Acute Myeloid Leukemia Manifesting Initially as a Conjunctival Mass in a Patient With Acquired Immunodeficiency Syndrome

The ophthalmic manifestations of human immunodeficiency virus (HIV) infection range from molluscum contagiosum of the eyelid to cotton-wool spots of the retina.1-4 Additionally, HIV infection is associated with several opportunistic cancers of the eye and orbit,2 including conjunctival squamous cell carcinoma,3 Kaposi sarcoma,4 and non-Hodgkin lymphoma.4 In this report, we illustrate the rare association of HIV infection with acute myeloid leukemia that manifested initially as an epibulbar mass.

Report of a Case. A 47-year-old African American man with acquired immunodeficiency syndrome (AIDS) who was being treated with highly active antiretroviral therapy developed bilateral pink conjunctival lesions during a 2-week period. There were 3 lesions noted on the bulbar conjunctiva of each eye (Figure 1). The subconjunctival tumors measured up to 7 mm in basal diameter and 2 mm in thickness and had no apparent intrinsic vasculature. Dilated, tortuous blood vessels fed each tumor. Visual acuity was 20/20 OU, and both fundi were normal.

Excisional biopsy of one of the lesions was performed to rule out Kaposi sarcoma, non-Hodgkin lymphoma, leukemia, or an opportunistic infection. Routine histopathologic examination showed a diffuse infiltrate of poorly differentiated malignant cells that had large, irregular vesicular nuclei, prominent nucleoli, and relatively abundant cytoplasm (Figure 2A). The cells showed positive immunoreactivity for CD43 (myeloid marker), lysozyme (leukocyte marker), and KP-1 (CD68, monocyte cytoplasmic antigen marker). They stained negative for lymphocyte markers CD20 (B lymphocyte marker) and UCHL-1 (T-lymphocyte marker), cytokeratin (epithelial marker), and melanoma markers HMB-45 and S100 protein. A stain for myeloperoxidase was weakly positive, and the Leder chloroacetate esterase stain disclosed cytoplasmic granules in tumor cells evincing granulocytic differentiation (Figure 2B). The findings were consistent with granulocytic or myeloid sarcoma. Myeloid sarcoma indicates tissue involvement by acute myeloid leukemia cells.

The patient reported previous small subcutaneous lesions on his arms, back, abdomen, and legs, most of which had appeared and regressed during the prior 10 weeks. An excisional biopsy specimen of one of the skin tumors originally was diagnosed elsewhere as a high-grade lymphoma, but the tumor was reclassified by the National Cancer Institute as an immature hematopoietic malignancy consistent with myeloid sarcoma with monocytic differentiation. Additional immunohistochemical studies performed at the National Cancer Institute confirmed that the tumor cells were reactive for lysozyme, KP-1, and CD43 but were negative for CD20 (B lymphocyte marker), CD79A (B lymphocyte marker), myeloperoxidase (leukocyte marker), CD30 (B lymphocyte, T lymphocyte, and monocye marker), CD34

Figure 1. The left eye of a patient with acquired immunodeficiency syndrome shows a pink bulbar subconjunctival mass with dilated feeder vessels.

Figure 2. A, A photomicrograph shows a section of conjunctival granulocytic sarcoma with large cells, prominent nuclei, eosinophilic nucleoli, and relatively abundant cytoplasm (hematoxylin-eosin, original magnification ×250). B, A photomicrograph of a section of conjunctival granulocytic sarcoma stained with Leder chloroacetate esterase demonstrates the presence of cytoplasmic lysozyme granules (original magnification ×250).
Acute myeloid leukemia occurs most commonly in white men, and its incidence increases with age. The average age at diagnosis is older than 65 years. The initial symptoms of acute myeloid leukemia include fatigue, weight loss, bleeding, easy bruising, and susceptibility to infection. The incidence of acute myeloid leukemia in patients with AIDS is approximately 2-fold compared with the general population. Acute myeloid leukemia is caused by numerous nonrandom chromosomal abnormalities, the majority of which are translations, and environmental carcinogens.

Granulocytic sarcoma is a variant of acute myeloid leukemia that occurs as an invasive solid mass, most frequently in bone. Zimmerman and Font described 33 patients with granulocytic sarcoma of the ocular tissues, involving the orbit (26 patients), eyelid (4 patients), lacrimal gland (3 patients), uveal tract (2 patients), and conjunctiva (1 patient). In 52% of these patients, hematologic evidence of leukemia was present at diagnosis. In 88% of patients, the ophthalmic lesion was the initial sign of leukemia. In a series of 121 children from Turkey with acute myelomonocytic leukemia (M4), 27% presented with granulocytic sarcoma in either the orbit or eyes.

The pink conjunctival tumors present in our patient were initially suspicious for Kaposi sarcoma, lymphoma, or leukemia. All 3 malignancies can be associated with HIV infection. The immunodeficient patient should be watched carefully for opportunistic infections and malignancies. Appropriate diagnosis is crucial for providing proper treatment. Thus, in addition to Kaposi sarcoma, non-Hodgkin lymphoma, and squamous cell carcinoma, acute myeloid leukemia should also be recognized as a conjunctival malignancy associated with AIDS.

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mal layers were measured and analyzed. The advantages of in vivo confocal microscopy for microstructural analysis of a living human cornea might provide useful information about the natural history of crystal deposition and growth throughout the stromal layers in subjects with cystinosis.

Infantile nephropathic cystinosis may affect vision due to corneal disease, retinopathy, or glaucoma.1 Of these 3 complications, glaucoma is the one most commonly associated with significant visual loss in adult subjects.2 Corneal crystals may be observed as early as age 1 year, but they generally have a benign course and rarely cause severe visual loss, although photophobia is a common symptom.3 Recently, corneal crystals have been successfully treated with cysteamine drops.3,4

**Report of a Case.** A 24-year-old man received a diagnosis of cystinosis at the age of 14 years and underwent renal transplantation at the age of 22 years. From the age of 1 year he was treated with oral cysteamine hydrochloride that was changed to oral cysteamine bitartrate because of a manufacturer’s change in 1999. He has always been aware of having photophobia but reported a worsening of his symptoms following the change in his systemic medication; however, because of serious life-threatening problems, his eye symptoms have been considered less important. Unfortunately, the subject cannot be offered treatment with topical cysteamine drops because the medication is currently not registered in New Zealand.

The subject’s examination in our unit included photobiomicroscopy, in vivo confocal microscopy, tonometry, and fundus dilatation. The subject had a visual acuity of 6/6 OU. Slitlamp biomicroscopy revealed dense, hyperreflective cysteine crystals corresponding to a score of 2.75 to 3.00 in both eyes based on the library published by Gahl et al.3 Careful examination of the optical section revealed a random distribution of the crystals throughout the corneal thickness; however, there was apparently greater density toward the limbus (Figure 1).

Crystals were also identified over the anterior surface of the iris. Intraocular pressures were 12 and 13 mm Hg, OD and OS, respectively, and there were no signs of posterior segment involvement.

**Results.** The methodology for in vivo confocal examination has been published previously.5 In the case reported herein, 4 passes at a 900-µm working distance were used. To minimize image glare and reflections from the hyperreflective crystals, the intensity of the light was decreased to approximately half the usual intensity for human subjects. The bright reflections prevented visualization of the cellular elements of the stroma, but the endothelial mosaic and superficial epithelial layers were clearly recognizable. Only

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**Figure 1.** Slitlamp biomicroscopy of the cornea demonstrating dense hyperreflective cysteine crystals distributed throughout the entire cornea of the right (A) and left (B) eyes. Careful examination of the optical section reveals random distribution of the crystals throughout corneal thickness (C and D).
the central cornea was examined because the reflections from the peripheral cornea were very bright. Two acquisitions were performed for each eye and a total of 900 images were saved onto a hard disk drive. Despite being very photophobic the subject had no difficulties undergoing the examination.

In vivo confocal microscopy visualized the crystals in detail and their appearance in both eyes was very similar. Immediately in front of Descemet membrane the crystals were dense and polyhedral, the longitudinal and transverse diameters measuring $85 \pm 37 \mu m$ to $43 \pm 29 \mu m$ (mean±SD) (n=50 measurements), respectively. Anteriorly, a few larger crystals were highlighted; however, most of the smaller crystals were needle shaped. Crystals in the anterior fifth of the stroma appeared to be crisscrossing and of similar density, with longitudinal and transverse diameters measuring $57 \pm 41 \mu m$ to $21 \pm 17 \mu m$ (mean±SD) (n=50 measurements), respectively. However, quantitative assessment suggested that crystal density was lowest in the middle stroma (Figure 2). The corneal endothelium and epithelium appeared to be normal in respect to structure and cell density; however, stromal keratocytes were shadowed by the crystals thus making evaluation impossible.

