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Ocular and Systemic Autoimmunity after Successful Tumor-Infiltrating Lymphocyte Immunotherapy for Recurrent, Metastatic Melanoma

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Abstract

Objective—To describe the ophthalmic and systemic autoimmune findings after successful adoptive cell transfer of ex vivo expanded, autologous tumor-reactive tumor-infiltrating lymphocytes (TIL) for metastatic melanoma.

Design—Retrospective, interventional case report.

Participant—A 35-year-old man who underwent immunotherapy for metastatic melanoma with adoptive cell transfer of tumor-reactive TIL.

Methods—A 35-year-old man with metastatic melanoma was treated with TIL plus interleukin-2 (IL-2) therapy after a lymphodepleting regimen of cyclophosphamide and fludarabine for metastatic melanoma, which led to a complete and durable remission. Bilateral panuveitis, hearing loss, vitiligo, poliosis, and alopecia developed in the patient, requiring local ophthalmic immunosuppressive therapy. The clinical course, diagnostic testing, and therapeutic interventions over a 2-year period are reviewed.

Main Outcome Measures—Visual acuity, anterior chamber and vitreous inflammation, optical coherence tomography findings, serial electro-oculograms (EOGs), microperimetry (MP-1) testing, flow cytometric analysis of cells derived from the aqueous humor, and aqueous humor cytokine profiles were evaluated.

Results—After melanoma immunotherapy, complete tumor regression was achieved at 5 months after treatment with a durable, ongoing, complete remission at 24 months. Early in the treatment course, a high fever, a diffuse rash, hearing loss, and bilateral anterior uveitis developed acutely in the patient. Late autoimmune sequelae included the development of alopecia, vitiligo, poliosis, and bilateral panuveitis with diffuse retinal pigment epithelium (RPE) hypopigmentation, reminiscent of Vogt-Koyanagi-Harada (VKH) syndrome. Bilateral cystoid macular edema also developed that was

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responsive to acetazolamide. Serial EOGs showed alterations in RPE standing potentials in dark conditions, and MP-1 testing revealed diminished foveal and perifoveal sensitivity. An aqueous humor aspirate revealed a high concentration of melanoma tumor antigen-reactive T cells compared with that of peripheral blood samples, as well as a proinflammatory aqueous cytokine profile. At the time of cataract surgery 22 months after immunotherapy, a repeat aqueous humor sample showed the disappearance of the previously seen melanoma differentiation antigen-reactive lymphocytes, but the proinflammatory cytokine profile persisted.

Conclusions—Ocular and systemic autoimmune sequelae resembling VKH may develop after successful melanoma immunotherapy. This report provides insight into the pathogenesis of VKH disease. The patient's clinical course illustrates the fine balance between tumor-specific immunity and loss of self-tolerance.

The prognosis of stage IV metastatic melanoma is extremely poor with a reported 5-year survival rate varying from 6% to 8%.¹⁻³ Combination chemotherapy can result in objective melanoma regression that is temporary but rarely curative. Immunotherapies evaluated at the Surgery Branch, National Cancer Institute, for the treatment of melanoma have included vaccine-based adjuvant therapies, biologic response modifiers, and adoptive cell transfer of ex vivo expanded, autologous tumor-reactive tumor-infiltrating lymphocytes (TILs).^{4,5} Approximately 15% of patients treated with interleukin-2 (IL-2) experience an objective tumor regression that is durable in some patients.⁶ Adoptive cell transfer of TILs plus IL-2 after preparative lymphodepleting chemotherapy can mediate tumor regression in approximately 50% of patients, some of whom experience a complete and durable response.⁷ Further studies are underway to determine if potent TILs may be generated via genetic engineering of autologous lymphocytes by the insertion of high-affinity, antitumor T-cell receptors.^{8,9}

Autoimmune manifestations secondary to immunotherapy for melanoma, including vitiligo, uveitis, or a combination of vitiligo and uveitis, were observed in a prior study of patients treated with TILs plus IL-2 after a lymphodepletion regimen.⁷ In the 35 patients treated in this study, uveitis developed in 5 patients and all were treated successfully with topical corticosteroids alone, with a complete resolution of intraocular inflammation and the maintenance of good visual acuity. However, although there was no clear statistical relationship found between autoimmune manifestations and objective antitumor response among the patients treated with TILs specific for melanocyte differentiation antigens, there was an anecdotal correlation between increased autoimmune sequelae and antitumor response.

