-specific IgE occur at a high rate in the long-term after BMT from atopic donors.^{1,2} T helper cells may lead to a series of events leading to isotype switching and production of IgE.⁷ The findings in this report likely represent the recipient acquisition of T cells with T helper 2 (Th2) phenotype from the donor. Adoptive transfer of T-cell clones occurs after BMT, as evident by the persistence of donor-derived purified protein derivative-specific T cells.⁸

B cells and T cells differentiate from a common lymphoid progenitor in the bone marrow. Progenitor B cells differentiate into precursor B cells and into final differentiation of antibody-producing plasma cells.⁹ This differentiation is maintained actively by the *Pax-5* gene. Cobaleda and associates showed that inactivation of the *Pax-5* gene in mature B cells results in dedifferentiation to the progenitor B-cell stage and the generation of T cells.⁹ The implication of these findings in atopic disorders remains to be elucidated.

Bone marrow-derived progenitor cells for eosinophils-basophils are increased in the peripheral blood of the recipient patient and may come to the conjunctiva, leading to VKC signs and symptoms. These cells may infiltrate the conjunctiva and participate in the development of the allergic disorder. After BMT, populations of mature memory cells are replaced by cells derived from donor hematopoietic progenitor cells.¹

Our report, however, has certain limitations. We cannot exclude the possibility of the development of VKC and AKC after BMT. The allergic disease may have been a consequence of immune dysregulation after BMT.^{10,11} Acquisition of AKC and elevated total IgE after BMT occurred after discontinuation of the immunosuppressive therapy. This indicates that the predisposition to develop allergy is transferred from atopic donor to recipient. Immunocompetent cells Th2 phenotype orchestrate many of the events leading to isotype switching and production of IgE.⁷ One patient had GVHD. Recent studies have focused on CD4+CD25+ regulatory T cells (Tregs) and their relationship to chronic GVHD.¹²⁻¹⁷ In several studies, the number of Tregs was found to be diminished in patients with chronic GVHD, and patients who undergo remission from this disease display a normal number of Tregs. The mechanism by which Tregs suppress GVHD is unclear, but there is evidence to suggest that suppression is mediated by cytokines such as transforming growth factor- β and interleukin-10 or by contact with dendritic cells through indoleamine 2,3-dioxygenase.¹⁸ Tregs also may accept inhibitory effects directly in the target tissue. Furthermore, decrease in mucosal Tregs has been documented in the

patients with chronic GVHD compared with normal controls without the disease.

The concurrent presentation of GVHD and AKC may be difficult to confirm. The presence of eosinophils in the conjunctiva suggests an allergic process, whereas predominant lymphocytes may suggest GVHD. Elevation in total IgE is known to occur after BMT; however, this seems to be a transient phenomena that occurs early after BMT without long-term persistence.¹⁹ It is of crucial importance

to differentiate GVHD from VKC and AKC to provide the appropriate therapy.

The data in this article suggest that bone marrow-derived immune cells from a donor with atopy can be transferred to recipient. This finding supports the primary role of bone marrow-derived immune cells in the development of VKC and AKC and suggests that an allergic disorder such as VKC represents a systemic disease with local ocular manifestation.

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