Comment. The cornea has been called “the window to cystinosis”; however, the cause for the severity and progression of the corneal presentation is still not clear. It has been proven that cysteamine drops may have a beneficial effect in up to 62% of symptomatic patients and patients with recurrent erosion syndrome. However, the effect of the medication has been evaluated “semi-quantitatively” on the basis of clinical photography.

We report the application of in vivo confocal microscopy for imaging both corneas of a subject who has nephropathic cystinosis. By careful modulation of the confocal settings, the crystals can be visualized in detail, providing an excellent opportunity for qualitative and quantitative analysis. We found the central cornea to be best for analysis in our subject, but we believe that this site may be beneficial for several reasons: the central cornea is thinner with fewer crystals, providing easier structural discrimination and measurement, the examination can be repeated using the pupillary margin as a landmark, and, finally, the dynamics of the central cornea may be more closely associated with the patient’s symptoms such as photophobia and glare. In addition, the examination by in vivo confocal microscopy is relatively quick (2-5 minutes) and in this report our subject coped well with the procedure with no unusual symptoms.

An alternative method of examination in these subjects is ultrasound biomicroscopy (UBM). The advantage of this technique is visualization of a larger area of the cornea and adjacent structures including the conjunctiva, iris, anterior chamber angle, and lens. However, owing to low magnification, comparable to the conventional slit-lamp, UBM provides only a semi-quantitative analysis of the corneal
crystals.2 Our report demonstrates the advantage of in vivo confocal microscopy, not only in visualizing the crystals but also in accurately measuring their dimensions. In vivo confocal microscopy will equally cover the same age groups as previously examined by UBM (>16 years); however, it might provide better follow-up of the corneal changes especially following application of cysteamine eyedrops.2

Our in vivo confocal observations of the distribution of the corneal crystals throughout the corneal thickness (z-dimension) did not concur with the slitlamp observations. In the latter the crystals appeared to be evenly distributed throughout the optical slice, whereas, confocal microscopy highlighted greater density anteriorly and posteriorly, with least crystal density in the middle stroma. By isolating the area of interest, confocal microscopy offers the advantage of minimizing the effect of adjacent regions and in the future might provide useful information about the natural history of crystal deposition and growth throughout the stromal layers in subjects with cystinosis.

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# Lymphoepithelial Carcinoma of the Lacrimal Gland

The association of benign lymphoepithelial lesions with Sjögren syndrome is well recognized; however, such lesions can also develop in patients without clinical features of this syndrome.3 The lymphoid infiltrate or the epithelial component of the lymphoepithelial lesions can undergo malignant transformation, resulting in B-cell lymphomas or lymphoepithelial carcinoma. The development of such carcinomas in the salivary glands and other sites has been amply documented.2-5 Recently, Bloching et al6 briefly described a lacrimal gland tumor, which they called “lymphoepitheloma-like carcinoma.” The tumor they described could be the first reported case of lymphoepithelial carcinoma. In the present article, we describe in detail the clinical and histopathologic features of a primary lacrimal gland lymphoepithelial carcinoma with immunohistochemical and molecular analysis.

Report of a Case. A 63-year-old white woman visited an ophthalmologist with a history of dry eyes, “fullness” around the superotemporal aspect of the left eye, proptosis, and binocular horizontal diplopia on left gaze, during the past several months. She gave no reports of pain, local tenderness, or headache. Her medical history was significant for obesity and hypothyroidism; the latter was being treated with levothyroxine sodium. On examination, visual acuity was 20/25 OU. There was no afferent pupillary defect, and color vision was normal. The left eye was proptotic, and Hertel exophthalmometry measurements were 14 mm OD and 20 mm OS across a base of 100 mm. There was mild-to-moderate resistance to retropulsion of the left globe. The patient was orthophoric in all gaze positions except for left gaze, where she had a 15-diopter esotropia. Ductions were full except for a 20% limitation of left eye abduction. Visual field and funduscopy findings were unremarkable. The clinical impression was a benign mixed tumor of the lacrimal gland. Computed tomographic scans of the orbit showed an enlarged left lacrimal gland without bone involvement, and magnetic resonance imaging scans revealed a solid, 3-cm mass in the region of the lacrimal fossa. The mass was somewhat homogenous with respect to signal, and enhanced with gadolinium (Figure 1). The patient underwent en bloc excision via Kronlein lateral orbitotomy, and the entire mass was removed with care to avoid rupture of the pseudocapsule of the presumed benign mixed-cell tumor. However, there was adherence to the posterior lateral scleral wall that required shaving off the sclera. The patient subsequently received 3500 rad (35 Gy) of radiotherapy to the left orbit. Six months following the treatment, she had full levator function and 20/25 visual acuity without recurrence or metastasis.

Figure 1. A, Computed tomographic scan of the left orbit shows a large mass occupying the lacrimal fossa and lateral orbit. B, Magnetic resonance imaging scan of the left orbit shows a large lacrimal mass.
The orbital tumor was roughly oval and measured 31 × 29 × 28 mm. The mass appeared partially encapsulated, and the cut surface was tan-white. Histologic examination of the tumor revealed a circumscribed mass containing irregularly shaped nests of epithelial cells, dense lymphocytic infiltrates, lymphoid follicles containing germinal centers, and fibrous tissue stroma (Figure 2). The epithelial nests were frequently permeated by lymphocytes, and small islands of these epithelial cells were widely separated by the lymphoid infiltrates and fibrous septae (Figure 3). The undifferentiated epithelial cells showed indistinct cell boundaries and eosinophilic cytoplasm containing large vesicular nuclei and prominent nucleoli. There were frequent abnormal mitotic figures (Figure 2, inset). The carcinoma cells formed cords, small irregular nests, and syncytial aggregates, distinctly surrounded by lymphoid-rich stroma (Figure 3). The lymphoid infiltrate was primarily made up of small lymphocytes admixed with a few plasma cells and occasional polymorphonuclear leukocytes and eosinophils.

On immunohistochemical analysis, the epithelial component stained positive with Pan-keratin (Ventana Medical Systems Inc, Tucson, Ariz), and the lymphoid infiltrate was positive for common leukocyte antigen (Figure 4). These stains confirmed the presence of permeated leukocytes in the nests of epithelial cells. The lymphoid-rich stroma were mainly stained with CD-3 (Pan T-cell marker; Figure 5 A). The CD-68–positive (macrophage marker) cells were seen encircling the lobules and cords of neoplastic cells (Figure 5 B). The CD-20–positive (B-cell marker) cells were present mainly in the lymphoid follicles, whereas the CD-3–positive cells were widely distributed. This heterogeneous lymphoid and mononuclear cell infiltration was also noted in the lacrimal gland tissue present at the periphery of the tumor (Figure 2). The morphologic features, in addition to the immunohistochemical results, were supportive of the diagnosis of lymphoepithelial carcinoma of the lacrimal gland.

Immunohistochemical (DAKO, Carpinteria, Calif) and in situ hybridization tests to detect Epstein-Barr viral antigen and the viral genome gave negative results (Enzo Diagnostics, Farmingdale, NY). The polymerase chain reaction (PCR) using paraffin-embedded sections of the tumor, and primers specific for Epstein-Barr virus (forward primer L1 [5’-GTTAGATCTTACCAAGTAA-3’] and reverse primer L2 [5’-TTATGAGTGACTGGACTGAGGA-3’])7 showed the absence of amplified products.

Comment. The present case shows the typical histopathologic features of lymphoepithelial carcinoma, characterized by islands of undifferentiated large carcinoma cells permeated and enveloped by an admixture of T lymphocytes, macrophages, and a few B lymphocytes (Figures 2 and 3). These histologic features are virtually identical to those seen in lymphoepithelial carcinomas occurring in the salivary glands and other sites.3,4 Under low magnification, the lacrimal gland carcinoma showed indistinct epithelial components and distinct heavy infiltration of lym-
phoid cells, simulating a lymphoma. Higher magnification disclosed nests of malignant epithelial cells, exhibiting eosinophilic cytoplasm with ill-defined cell borders and frequent abnormal mitotic figures (Figure 2, inset). Although lacrimal gland acini were seen juxtaposed to the malignant epithelial lobules, the lacrimal gland acini did not show epimyoepithelial proliferation, but local lymphocytic infiltration was present. These features, as well as the gross appearance of the lacrimal gland, suggest that the tumor arose de novo from the lacrimal gland rather than from a preexisting benign lymphoepithelial lesion. Although the patient was not given a workup for Sjogren syndrome, her history of unilateral dry eye in the involved eye, unaccompanied by dryness in any other body part, makes the diagnosis of Sjogren syndrome less likely, and accordingly supports a de novo origin of the tumor.