Herein, a case of chronic, severe bilateral panuveitis, vitiligo, poliosis, hearing loss, and alopecia reminiscent of Vogt-Koyanagi-Harada (VKH) disease is reported in a patient who has sustained a durable and complete remission after TIL plus IL-2 immunotherapy for recurrent, metastatic melanoma. The ocular autoimmunity observed in the patient differed from prior reports of uveitis after melanoma immunotherapy in its severity and its poor responsiveness to local immunosuppressive therapy. An aqueous humor aspirate from this patient revealed CD8+ T cells specific for melanocyte differentiation antigens. In addition, aqueous humor cytokine studies revealed a proinflammatory cytokine profile that persisted at long-term follow-up despite the disappearance of the previously observed tumor-reactive lymphocytes. The case illustrates the risk of ocular and systemic autoimmune sequelae inherent to melanoma immunotherapy targeting melanoma differentiation antigens and the fine balance between tumor surveillance and loss of self-tolerance.

Case Report

Course of Metastatic Melanoma

A 35-year-old white man with a history of metastatic melanoma was enrolled in an adoptive immunotherapy protocol in the Surgery Branch of the National Cancer Institute in May 2006. The National Cancer Institute Institutional Review Board and Ethics Committee approval was obtained for the protocol and written informed consent was obtained from the patient for participation before enrollment. All research adhered to the tenets of the Declaration of Helsinki.

In January 2003, the patient was diagnosed with a dysplastic junctional halo nevus via excisional biopsy of a back lesion. In December 2003, right axillary lymphadenopathy developed that showed positive results for melanoma on biopsy and subsequently was resected surgically. In 2004, he received a MART-1 adjuvant vaccine for 9 months. The treatment was terminated when further tumor metastases developed in the cervical lymph nodes that required excision. The patient then received high-dose IL-2 infusions in 2005, which resulted in a minor antitumor response. In May 2006, positron emission tomography scanning revealed evidence of increased metabolic activity, indicating possible melanoma metastases in the abdominal cavity, right colon, and supraclavicular nodes bilaterally, as well as extensive subcutaneous disease. A right hemicolectomy was performed in May 2006 and confirmed melanoma invasion of the right colon.

The patient subsequently was admitted in July 2006 for TIL plus IL-2 treatment. After a lymphodepleting regimen consisting of cyclophosphamide (60 mg/kg for 2 days), fludarabine (25 mg/m²), and 12 Gy total body irradiation (2 Gy twice daily for 3 days), 1.4×10^{11} autologous TIL cells generated as previously described¹⁰ were administered. Four infusions of IL-2 (720 000 IU/kg every 8 hours) then were administered before cessation of IL-2 therapy because of transient mental status changes.

Acute Events after Tumor-Infiltrating Lymphocyte Plus Interleukin-2 Immunotherapy

In July 2006, after TIL plus IL-2 therapy, the patient experienced high fevers, a diffuse, erythematous full-body rash, hearing loss, and bilateral, low-grade anterior uveitis. Visual acuity was 20/20 in both eyes, and the anterior uveitis improved initially with topical prednisolone acetate 1% 4 times daily in both eyes. Biopsy of the rash revealed a dermal CD8 + T-lymphocyte infiltrate. Audiologic evaluation revealed low- and high-frequency hearing loss with resolution of low-frequency hearing loss 1 month after intra-auricular corticosteroid injections. Insomnia also developed in the patient 1 month after TIL plus IL-2 therapy that required amitriptyline.

In October 2006, partial regression (>30%) of all metastatic lesions was observed by computed tomography scan according to Response Evaluation Criteria in Solid Tumors criteria.¹¹ In December 2006, a complete remission of all lesions was documented (Fig 1A-D). Physical examination showed diffuse pigmentation loss including patchy vitiligo, poliosis, and alopecia (Fig 1E,F).

Course of Uveitis, Diagnostic Evaluation, and Management

In October 2006, the uveitis service was consulted because of persistent anterior uveitis after several attempts to taper off the corticosteroid. Visual acuities were 20/20 in the right eye and 20/25 in the left eye. Ophthalmic examination revealed 1+ anterior chamber cells in both eyes, but no evidence of vitritis or chorioretinitis was observed. Minimal late-phase perifoveal hyper-fluorescence was observed on fluorescein angiogram with no evidence of cystoid macular edema (CME) on optical coherence tomography. Diffuse urticaria developed after

fluorescein infusion that precluded subsequent angiograms. Topical prednisolone acetate 1% therapy was initiated every 2 hours with a decrease in the anterior chamber inflammation to rare cell in both eyes, and the corticosteroids were tapered off over a 6-week period.

Three weeks after discontinuing the topical corticosteroids, the patient reported photophobia and ocular pain. Visual acuity was 20/40 in both eyes. Ophthalmic examination showed 1 to 2+ anterior chamber cell and flare in both eyes and 1 to 2+ vitreous cell with trace haze in both eyes. Cystoid macular edema also was observed in both eyes with a central retinal subfield thickness (optical coherence tomography 3, area A1) of 387 μm in the right eye and 351 μm in the left eye. Two sub-Tenon periocular triamcinolone acetonide (40 mg) injections 4 weeks apart were given in the right eye, as well as 1 sub-Tenon triamcinolone acetonide injection in the left eye, but no improvement in CME was observed in either eye. After the periocular injections, the patient's visual acuity had declined to 20/63 in the right eye and 20/80 in the left eye with 2+ anterior chamber cell and flare in both eyes and 2+ vitreous cells in both eyes. The CME also had worsened, with central retinal thicknesses of 532 μm in the right eye and 509 μm in the left eye.

Oral acetazolamide (500 mg extended-release sequels, twice daily) then was started, and topical prednisolone acetate 1% 4 times daily was continued. In February 2007, 1 month after the initiation of acetazolamide therapy, visual acuity improved to 20/25 in the right eye and 20/32 in the left eye. Anterior chamber inflammation had resolved in both eyes and only trace vitreous cell was detected in both eyes. An improvement in CME was also found, with central macular thickness decreasing to 387 μm in the right eye and 255 μm in the left eye.

The patient's ocular status remained stable for the ensuing 2 months; however, in April 2007, 2+ anterior chamber cells and 1+ vitreous cell again were observed in both eyes, although the patient's visual acuity remained stable. Topical prednisolone acetate 1% was increased to every 2 hours. However, his visual acuity declined to 20/63 in the left eye and the ocular inflammation persisted with 2 to 3+ anterior chamber cells and 2+ vitreous cell and haze. The patient's CME also worsened with a central macular thickness of 351 μm . Marked hypochromia of the patient's irides was observed in both eyes on slit-lamp biomicroscopy. In addition, diffuse hypopigmentary fundus changes with a sunset-glow appearance were observed on dilated funduscopy examination, suggestive of widespread changes in the pigmented cells in the RPE and choroid (Fig 2A-D).

An EOG at this time showed light-dark Arden ratio in both eyes within normal limits. However, the Arden ratios of 4.10 in the right eye and 4.51 in the left eye in May 2007 were elevated when compared with a prior electro-oculogram in December 2006, which showed an Arden ratio of 2.98 in the right eye and 3.10 in the left eye (Fig 3A,B; available at <http://aaojournal.org>). This change in the Arden ratio in both eyes was likely the result of a decrease in the dark trough amplitude from 190 mV in the right eye and 189 mV in the left eye in December 2006 to 143 mV in the right eye and 109 mV in the left eye in May 2007. Microperimetry-1 10-2 testing revealed decreased sensitivity in the perifoveal region, as well as central scotomata in both eyes (Fig 4A-D; available at <http://aaojournal.org>).

Because of the declining visual acuity and persistent panuveitis, intravitreal triamcinolone acetonide (IVTA) was administered in the left eye in June 2006. At the time of IVTA administration, an aqueous fluid aspirate was obtained for immunophenotyping and functional analysis of the ocular-derived cells, as well as for cytokine analysis.

Flow Cytometry and Cytokine Evaluation of Aqueous Fluid and Peripheral Blood

Flow cytometry of ex vivo expanded cells revealed high percentages of melanoma tumor antigen-specific CD8+ MART-1 tetramer-positive cells in the eye compared with the

peripheral blood after adoptive cell transfer (Fig 5A-C). Of the patient's TIL infusion, there were 4.6% CD8+ MART-1 tetramer-positive cells. At the time of aqueous humor sampling, 2.5% of the peripheral blood lymphocytes (PBLs) were CD8+ MART-1 tetramer positive. Interestingly, 3.9% of the aqueous humor-derived T cells were CD8+ MART-1 tetramer positive (Fig 5A), suggesting that CD8+ T cells specific for MART-1 antigen were increased in ocular tissues, potentially because of the abundance of melanocytes in the iris, ciliary body, and choroid. The development of marked iris hypochromia and widespread fundus depigmentation during the evolution of the patient's uveitis was consistent with autoimmunity caused by the prolonged presence of melanocyte differentiation antigen-specific T cells.