There is a proclivity for the occurrence of nasopharyngeal and salivary gland lymphoepithelial carcinomas in individuals with Mongolian ancestry. The carcinoma can also develop in individuals with non-Mongolian ancestry, but this group constitutes less than 15% of such carcinomas. The tumor affects both sexes, with a female-male ratio of 1.5:1.0. Familial clustering of nasopharyngeal lymphoepithelial carcinomas has been previously reported. The age at diagnosis ranges from 10 to 86 years, with a median age of approximately 40 years. Although the present patient with the lacrimal gland lymphoepithelial carcinoma was a 63-year-old woman, she has no known Mongolian lineage, and there is no history of the occurrence of such tumors in her family.

Lymphoepithelial carcinomas, in particular those occurring in the nasopharynx, are often associated with Epstein-Barr virus infection. Such an association is present in a significant number of individuals with Mongolian ancestry, but it is rarely seen in non-Mongolian people. The tumor samples from this patient were negative for Epstein-Barr virus infection when examined by the immunohistochemical stain, in situ hybridization, and PCR methods.

The characteristic lymphoid infiltration seen in lacrimal gland carcinoma consists primarily of T lymphocytes, followed by CD-68-positive macrophages and B lymphocytes (Figure 5). The predominant presence of T-lineage cells suggests that cell-mediated immunity may play a role in the tumor progression and metastasis. Overall, irrespective of their site of origin, lymphoepithelial carcinomas carry a better prognosis than similar carcinomas that are devoid of such lymphoid infiltration. It has been proposed that the T-cell-mediated immunity and the cytokines generated by these cells may contribute to long-term survival.

Lymphoepithelial carcinoma shows histopathologic features similar to those noted in benign lymphoepithelial lesions; however, the former is distinguished by the presence of malignant cytologic features in the epithelial structures and by the invasion of adjacent tissues. Large-cell lymphomas, histiocytic neoplasms, and amelanotic melanoma need to be considered in the differential diagnosis, but immunohistochemical methods can distinguish these tumors from lymphoepithelial carcinoma.
Because of the rarity of lymphoepithelial carcinomas of the lacrimal gland, optimal therapy is unknown. The rationale for therapy in our patient was based on the clinical experience with the more common lesion in the salivary gland, which shows improved survival with surgical excision of the mass, followed by irradiation. Although lymphoepithelial carcinoma rarely occurs in the lacrimal gland, our immunohistochemical and molecular studies suggest that its pathogenesis at this site may be independent of previous Epstein-Barr virus infection.

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**Diffuse Hyperplasia of Intratarsal Ectopic Lacrimal Gland Tissue**

Diffuse bilateral ectopia of lacrimal gland tissue in the tarsal plate has not been recorded previously, to our knowledge. This abnormality was studied in tissue removed from a middle-aged female patient who had bilateral nongranulomatous conjunctivitis and superficial punctate keratopathy. In addition, the patient had microcore myopathy, hypertension, and brittle diabetes mellitus. Clinical investigation revealed surface irregularities in the tarsal plate, and morphologic studies demonstrated large ectopic glands throughout the tarsal plate. Chronic inflammatory cell infiltration was present in the perilacrical fibrous tissue, and this progressed to fibrofatty replacement of the glandular tissue. Dilatation of the ductules suggested that blockage of the acinar secretions led to, or was caused by, chronic inflammation in the overlying conjunctival stroma. The symptoms were relieved after excision of both tarsal plates.

Ectopic lacrimal glands on the bulbar conjunctiva within the uveal tract and on the surface of the cornea are a well-recognized source of choriostomatous tumors, which are usually identified in early childhood. When ectopic lacrimal gland tissue gives rise to tumors in the orbit, the age of the patient may vary between childhood and middle age. Retention of secretions at this site has led to the formation of pseudotumors. In this report, we describe a diffuse bilateral hyperplasia of ectopic lacrimal gland tissue within the upper tarsal plates in association with chronic keratoconjunctivitis.

**Report of a Case.** A 58-year-old woman had poorly controlled diabetes for many years. She was referred by specialists in diabetes to the university eye department because she complained of a reduction in vision and severe photophobia. Twelve months prior to this, she had an allergic blepharitis when she received new spectacles. On examination, she was found to have superficial punctate keratopathy, although tear function was normal. Her visual acuity was 20/120 OD and 20/80 OS, and the intraocular pressure was normal in both eyes. Mild background diabetic retinopathy was noted on funduscop[y. Extraocular movements and eyelid function were normal. On eversion, the upper tarsal conjunctiva on each side contained numerous concretions, and deeper in the tarsal plate there were multiple small mounds (Figure 1). The lower tarsus was normal on each side. A biopsy specimen was obtained from the tarsal plate on the left side, and following the initial pathologic analysis, the left tarsal plate was resected. The keratoconjunctivitis settled in the left eye. There was a similar clinical outcome after the right tarsal plate was resected.

The patient had severe insulin-dependent diabetes for 21 years. Since 1995, she had complained of progressive weakness in her limb muscles. When she attended the Tennent Institute (Glasgow, Scotland), she was unable to lift herself from her wheelchair; her shoulder muscles were extremely wasted. A muscle biopsy in 1995 revealed a microcore myopathy (David Doyle, MD, Institute of Neurological Sciences, Glasgow).

The patient is a carrier of cystic fibrosis and she has 1 daughter who is also a carrier and 1 grandson who is asthmatic and requires inhaler but does not have cystic fibrosis. The daughter and the grandson do not have ocular disease.

The biopsy specimen measured 4 x 2 x 2 mm, and the left and right tarsal plate resections measured approximately 12 x 8 x 5 mm. Each specimen was fixed in 2% buffered glutaraldehyde, and samples were obtained for routine paraffin histologic analysis (hematoxylin-eosin and periodic acid-Schiff stains). For conventional transmission, electron microscopy using toluidine blue for semithin sections was performed. The morphologic features were essentially the same in each of the specimens.
In some areas, the conjunctival epithelium was hyperplastic and goblet cells were plentiful, while elsewhere the epithelium was atrophied or ulcerated. Surface stratification was not present, and the pattern was not that of keratoconjunctivitis sicca. The superficial stroma contained a dense nongranulomatous chronic inflammatory infiltrate and dilated lymphatics. Pseudoglands of Henle were prominent and many were enlarged by concretions. The tarsal plate contained large ectopic lacrimal gland elements, which retained identifiable architecture and almost extended to the surface epithelium (Figure 2). In most heterotopic glands, there was no evidence of a hilum, and the acinar tissue was distorted and infiltrated by fibrous tissue that contained a lymphocytic infiltrate. Fibrofatty tissue surrounded and penetrated some lobules. Dilated ductules were present within the glands and superficial stroma. The acinar cells possessed eosinophilic cytoplasm in some lobules, but in many atrophic lobules the cells were small and the cytoplasmic staining was weaker. In the well-preserved lobules, the acini appeared to be hyperplastic and the normal cuboidal architecture of the epithelial cells was lost (Figure 3). In some areas, the acini were surrounded by fibrous tissue and appeared shrunken and distorted. The presence or absence of secretory granules was easily determined in appropriately stained semithin sections; many acinar cells were devoid of these organelles. The ductules were of normal appearance. In fortuitous section planes it was possible to see a tubuloacinar architecture (Figure 3).

At the ultrastructural level, the cuboidal acinar cells contained lipid droplets and a variable number of secretory granules located in the apical part of the cell (Figure 4A). The intercellular attachment systems and the basal lamina were identifiable but the apical microvillar surface was flattened. The hyperplastic acini contained cells that were enlarged by swollen mitochondria, accompanied by irregular distribution of the secretory granules and the organelles throughout the cytoplasm (Figure 4B). In the latter acini, the normal intercellular attachments were disorganized, and in parts, the basement membrane was lost. Myoepithelial cells, nonmyelinated nerve fibers, and lymphocytes were in the interstitium. Viral particles and bacterial and fungal elements were not identified.

**Comment.** The presence of numerous lacrimal gland elements within the tarsal plates in the specimens analyzed in this case of chronic keratoconjunctivitis was an unex-

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**Figure 1.** The appearances of the right (A) and left (B) upper tarsal plates. Note the pale nodular areas beneath the yellow concretions.