The patient's ocular-derived cells also were cultured in vitro, and functionality was assessed by coculture with target cells bearing various melanoma antigens (Fig 5B) or HLA-matched (me1526, me1624) or mismatched (me1888, me1938) melanoma tumors (Fig 5C). The ocular-infiltrating cells were highly reactive to MART-1₂₆₋₃₅ tumor antigen and, to a lesser degree, to gp100₂₀₉₋₂₁₇ tumor antigen at levels substantially higher than PBL from the same patient. These cells also were reactive against HLA-matched MART-1+gp100+ melanoma tumors, but not HLA-mismatched tumors. This assay confirmed that the T cells harvested from the aqueous humor aspirate demonstrated the same antigen specificity as the TILs from PBLs.

Cytokine analysis of aqueous fluid showed a proinflammatory profile with elevated levels of IL-6 (409 pg/ml), IL-8 (64.4 pg/ml), and tumor necrosis factor- α (15.5 pg/ml). Levels of anti-inflammatory cytokines were low with levels of IL-4 (5.1 pg/ml), IL-5 (4.2 pg/ml), and IL-10 (6.3 pg/ml).

Response to Acetazolamide Therapy

Two months after IVTA injection, the patient's CME had resolved and visual acuities were 20/32 in the right eye and 20/25 in the left eye. Topical prednisolone acetate 1% application was tapered and then maintained at twice-daily dosing to control the anterior chamber inflammation. Throughout this period, acetazolamide (500 mg extended-release sequels) was continued. However, because of an elevation of the patient's creatinine to 1.8 mg/dl in September 2007 and the concern that this change was related to acetazolamide therapy, acetazolamide was discontinued briefly. A severe exacerbation of the patient's CME was observed 1 month after cessation, and acetazolamide was restarted. After resumption of acetazolamide, a dramatic resolution of CME was observed bilaterally (Fig 6A-F). Creatinine levels have remained stable at 1.7 to 1.8 mg/dl, and the increase in creatinine was attributed to radiation therapy.

Long-term Follow-up of Uveitis and Response of Metastatic Melanoma

The patient's visual acuity in January 2008 was 20/20 in the right eye and 20/63 in the left eye. Ophthalmic evaluation showed rare anterior chamber cells in both eyes, trace vitreous cells in both eyes, and mild macular edema in the right eye only. The patient underwent cataract extraction, posterior synechialysis, and intraocular lens implantation in the left eye in May 2008. An aqueous humor aspirate was obtained for repeat immunophenotyping and cytokine analysis. Flow cytometry of the aqueous humor content revealed that less than 1% of the cells were CD3+ T cells (both CD4+ and CD8+). After expanding these T cells in vitro, none were specific for MART-1 tetramer or gp100₂₀₉₋₂₁₇tetramer (Fig 7). Interestingly, proinflammatory cytokines remained elevated, including IL-6 (324 pg/ml), IL-8 (59.8 pg/ml), and tumor necrosis factor- α (30.1 pg/ml). Levels of anti-inflammatory cytokines remained low, including IL-4 (1.8 pg/ml), IL-5 (2.2 pg/ml), and IL-10 (1.6 pg/ml).

Three weeks after surgery, visual acuity was 20/25 in the right eye and 20/30 in the left eye, with trace anterior chamber inflammation, trace vitreous cells, and no evidence of macular

edema. Acetazolamide has been maintained at 500 mg twice daily. At the 2-year follow-up, repeat computed tomography scans confirmed an ongoing, durable, and complete remission of the patient's metastatic melanoma.

Discussion

This report highlights the clinical course of a patient in whom, after successful eradication of metastatic melanoma with adoptive cell transfer therapy, severe, chronic, bilateral panuveitis that was recalcitrant to local immunosuppressive therapy developed. Although the patient did not have the typical features of acute VKH disease with bilateral, serous retinal detachments at presentation, his sunset-glow fundus resembled the convalescent ophthalmic phase observed in patients with the chronic form of VKH disease. He met criteria for the complete VKH syndrome according to the revised diagnostic criteria for VKH.¹² His ocular and systemic autoimmune manifestations were characterized by evaluating the cytokine response of his PBLs and aqueous humor inflammatory cells when stimulated with melanocyte antigens. The high percentage of tumor-reactive T cells obtained from the aqueous fluid also was notable and indicative of a breakdown of the blood-ocular barrier, loss of immunoprivilege, and T-cell homing to melanocytes within the iris, ciliary body, and choroidal tissues.