**Figure 2.** A, A lobule of lacrimal gland tissue with a disorderly arrangement of the acini is located in the tarsal plate beneath the conjunctival stroma, which contains a nongranulomatous infiltrate. The acinar tissue is atrophic and surrounded by fibrous bands. Fibrofatty tissue surrounds the lobule (hematoxylin-eosin; original magnification ×100). B, In some lobules, the acinar cells retain eosinophilic cytoplasm in contrast to those in a lobule that is almost entirely replaced by fibrous tissue. Note the dilated ductules in the lobules (hematoxylin-eosin; original magnification ×100).
Figure 3. A. While some acini possess a cuboidal monolayer, others are filled by cells that are irregularly arranged (hematoxylin-eosin; original magnification ×350). B. Dense fibrous tissue distorts the surviving acini (toluidine blue/semithin section; original magnification ×200). C. The tubuloacinar pattern in the lobules demonstrates the similarity of the tissue to accessory lacrimal gland tissue. Note the secretory granules in the acinar cells (toluidine blue/semithin section; original magnification ×350). D. Cells with vacuolated cytoplasm are within the acini (toluidine blue /semithin section; original magnification ×400).
expected finding. The glands were identified beneath the concretions overlying the center of the tarsal plate. This excluded the possibility that the lacrimal gland elements were the normal accessory lacrimal glands of Wolfring, which are located in the upper end of the tarsal plate and are usually small and inconspicuous. In the accessory lacrimal glands located in normal sites, the acini and tubules contain cells that form epithelial monolayers in a tubuloepithelial pattern (unlike the tubulocinar pattern of the lacrimal gland). Thus, the intratarsal glands should be regarded as ectopic accessory lacrimal glands.

In some lobules, periacinar fibrosis was prominent and there was evidence that continuing inflammation had led to fibrofatty replacement of preexisting ectopic lacrimal glands. The presence of chronic inflammation and repair in the ectopic lacrimal tissue in the tarsal plate was similar to that found in the ectopia of lacrimal gland tissue in the orbit, where presumably there was obstruction to outflow secretion. In contrast, the lacrimal gland component of a choristoma in the upper eyelid possessed normal histologic characteristics, presumably because tear flow was not obstructed. In many of the case reports of intraocular lacrimal gland choristomas, the acinar architecture was described as being well preserved and inflammatory infiltration was minimal, although cyst formation was common. In our case, it was possible to demonstrate dilatation of the ducts and retention of secretion in the ductules so that inspissation could be an acceptable explanation for the periacinar inflammatory infiltrate. An alternative possibility is that there could have been an extension from the inflammatory process in the conjunctiva.

At the ultrastructural level, it was of interest to compare the features of ectopic glands with those of normal accessory glands and an intraocular lacrimal gland choristoma. There was much similarity among the 3 entities but the main differences were the presence of an inflammatory infiltrate in the ectopic tarsal glands and the changes that had occurred in the acinar cells. Within individual acini, there was cytoplasmic rarefaction and vacuole formation in degenerating cells, a feature that is absent from descriptions of accessory glands or a choristoma. One feature of normal accessory lacrimal glands is an irregular distribution of secretory granules; this was a common feature in many of the cuboidal and hyperplastic acinar cells in the specimens in our case.

Hyperplasia in the acini of the ectopic lacrimal glands could be explained by the chronic nongranulomatous inflammation in the conjunctival stroma and eyelids, leading to the production of growth factors, eg, fibroblastic growth factor, which has been identified in the normal lacrimal gland after damage to the cornea. In transgenic mice that have been engineered to overexpress fibroblastic growth factor, ectopic glands will form in the cornea, and ectopic lacrimal buds will form in ocular explants that are exposed to fibroblastic growth factor. It is not unreasonable to suggest that growth factors could have entered the tarsal plate to stimulate proliferation in pre-existing ectopic acinar cells in the 12-month period during which there was chronic inflammation in the tarsal conjunctiva.

The fact that the patient is a carrier for cystic fibrosis could be a contributory factor in the patient's keratitis. One study has shown that patients with full-blown cystic fibrosis have severe xerophthalmia, although a carrier status is not generally recognized as a risk factor for ocular surface problems. In cystic fibrosis, ocular surface disease may be the consequence of vitamin A deficiency due to malabsorption, or to changes in the production or stability of the tear film. In our case, some sectors of the conjunctival epithelium were hyperplastic with numerous goblet cells; this supports the clinical observation that the patient did not have keratoconjunctivitis sicca.

The association of ocular surface disease with a muscle wasting disease is intriguing but probably irrelevant. Microcore myopathy or multicore myopathy is manifest as central areas within enlarged muscle fiber in which there is negative staining for phosphorylation, adenosine triphosphatase, and glycogen.
these areas, mitochondria are absent and the Z-bands exhibit streaming on electron microscopy. A few case reports refer to ocular disease in myopathy, although in one report, a 15-year-old patient with myopathy was described as having features of ectodermal dysplasia, conical teeth, scaly skin, and sparse hair, without evidence of ocular surface disease.

The most acceptable proposal for the pattern of disease in our case is that the ectopic lacrimal glands were present at birth and were innocuous, but the isolated attack of blepharoconjunctivitis initiated conjunctival stromal inflammation and fibrosis, which led to ductal compression, retention of secretions, and consequent chronic inflammation in the ectopic glands. This started a vicious circle of conjunctivitis and dacryoadenitis that was self-propagating. Resolution of the keratitis after resection of the tarsal plate (by removing inflamed tissue) supports this explanation.

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Idiopathic Central Retinal Vein Occlusion in 2 Siblings With the 20210 G→A Prothrombin Variant

Genetic variations in clotting factor genes may be very important in both venous and arterial thrombosis. Inherited thrombophilia has been associated with a deficiency of anticoagulant proteins such as protein C, protein S, antithrombin III (AT III), and factor V Leiden mutation. Another procoagulant mutation, located in the 3′-untranslated region of the prothrombin (PT) gene 20210 G→A PT mutation has recently been associated with an increased risk of venous thrombosis. Franco et al thought the prevalence of the PT G→A mutation was found to be 2- to 7-fold higher among patients with atherosclerotic disease than in healthy controls. Heterozygosity for the 20210 A allele was reported to be associated with increased PT (factor II of coagulation) and venous thromboembolism. We report 2 cases of retinal vein occlusion (RVO) in 2 siblings who tested positive for the clotting factor II 20210 A variant.

Report of a Case. A 38-year-old white woman (patient 1) reported painless decrease in vision of 2 days' duration in her right eye. On admission, the patient’s best-corrected visual acuity was 20/60 OD and 20/20 OS. She also had a right relative afferent pupillary defect. Slitlamp examination of both eyes was unrevealing. Applanation tonometry disclosed an intraocular pressure of 14 mm Hg OD and 18 mm Hg OS. Ophthalmoscopic examination of the patient’s right eye showed the presence of a central RVO (Figure 1A), which was confirmed by fluorescein angiography (Figure 1B). Fundus examination of the left eye revealed a normal posterior pole. One week later, visual acuity in the right eye deteriorated to 20/200 as well as the fundus aspect (Figure 1C). Her family medical history had some remarkable points. At age 33 years, she suffered from deep-vein thrombosis in her right leg. Her father had an ischemic stroke at the age of 51 years and died at 56 years. Alcohol abuse and cigarette smoking were excluded as well.

Eleven months later, the patient’s 41-year-old brother (patient 2) was admitted to our department with a diagnosis of papillophlebitis in his left eye (Figure 2). Best-corrected visual acuity was 20/30 OS and 20/20 OD. Slitlamp examination did not disclose any abnormality in the anterior segment of either eye.

Complete ophthalmic history and examination, as well as general medical history and physical examinations investigating factors associated with an increased risk of retinal vein occlusion, were obtained in both patients and were negative. Laboratory testing, including a complete blood cell count, serum chemistries, glucose tolerance, hemoglobin electrophoresis, erythrocyte sedimentation rate, serum lipids, quantitative immunoglobulins, antinuclear and anticardiolipin antibody titers, human immunodeficiency virus (HIV) serology, presence of lupus anticoagulant, and syphilis serology, had normal results. Common coagulation tests (PT, partial thromboplastin time, fibrinogen) and studies for congenital causes of hypercoagulability, including AT III, protein C, protein S, resistance to activated protein C deficiencies, and factor V Leiden mutation, were also within normal

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The mutation of PT G→A variant is linked to an increased thrombotic tendency, and has been associated with both artery and venous disease. This feature is probably mediated by various conditions. Firstly, the heterozygosity for the 20210 A allele is associated with a 25% increase in circulating PT levels. Secondly, these elevated PT levels are associated with increased thrombin formation and activation of the coagulation. Franco et al detected plasma PT levels in carriers (1.26±10 U/mL) were higher than in noncarriers (1.03±1 U/mL, P=.02). A “prothrombic” interpretation is also in keeping with the fact that 20210 mutation was originally described as a risk factor for venous thrombosis, a fact that has been confirmed in other recent studies.

In our patients, this mutation leads to an increase in plasma PT rate of the order of 30% too. In these 2 cases, who tested positive for the 20210 A mutation, the plasma PT levels were 1.62 U/mL (normal plasma PT levels=1.0 U/mL) and 1.51 U/mL, respectively. They were performed by a thromboplastin-based assay using factor II – deficient plasma (Instrumentation Laboratory UK, Warrington, England) on a Sysmex CA 6000 (Globe Scientific Inc, Paramus, NJ) coagulation analyser. Our patients represent a documented association between RVO and the 20210 G→A heterozygous genotype. Even if this correlation cannot be demonstrated solely by these patients, the history of deep-vein thrombosis at age 37 years further supports the presence of a specific thrombophilic disorder in one of these patients. Although we cannot conclude that the RVO was a direct result of the 20210 G→A mutation, this association was the only known risk factor for thromboembolism we found in these 2 patients. But this association, PT 20210 A variant and RVO, is strengthened in the first case by another relative to RVO. We have found higher plasma levels of homocysteina in the woman with RVO compared with the second case of RVO. A fact that is known as a possible new risk factor for RVO.

A laboratory evaluation for coagulopathy, including the PT 20210 A variant and homocysteinemia, may be considered in young patients with RVO or in older patients with RVO, especially those without obvious venous thrombosis risk factors and coagulopathies. Thus, this PT gene sequence variation and the homocysteine plasma levels add to the list of recognized genetic risk factors for thrombophilia. Additional genetic in-

Figure 1. A, Fundus photograph of the right eye, showing a central retinal vein occlusion with venous tortuosity, disc edema, cotton-wool spots, and hemorrhages in all quadrants. B, Fundus angiogram of the right eye (292 seconds of fluorescein injection). C, Fundus photograph of the same right eye, showing a central retinal vein occlusion 1 week later. Disc swelling, venous engorgement with flame-shaped hemorrhages on the disc and the surrounding retinal tissue.
vestigations in a sufficiently large number of patients are needed to establish the presence of a significant correlation between mutations of the PT gene, homocysteinemia, and RVO.

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Endogenous Fungal Retinitis in a Patient With Acute Lymphocytic Leukemia Manifesting as Uveitis and Optic Nerve Lesion

Ocular infections continue to be an increasingly common complication in immunosuppressed patients. Endophthalmitis has been reported in immunosuppressed patients and patients who use intravenous drugs. Candida albicans is the most frequent cause of endogenous mycotic endophthalmitis. Other organisms include the Aspergillus and Fusarium species, Cryptococcus neoformans, Coccidioides immitis, Sporotrichum schenckii, Blastomyces dermatitidis, and Histoplasma capsulatum. Non-fungal organisms, such as the Pseudomonas and Salmonella species, may also cause endophthalmitis in immunosuppressed individuals.

Ocular signs may be the first manifestation of leukemia or may be a manifestation of relapsed leukemia. Although the choroid is the most frequently affected ocular site in histopathologic studies, choroidal involvement may not be evident clinically. Leukemic retinopathy, infiltrates, microaneurysms, orbital and eyelid involvement, leukemic hypopyon, retinal detachment, and optic nerve head infiltration by leukemic cells have also been reported. Optic nerve involvement occurs mainly in children with acute lymphocytic leukemia. It is occasionally seen on routine examination without ocular complaints such as pain. Edema, hemorrhage, and retrolaminar infiltration of the optic nerve head may be present. In the case of leukemic optic nerve involvement, radiation therapy should be initiated promptly.

Report of a Case. A 3-year-old boy was referred to the Bascom Palmer Eye Institute (Miami, Fla) for decreased vision in the left eye and esotropia of 2 days. Two months prior to this examination, the patient was diagnosed as having acute lymphocytic leukemia without central nervous system involvement. He had undergone 2 uneventful courses of induction therapy, including dexamethasone and intrathecal methotrexate. During the course of treatment, the patient was hospitalized for fever and pneumonia and candidal skin infections. The results of all fever work-ups were negative.

Four weeks prior to our examination, at the end of his induction course, the patient had a red, painless left eye. He was diagnosed as having anterior uveitis of the left eye and was treated with 1% topical prednisolone acetate. The patient started receiving systemic dexamethasone. The day prior to our examination, the patient was noted to have esotropia and stated that he could not see from his left eye. The patient did not have any systemic complaints. He denied headache, nausea, or vomiting.

On examination, the child was afebrile, with a visual acuity of 20/25 OD and no light perception OS. Twenty prism diopeters of esotropia was noted with full motility. An amautor 4+ relative afferent pupillary defect of the left eye was present. The left cornea disclosed mild, diffuse anterior stromal haze with 360° of posterior synechiae. There was no hypopyon. The right eye was unremarkable.

Indirect ophthalmoscopy of the left eye through a small pupil disclosed 3+ vitreous haze. The right eye was unremarkable. Echography revealed dense vitreous opacities and a pedunculated retinal lesion anterior to the optic nerve head, with subretinal extension (Figure 1). Results of magnetic resonance imaging of the brain and orbits, using gado-

![Figure 1. Echography of the left eye reveals a pedunculated lesion anterior to the optic nerve head. Adjacent subretinal involvement is present.](https://jamanetwork.com/)

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linium contrast medium, were consistent with a lesion anterior to the left optic nerve head without central nervous system involvement.

Examination with the patient anesthetized revealed a yellow, creamy pedunculated retinal lesion adjacent to the anterior optic nerve head, with a dense overlying vitritis (Figure 2). Fungal endophthalmitis was suspected, and enucleation of the left eye with implantation of a hydroxyapatite implant was performed.

A specimen of the enucleated eye and the lesion were sent for culture. Enucleation was selected as the diagnostic, therapeutic surgery of choice because of the absence of light perception and the possibility of an intraocular malignancy. The remainder of the tissue was placed in 10% neutral buffered formalin, processed, and sectioned serially through the retinal lesion. Blood cultures were obtained.

Gross examination of the left eye disclosed an endophytic yellow retinal mass in the posterior pole anterior to the optic nerve head (Figure 3). Light microscopic examination of the left eye disclosed an endophytic peripapillary retinal lesion measuring 5.0 mm in height and 4.0 mm in base. The lesion contained fungal elements, a focus of central necrosis, and an acute and chronic inflammatory cell infiltrate. An acute and chronic inflammatory cell infiltrate was present over the apex of the lesion, with extension into the vitreous. No leukemic cells were identified (Figure 4A and B). The iris, angle, ciliary body, and lens were unremarkable. The inner retina contained a chronic inflammatory cell infiltrate in the area of the lesion. Retinal vasculitis was focally present. The choroid, sclera, and optic nerve were unremarkable.

Gomori methenamine silver stain disclosed a dense collection of fungal elements suggestive of candidal infection (Figures 4C and D). Cultures of the intraocular contents at the time of enucleation were negative for organisms as were 2 blood cultures. A systemic work-up for possible sources of fungus was performed.
negative, with the exception of a resolved cutaneous candidal infection.

**Comment.** Intraocular fungal infections are uncommon. Fungal endophthalmitis has been most commonly reported in immunosuppressed individuals and patients who use intravenous drugs. The most common organisms are from the Candida species. Candida endophthalmitis has been reported as a complication of disseminated fungal infection in a patient with acute nonlymphocytic leukemia.¹⁰

Leukemic recurrences are rare and may be indicated by retinal vessel changes, hemorrhages, and leukemic infiltration. Of 657 children diagnosed as having acute leukemia, 52 (9%) had ocular abnormalities. Retinal hemorrhages were present in 19 (37%) of 52 patients. Invasion of the optic nerve, retina, iris, or orbit occurred in 29 (56%) of those patients.⁴

In our patient, the presence of a retinal lesion with overlying vitritis was discovered after a thorough ocular examination. This patient had retinal infiltration with fungal elements, retinal, and subretinal infiltration of acute and chronic inflammatory cells, necrosis, and retinal vasculitis. Optic nerve infiltration has been reported to occur mainly in children with acute leukemia, particularly in acute lymphocytic leukemia.⁹,¹⁰ Because of the vitritis and the intraocular mass in an immunocompromised patient, an opportunistic ocular infection was suspected.