The pathogenic mechanisms underlying VKH are incompletely understood, but seem to involve CD4+ and CD8+ T cells directed against melanocyte antigens. Vogt-Koyanagi-Harada disease previously was associated with human leukocyte antigen (HLA)-DR4, and CD4+ T-cell clones harvested from HLA-DR4+ VKH patients have been observed to produce interferon- γ in response gp100 and tyrosinase peptides.¹³ Previous work also has shown that MART-1 peptide-specific CD8+ T-cell clones obtained from the aqueous humor and peripheral blood of VKH patients are capable of lysing melanocytes and melanoma cells in an HLA-A2-restricted manner.¹⁴ This phenomena also was observed in a patient with sympathetic ophthalmia, which also features autoimmune disease targeting organs that contain melanocytes, including the eye, ear, skin, and meninges.¹⁴

The TILs from the patient responded to epitopes of MART-1 and gp100 peptides, and ocular and systemic autoimmune sequelae would seem to be an inherent risk of melanoma immunotherapy. After a variety of immunotherapeutic regimens, uveitis has been reported previously, albeit infrequently. In 1974, Donaldson et al¹⁵ reported the occurrence of uveitis and vitiligo after bacillus Calmette-Guérin therapy for malignant melanoma. More recently, antibody blockade of CTLA-4 along with IL-2 administration with and without vaccination with gp100 was associated with uveitis and other systemic autoimmune manifestations.^{16,17} The development of the VKH after the successful surgical removal malignant melanoma also has been observed.^{18,19} In one of these cases, metastatic disease occurred several years after the initiation of systemic immunosuppression; however, the precise relationship of metastatic melanoma to immunosuppression was not clear.¹⁸ Vitiligo in the absence of uveitis has been described in patients undergoing melanoma immunotherapy and has been associated with melanoma regression.²⁰⁻²³

When uveitis has occurred in other patients treated with melanoma immunotherapy using adoptive cell transfer of TILs, the previously described cases have been mild and reversible with topical corticosteroid therapy.⁷ Twenty-five patients were treated with the same intensive preparative chemoreduction regimen used in the patient reported herein. Although mild anterior uveitis was seen in other patients, this patient was the only 1 of the 25 to experience the severe bilateral panuveitis and systemic autoimmune manifestations resembling VKH syndrome.

The severity of the ocular and systemic sequelae in this patient was remarkable, and his clinical course may have implications from both efficacy and safety standpoints. At the 24-month follow-up, the patient remained in a durable, ongoing, and complete remission; however, during this same period, ocular autoimmunity was recurrent and persistent. His degree of autoimmunity parallels data from the pmel-1 murine model of melanoma,²⁴ in which tumor response seems to be significantly correlated with ocular autoimmunity.²⁵ Systemic immunosuppression, the most desirable therapy for bilateral, recalcitrant noninfectious uveitis, was not an option because of concern of abrogating the melanoma tumor surveillance conferred by the patient's prior TIL therapy. Local therapies with topical corticosteroids, periocular triamcinolone acetonide, and IVTA provided only modest benefit during the exacerbations of the patient's uveitis.

Interestingly, acetazolamide did seem to decrease the CME on several occasions. Acetazolamide is thought to increase the outward active transport of fluid past the blood-retinal barrier²⁶ and has been used successfully for the treatment of retinitis pigmentosa-associated CME²⁷ and to decrease angiographic edema associated with endogenous uveitis.²⁸ The electro-oculogram changes also are supportive of alterations in retinal pigment epithelium (RPE) barrier function. The precise pathogenic mechanisms underlying these changes are unclear; however, the authors hypothesize that underlying choroidal inflammation might have played a role in mediating the RPE dysfunction that was ameliorated with acetazolamide therapy. The alterations in perifoveal and foveal sensitivity by microperimetry-1 testing suggest that the RPE dysfunction and subsequent photoreceptor damage in this patient likely represents a diffuse process. In patients with uveitis, a diffuse pattern of macular edema may be observed in up to 55% of patients.²⁹

Besides alterations in RPE function, other inflammatory mechanisms likely played a role in the patient's persistent uveitis and chronic macular edema. The proinflammatory cellular and cytokine milieu of the aqueous fluid were suggestive of persistent uveal inflammation, which responded partially to local corticosteroids. However, the systemic persistence of melanocyte-reactive T cells, loss of integrity of the blood-aqueous barrier, and possibly defective T-cell regulation also might have contributed to his persistent, recurrent course.