A diagnostic enucleation was performed to determine whether the ocular mass contained leukemic cells, infectious organisms, such as fungus, or both. A globe-conserving biopsy would likely not have revealed positive cultures and would have been interpreted as nondiagnostic, leading to a therapeutic dilemma (in the face of negative cultures from direct enucleation of a portion of the lesion and surrounding ocular tissue). A patient with acute lymphocytic leukemia with both endogenous Fusarium endophthalmitis and leukemic ocular infiltrates has been reported.¹¹

Our patient showed no evidence of central nervous system leukemic involvement and no evidence of leukemic recurrence. He had a history of a skin rash secondary to Candida, which presumptively was felt to be the source of infection.

This case demonstrates the importance of careful ophthalmic examination of immunosuppressed patients, particularly those undergoing chemotherapy for hematologic malignancies. Distinguishing between infectious and neoplastic recurrence in patients with hematologic malignancies may be difficult and requires careful clinical evaluation as well as systemic work-up to ascertain the cause.

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**Bilateral Multifocal Chorioretinopathy in a Woman With Cutaneous Malignant Melanoma**

Melanoma-associated retinopathy (MAR) is a paraneoplastic retinopathy that occurs predominantly in males as a distal effect induced by the immune system’s response to a cutaneous malignant melanoma (CMM).¹ Onset and survival differ markedly, with associated vision problems occurring, on average, 3.6 years (range, 2 months to 19 years) following the diagnosis of CMM, and 1.9 years (range, 1 month to 15 years) subsequent to the finding of metastases. Survival time following the diagnosis of CMM is 5.9 years on average, ranging from 1 to 19.5 years.¹ The MAR syndrome typically manifests as a sudden onset of disabling glare or night blindness that is thought to result from the production of autoantibodies reactive with retinal depolarizing bipolar cells.² While the physical appearance of the retina is frequently normal, changes in the retinal pigment epithelium (RPE), such as a slight mottling, have been reported.³ Together with optic disc pallor, retinal vessel attenuation, and the presence of vitreous cells,² Melanoma-associated retinopathy with retinal periphlebitis has also been described in a patient,⁴ which further illustrates the diversity of findings that accompany this syndrome. Here we report a woman with MAR with unusual fundus findings not previously described to our knowledge.

**Report of a Case.** A 33-year-old white woman had a 4-week history of sudden-onset bilateral disabling glare and night blindness in June 2000. While she could still make out her surroundings she described a white, central scotoma, and experienced photopsias on closing her eyes.

The patient had a history of familial dystrophic nevus syndrome. She was first diagnosed with CMM (nodular malignant melanoma; tumor thickness, 2.0 mm; Clark level III) in 1996. In 1997, the right ovary had to be removed due to metastas-
sis. At this time, she received immunotherapy with anti-idiotypic melanoma–specific mouse antibodies, interleukin 2, and granulocyte macrophage colony stimulating factor. Her tumor status at that time was stage IV, pT3, N0, M1b (Union Internationale Contre le Cancer classification). The patient had not been taking systemic steroids and did not experience hypertension or renal problems.

On examination, visual acuity was 20/20 OU. The intraocular pressure was 8 mm Hg OU. A nevus was observed on the right lower eyelid. Results of slitlamp examination of the anterior segment were otherwise unremarkable. On ophthalmoscopy, lesions suggestive of multiple well-circumscribed detachments of the RPE were seen on the posterior pole of both eyes (Figure 1). Each detachment contained a small yellow-orange lesion.

Fluorescein angiography showed stable hyperfluorescent spots in some of the small yellow-orange lesions, as well as a stable, mild hyperfluorescence in the areas of the RPE detachment. Indocyanine green angiography showed multifocal staining, extending the areas of the RPE detachments (Figure 2).

Testing of the visual fields failed to reveal any corresponding dysfunction. On kinetic perimetry (Goldmann III/4; Haag Streit, Bern, Switzerland), the visual field of either eye extended to 70° caudally, 50° cranially, 80° temporally, and 50° nasally. Testing of the central 30° using static perimetry (Octopus d32; Interzeag AG, Schlieren, Switzerland) revealed the following: mean defect (MD), 2.8 dB; loss variance (LV), 5.4 dB² OD, and MD, 4.4 dB; LV, 7.1 dB² OS. At a follow-up 2 months later, these values were as follows: MD, 0.9 dB; LV, 4.1 dB² OD, and MD, 1.7 dB; LV, 3.8 dB² OS. The MD and LV are comparative measures that represent the difference between the age-corrected normal data and the actual measured results. The MD is an index related to global damage whereby a loss of 1 dB corresponds to approximately a 10% loss of visual function. The tolerance for normality lies between −2 dB and +2 dB. The LV indicates localized damage. It is calculated from the individual deviation of all measured locations from the MD value. In combination with a normal MD, a value greater than 6 dB² signifies a localized defect.

Nystagmometry (Rodenstock, Munich, Germany) provides information on vision in dim light and thus can be seen as an indicator for the quality of night vision. Increasingly weaker contrasts are presented at a particular adaptation level; thus, sensitivity to different illumination is tested. In our patient, on nystagmometry, stimuli with a decreasing contrast of 1:23.5, 1:5.0, 1:2.7, 1:2.0, 1:1.66, and 1:1.46 were presented, first without glare (surrounding luminance: 0.032 candela [cd/m²]) and then with glare (surrounding luminance: 0.1 cd/m², glare source with a diameter of ∼15 minutes of arc, a 3° angle of glare, and a corneal luminance of 0.35 lux). While most healthy young people can easily see

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Figure 1. June 2000. Color photographs of the posterior pole, showing multiple well-circumscribed detachments of the retinal pigment epithelium in both eyes (A, right eye; B, left eye), each of which contains a small yellow-orange lesion.

Figure 2. Early-phase (A) and late-phase (B) fluorescein angiography of the left eye, depicting a mild hyperfluorescence that did not increase in leakage. C, indocyanine green angiography of the left eye, with staining extending the area of the retinal pigment epithelium detachments.
a contrast of 1:2.7 with or without glare, our patient could not detect any stimulus either with or without glare.

Electrophysiologic testing (pattern electroretinogram [P-ERG], Ganzfeld ERG [Haag Streit], and electro-oculogram [Medelec, Surrey, England]) was performed according to the standard of the International Society for Clinical Electrophysiology of Vision. The electro-oculogram results were within the normal range, with an Arden ratio of 1.9 OD and 2.4 OS.

The P-ERG showed normal amplitudes for N35P50 (3.05 µV OD, 1.7 µV OS [normal range, 1.46-4.9 µV]) and for P50N95 (7.1 µV OD, 4.9 µV OS [normal range, 2.0-8.6 µV]) as well as normal latencies (eg, P50: 53.9 ms OD, 51.6 ms OS [normal range, 49-59 ms]).

The Ganzfeld ERG showed a selective reduction of the isolated rod scotopic b-wave amplitude (luminance: 0.0025 cd/m²; 16.5 µV OD, 20.7 µV OS [normal, >110 µV]) (Figure 3A). The a wave was normal with a maximal response amplitude of 35.4 µV OD and 45.9 µV OS (normal range, 33-48 µV; luminance, 2.8 cd/m²). Retinal function evaluation by multifocal ERG (mERG) (VERIS; Electro-Diagnostic Imaging, San Mateo, Calif) (Lmax 200 cd, Lmean 100 cd) showed reduced amplitudes in the central 4° OU where the mean amplitude N1P1 (first negative to first positive peak) was 24.1 nV/degrees² (deg²) OD and 24.4 nV/deg² OS (Figure 4A). This contrasts with the mean (SD) response of 69.0 (22.1) nV/deg² (deg²) in the central 4° of a normal reference control group of 15 individuals of similar age.

The central distribution of the reduced amplitudes observed in the multifocal ERG of our patient are comparable with the reduced central amplitudes observed in the multifocal ERG of patients with MAR, but reduced amplitudes (Figure 4) were not found in all areas of retinal lesions (Figure 1).

The patient’s serum was evaluated by indirect immunohistochemical analysis on 6-µm sections of rhesus monkey at a dilution of 1:100. Antibody reactions were visualized using fluorescein-isothiocyanate conjugated rabbit-antihuman polyclonal γ-globulins (Sigma F4637; Sigma, St Louis, Mo) at a dilution of 1:500. Serologic examination revealed abnormal immunologic activity consistent with MAR, showing a focus of antibody reactions within the inner nuclear layer, where the nuclei of the bipolar cells are located. Western blot reactions on an extract of rhesus optic nerve revealed additional abnormal antibody activity with myelin basic protein.

Intensive examination in October 2000 led to the recognition and removal of a metastasis in the lymph nodes of the right axilla (radical lymph node dissection, 3 of 7 lymph nodes were positive) followed by chemotherapy with vindesine.

In December 2000, the mERG recordings showed an improvement of the central amplitudes, with the mean amplitude N1P1 (first negative to first positive peak) improving to 33 nV/deg² OD and 28.3 nV/deg² OS, in contrast with a...
response mean (SD) of 69.0 (22.1) nV/deg² in the control group (Figure 4B).

In April 2001, the patient was able to see the bright background disc on which the stimulus was presented during nyctometry for the first time, although she still could not detect the stimulus itself.

At a follow-up nyctometry in July 2001, vision in the right eye had improved to where it could resolve a contrast of 1:2.7 without glare; with glare, however, no contrast stimulus was seen. The left eye was still unable to detect any stimulus, either with or without glare. Visual acuity and visual fields had remained stable.

The isolated rod scotopic ERG b-wave amplitude also recovered to 164 µV OD and 204 µV OS, respectively. The P-ERG continued to show normal amplitudes for N35P50 (2.91 µV OD, 1.66 µV OS [normal range, 1.46-4.9 µV]) as well as for P50N95 (7.02 µV OD, 4.89 µV OS [normal range, 2.0-8.6 µV]). The latencies of P50 also remained within the normal range (53.3 ms OD, 52.1 ms OS [normal range, 49-59 ms]).

On ophthalmoscopy, the detachments of the RPE had resolved while the yellow-orange lesions appeared to have consolidated continuously (Figure 5). These lesions showed autofluorescence, which may indicate lipid deposits in the RPE or inner choroid (Figure 6). Fluorescein angiography showed a marked blocking of the choroidal filling, with intact filling of the retinal vessels (Figure 6). The clinically apparent lesions therefore appeared to predominate in the RPE and/or inner choroid. The patient was aware of a negative scotoma in the area of the lesions when she closed her eyes. This effect indicated choroidal malfunction.

On further follow-up in February 2002, the patient reported improved night vision and a lessened sensitivity to glare. However, she complained of a recent onset of central metamorphopsia in the left eye. Visual acuity was 20/16 OD and 20/40 OS. When examined by nyctometry, it was found that the right eye could now resolve a contrast of 1:2.7 without glare and of 1:5 with glare, but the left eye was still unable to detect any stimulus either with or without glare.

On ophthalmoscopy, the yellow-orange deposits appeared to be reduced in size and density (Figure 7). Fluorescein angiography continued to show a blocking of the choroidal filling, with intact filling of the retinal vessels in the area of these lesions. Small filling defects...
Figure 7. February 2002. A, Color photographs show the yellow-orange lesions, which appear reduced in size. B, Corresponding fluorescein angiography. C, Indocyanine green angiography. Right eye, top row; left eye, bottom row.

Figure 8. June 2002. Right (A and B) and left (C and D) eyes. A and C, Color photographs depict the yellow-orange lesions, which appear even more reduced in size than in Figure 7. This can be appreciated more when their autofluorescence is viewed (B and D).
were seen by indocyanine green angiography. Neither fluorescein angiography nor indocyanine green angiography revealed a choroidal neovascular membrane or macular edema. The reduced central vision in the left eye was thought to be secondary to the observed central pigment epithelial changes.

At the latest follow-up in June 2002, the patient reported improved central metamorphopsia in the left eye. Visual acuity was stable (20/16 OD 20/40 OS). When examined by nyctometry, it was found that the right eye could resolve a contrast of 1:1.46 without glare and of 1:5 with glare. The left eye was now able to detect a contrast of 1:5 without glare. With glare, the left eye still could not resolve the stimulus. On ophthalmoscopy, the yellow-orange deposits appeared further reduced in size and density (Figure 8). To date, further electrophysiologic examinations were not performed.

Comment. We describe a patient with MAR who experienced subjective improvement of her night vision and of her glare sensitivity following removal of metastasis and treatment with chemotherapy. This recovery could also be observed in the normalization of a previously abnormal rod-isolated scotopic b-wave response as well as in the improvement of nyctometry results. This recovery is consistent with the recent experimental findings of Lei et al., who found electrophysiologic dysfunction typical of MAR to be a transient effect following intravitreal injection of MAR serum into the eye of a monkey.

Furthermore, our patient’s case is remarkable in that she had unusual fundus findings on initial examination, the origin of which remains unclear at present. The findings in our patient may be compared with those of Best disease, where multifocal vitelliform lesions of various size, similar to those we describe, may also occur. Multifocal vitelliform Best disease may also occur sporadically and may show normal electro-oculogram results, as were found in our patient. In Best disease, vitelliform RPE detachments can show a marked symmetry between the left and right eye and may develop over several years.8 Our patient had no familial history of Best disease; in contrast, she experienced a regression of RPE detachments in association with the removal of secondary melanoma metastases.

The vitelliform detachments of the RPE in Best disease have been described as acquiring a yellow discoloration and blocking choroidal fluorescence on fluorescein angiography.10 We found no “egg yolk” or “scrambled lesion” typical of Best disease in our patient.8 In addition, the vitelliform stage of her RPE detachments did not block choroidal fluorescence on fluorescein angiography; blocking only occurred following resolution of the RPE detachments and following the deposition of lipids. It is unlikely that our patient suffers from multifocal vitelliform Best disease. The combination of MAR and bilateral multifocal chorioretinopathy we described represents an additional example of the pathologic and immunologic heterogeneity that continues to emerge in descriptions of the MAR syndrome.

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Photodynamic Therapy in Adult-Onset Vitelliform Macular Dystrophy Misdiagnosed as Choroidal Neovascularization

In adult-onset vitelliform macular dystrophy (AOVMD), the yellowish subretinal material accumulating at the fovea may cause later hyperfluorescence, both with fluorescein angiography and with indocyanine green angiography, sometimes simulating choroidal neovascularization (CNV). We report 3 cases of AOVMD misdiagnosed as...
classic CNV secondary to age-
related macular degeneration that
were treated with photodynamic
therapy (PDT).

Report of Cases. Case 1. A 71-year-
old woman reported vision loss in
her right eye. Examination showed
atrophy of the choriocapillaris, and
yellowish subretinal material was
seen in the left eye (Figure 1A).
Best-corrected visual acuity was
20/200 OD and 20/30 OS. Fluores-
cence angiography showed early
blocked fluorescence at the left
macula, with perimacular stellate
aspect and mild late hyperfluores-
cence (Figure 1B). Indocyanine
green angiography also showed late
hyperfluorescence that was also
misinterpreted as CNV. Optical
coherence tomography (OCT)
revealed foveal hyperreflective
elevation of the profile of the reti-
nal pigment epithelium (RPE)–
Bruch membrane–choriocapillaris
complex (Figure 2A). The patient
received PDT in her left eye. Three
months later, the subretinal mate-
rial had disappeared, leaving in
place RPE mottling (Figure 1C);
visual acuity was unchanged. Fluoro-
scin angiography showed mild
window defect at the left macula
(Figure 1D). With OCT, the foveal
profile was restored because of
disappearance of the subretinal
mound (Figure 2B). One year after
PDT, visual acuity, as well as angi-
graphic and OCT findings (Figure
1E and F, and Figure 2C), were
substantially unchanged.

Case 2. A 74-year-old woman
had a vitelliformlike lesion in her left
eye on clinical examination. The
right eye displayed a roundish area
of chorioretinal atrophy at the
macula. The subretinal macular
deposits showed early, stellate blocked
fluorescence with fluorescein angi-
graphy, followed by abundant late
leakage. Best-corrected visual acu-
ity was 20/600 OD and 20/100 OS.
The left eye received PDT because
of suspected CNV. We obtained
fluorescein angiograms as early as 1
month after PDT. Although the an-
giographic picture was substan-
tially unchanged, we observed re-
sorption of the yellowish subretinal
material, and this aspect was main-
tained during the following months.
Visual acuity was 20/100 soon after
PDT, and was measured as 20/60
after 6 months. Thereafter, it de-
clined to 20/400 because of dense
subcapsular cataract. Cataract
extraction was advised approxi-
mately 1 year after PDT.

Case 3. Bilateral macular RPE
atrophy associated with reticular hy-
perpigmentation were seen in both
fundus of a 65-year-old man. The left
fovea had yellowish subretinal ma-
terial causing early, stellate blocked
fluorescence with fluorescein angi-
graphy, followed by abundant late
leakage. Best-corrected visual acu-
ity was 20/30 and remained stable throughout the follow-up.