The patient's unique constellation of symptoms and signs were reminiscent of the VKH syndrome and highlights the balance between tumor surveillance and loss of self-tolerance. The ability to target antigens common to both systemic neoplasm and ocular tissues may offer valuable insights into the mechanisms underlying ocular autoimmunity. Judicious monitoring of patients for ophthalmic complications associated with melanoma immunotherapy will be paramount for future treatment strategies.

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Figure 1.

Computed tomography scans showing (A) bulky supraclavicular lymph nodes (yellow arrows) and (B) an abdominal mass (green arrow) and subcutaneous disease (blue arrow) in July 2006 before tumor-infiltrating lymphocyte (TIL) plus interleukin-2 (IL-2) therapy. Computed tomography scans obtained in December 2006 showing that (C) the supraclavicular lymphadenopathy has regressed (yellow arrows) coincident with (D) the disappearance of the intra-abdominal lesion (green arrow) and subcutaneous lesion (blue arrow). Photographs of the patient (E) obtained at baseline in July 2006 and (F) after therapy in November 2006 showing whitening of the hair and eyebrows. The patient also experienced poliosis in both eyes (not shown).

Figure 2.

A and B, Fundus photographs obtained in October 2006 (3 months after tumor-infiltrating lymphocyte therapy) showing normal optic nerves, vessels, and maculae with moderate pigmentation in both eyes. **C and D,** Repeat fundus photographs obtained 7 months later in May 2007 showing a sunset-glow fundus with diffuse hypopigmentation of the choroid and retinal pigment epithelium in both eyes.

Figure 3.

A, Initial electro-oculogram showing Arden ratios of 2.98 in the right eye and 3.02 in the left eye in November 2006. **B**, Electro-oculogram obtained in May 2007 showing that Arden ratios are elevated to 4.10 in the right eye and 4.51 in the left eye, likely because of a decrease in the dark trough amplitudes in both eyes.

Figure 4. Microperimetry-1 10-2 evaluation obtained in November 2007 showing diffuse perifoveal depression, which was less pronounced in (A) the right eye than in (B) the left eye. C and D, Optical coherence tomography at this time showed no evidence of cystoid macular edema in either eye, suggesting that the decrease in sensitivity may be the result of photoreceptor dysfunction.

Figure 5.

T-cell flow cytometry and interferon- γ (IFN- γ) response to antigen stimulation. **A**, Before adoptive cell transfer (ACT), no CD8+ MART-1 tetramer-positive cells were observed in the peripheral blood lymphocytes (Pre ACT PBL), and 4.5% of the infused treatment (Tx) tumor-infiltrating lymphocyte (TIL) cells were CD8+MART-1 tetramer-positive. After TIL therapy, 2.5% of peripheral blood T cells (Post ACT PBL) were CD8+MART-1 tetramer-positive and 3.9% of ocular-derived T cells (Post ACT Eye) were CD8+MART-1 tetramer-positive. Bar graphs showing that with antigen stimulation on coculture with **(B)** MART-1₂₆₋₃₅ and gp100₂₀₉₋₂₁₇ peptide-bearing target cells or **(C)** HLA-A2+ melanoma cells, increased human IFN- γ was observed from the patient's peripheral blood lymphocytes (Post ACT PBL) and ocular-derived cells (Post ACT Eye) compared with 2 normal donor peripheral blood lymphocytes (PBLs) and the patient's pretreatment PBL.

Figure 6.

Optical coherence tomography (OCT) and response of cystoid macular edema (CME) to acetazolamide. **A**, Spectral-domain OCT scan obtained in September 2007 while receiving acetazolamide therapy showing moderate CME in the left eye with **(B)** a corresponding retinal contour map with a central retinal thickness of 392 μm . **C** and **D**, one month after acetazolamide cessation, an increase in CME to 535 μm was observed with loss of the foveal contour. The foveal contour and CME improved 2 weeks after restarting acetazolamide. **E** and **F**, Central retinal thickness was 215 μm .

Figure 7.

Flow cytometry from aqueous humor obtained during cataract surgery in May 2008 that differs from the previous sample obtained in June 2006. Cells obtained (left column) from aqueous humor and (right column) after in vitro T-cell expansion were stained with: (A) gp100 tetramer and immunoglobulin G (IgG)-negative antibody controls, (B) MART-1 tetramer and anti-CD3 antibody, (C) and anti-CD8 with anti-CD3 or MART-1 tetramer. None of the ocular infiltrating cells had T-cell receptors that recognized MART-1 or gp100 melanoma tumor antigens.