Figure 1. A, Vitelliform submacular lesion with red-free photograph in case 1 immediately before photodynamic therapy. Middle-phase fluorescein angiogram shows a stellate hypofluorescent lesion with mild foveal hyperfluorescence that was misdiagnosed as choroidal neovascularization. B, Three months after photodynamic therapy, the vitelliform lesion had disappeared (C and D); the picture was unchanged after 1 year of follow-up (E and F). Visual acuity was 20/30 and remained stable throughout the follow-up.
Comment. Adult-onset vitelliform macular dystrophy is a subtype of pattern dystrophy that resembles Best dystrophy, in which smaller vitelliform lesions are usually seen in middle-aged or elderly individuals.1 Lipofuscin material on either side of the RPE, as well as basal laminar and basal linear deposits, were observed throughout the macula in a recent clinicopathologic correlation.3

We saw 3 patients in whom a vitelliform macular lesion had been treated with PDT because of misdiagnosed CNV. Photodynamic therapy did not seem to cause any adverse effects despite the fact that it was done in the setting of no CNV, no intraretinal fluid, and possibly compromised choriocapillaris. Visual acuity was stable or possibly improved in all 3 instances. In 2 of 3 cases, the vitelliform subretinal material disappeared within 1 to 3 months of PDT treatment. Although this may be seen in the long-term in some eyes with AOVMD, it could also be hypothesized that the rather rapid resorption of the subretinal material is due to RPE stimulation by PDT, which is known to cause RPE damage followed by regeneration experimentally.4,5

In conclusion, we showed that AOVMD can be misinterpreted as CNV. Only practitioners experienced in clinical examination and fluorescein interpretation of macular degeneration should be performing PDT.

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Nodular Scleritis in a Patient With Pyoderma Gangrenosum

Pyoderma gangrenosum is a rare chronic reactive inflammatory disorder that involves ulceration of the skin, is commonly associated with inflammatory bowel disease and arthritis, and occurs mostly in women. The ulcerative lesions of pyoderma gangrenosum are typically at the site of minor trauma and begin as small erythematous papules progressing to tender sterile pustules with central necrosis. We report a case of nodular scleritis due to pyoderma gangrenosum and our experience excising the lesion.

Report of a Case. A 39-year-old woman complained of redness and a foreign body sensation in her right eye. She also had a large 8 × 20-cm ulcer involving her right lower leg. Her medical history is significant for pyoderma gangrenosum, hemolytic anemia, large granular lymphocytic disorder, nasopharynx papillomatosis, and occasional migratory arthralgias. Findings from slitlamp examination revealed a large erythematous, raised scleral nodule adjacent to the temporal limbus of the right eye (Figure 1). The nodule was tender and had an irregular surface similar to a papilloma.

The nodular scleritis appeared while the patient was receiving intravenous cyclosporine and methylprednisolone for the pyoderma gangrenosum ulcer of her leg. Because of the papilloma-like appearance of the scleral nodule, she was treated with topical ciclosporine in addition to topical cyclosporine and prednisolone acetate. After poor response to 3 weeks of medical treatment, a diagnostic/therapeutic excisional biopsy was performed. Bacterial, viral, and fungal cultures from the biopsy specimen were all negative for organisms. The specimen showed an inflammatory cellular infiltration of the tissue diagnostic of diffuse neutrophilic mucositis, consistent with pyoderma gangrenosum (Figure 2 and Figure 3). The nodular scleritis resolved after the excisional biopsy. Topical corticosteroid was tapered and its use discontinued over a 2-month period. Therapy with systemic corticosteroids and cyclosporine were continued for the treatment of the leg ulcer, which remained stable during therapy without complete resolution. No new skin lesions appeared during this period. She had no evidence of recurrence of the scleritis during the following 7 months (Figure 4).

Comment. Pyoderma gangrenosum is an autoimmune condition, re-
Figure 1. Initial slitlamp photograph of a scleral nodule adjacent to the limbus of the right eye. The yellow, elevated lesion with prominent vessels is surrounded by focal conjunctival hyperemia.

Figure 2. Microscopic section of the scleral nodule showing submucosal connective tissue with inflammatory cells that consisted mostly of neutrophils (white arrow). A vessel is seen (black arrow) (hematoxylin-eosin, original magnification ×20).

Figure 3. High-magnification microscopic section showing diffused neutrophilic infiltration consistent with pyoderma gangrenosum (white arrow). A vessel is noted (black arrow). No abscess or infectious agent is observed (hematoxylin-eosin, original magnification ×40).
sulting in painful skin ulceration after minor trauma. It is commonly associated with inflammatory bowel disease and arthritis, and approximately 10% of patients may have an IgA monoclonal gammopathy.1 Malignancies such as leukemia and lymphoma have also been associated with pyoderma gangrenosum.

The results of skin biopsies have led to formation or enlargement of ulcers.2 Because of this risk, the nodular scleritis was initially treated with immunosuppressants. Owing to the lack of response to medical treatment, an excisional biopsy of the scleral nodule was performed that did not result in additional inflammation or ulceration but rather in the resolution of the scleritis, possibly because of the preoperative and postoperative treatments with cyclosporine and corticosteroids. Of the 4 cases of pyoderma gangrenosum–related ulcerative keratitis and scleritis we reviewed,3–5 only 1 required biopsy, which did not result in ulceration.3

Biopsy specimens and tissue cultures are important in excluding other conditions that can mimic pyoderma gangrenosum, such as an infected ulcer. In this current case report, histopathologic findings of inflammatory cell infiltrate with or without abscess formation is consistent with, but not specific to, pyoderma gangrenosum.2

Patients with ocular involvement of pyoderma gangrenosum have responded to a variety of treatments. Three reported cases of ulcerative keratitis have been treated successfully with oral and topical corticosteroids, oral cyclophosphamide, and oral azathioprine.3,4 A case of scleral ulceration responded to cryotherapy and systemic cortisone.7 Our case of nodular scleritis resolved with a combination of an excisional biopsy with adjunctive systemic and topical immunosuppressants.

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From the Archives of the ARCHIVES

Sight having within forty-eight hours grown steadily worse leading to almost entire blindness, commencing to improve immediately after forcible massage—that is, pressure against the eyeball, with scarcely any other treatment, we may fairly claim that this exceptional recovery has been improved circulation from massage of the eye.

of their relevant pharmacokinetic and pharmacodynamic properties. Furthermore, consideration of factors such as biological variability and dose-response, which express therapeutic action in terms of efficacy as well as toxicity, are in large part poorly defined within the AREDS study design. Characterization of the pharmacologic response to various high-dose vitamin and nutrient administration requires stringent assessment of population-, disease-, and formulation-specific variables that may influence the occurrence of adverse effects in ways not described in the AREDS.

For example, changes in drug disposition with age are characterized by alterations in lean body mass, which influences the volume of distribution and partition coefficients pertinent to fat-soluble vitamins, particularly α-tocopherol. Furthermore, individuals who use vitamin A1 as a source of beta-carotene should be advised that absorption of vitamin A1 (retinol) varies considerably depending on the formulation of the preparation as well as the amount of dietary fat an individual typically ingests. In addition, febrile infections and stress may markedly decrease serum retinol, whereas chronic renal disease may result in significantly elevated serum retinol, requiring the need for an alteration in intake.

Moreover, the AREDS neglects to discuss assignment of causality, as well as the temporal relationship and outcome of reported adverse events, particularly those noted as “circulatory.” Furthermore, discussion of additive or synergistic effects, either observed or potential, of the AREDS therapy with various prescription and nonprescription products is lacking. The AREDS also does not address the need for continuing surveillance of the safety of vitamin and nutrient therapy for AMD in terms of elucidation of unexpected idiosyncratic reactions, an important yet complex task because of the ease of accessibility of such agents. Additionally, and perhaps of greater significance, it is unknown how the results of ongoing prospective trials of vitamin and nutrient therapy for disorders other than AMD will affect those currently following AREDS recommendations.

Vitamins and nutrients are not only ubiquitous in nature and easily obtained from nourishing diets, they are also aggressively marketed by pharmaceutical companies eager to promote perceived as well as validated claims of health benefit. In addition, the clever marketing strategies of pharmaceutical companies, such as those promoting doses that “exceed AREDS recommendations,” demonstrate the need for clinicians to closely monitor vitamin and nutrient intake. I believe that the AREDS findings are inadequate in the elucidation of clear and concise safety guidelines for entities that are largely unregulated and widely promoted with an array of ingredients, formulations, and equivalency provided for public interpretation.

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The author has no relevant financial interest in this article.


Correction

Author Name Omitted. In the Clinicothopathologic Reports, Case Reports, and Small Case Series article titled “Photodynamic Therapy in Adult-Onset Vitelliform Macular Dystrophy Misdiagnosed as Choroidal Neovascularization,” published in the December issue of the ARCHIVES (2002;120:1761-1763), Gianni Virgili, MD, was omitted and should have been listed in the signature block as the last author.