

amplification with a normal *CDH11* copy number (Figure 2). *MYCN* amplification may account for the aggressiveness of the ovarian tumor, as it does for highly fatal neuroblastomas.⁷

The evidence indicates that the ovarian tumor was an independent retinoblastoma rather than a metastasis. While our analysis did not attempt to reveal the cell of origin that underwent malignant transformation, marker analysis revealed that it was not of ovarian origin. Instead, we speculate that it may have been a retinal cell displaced into the ovary by an unknown mechanism. Alternatively, a primitive pluripotent cell persisting in the ovary may have acquired the second *RBI* and subsequent other mutations allowing the malignant transformation.

Shui Yen Soh, MB, BS
Helen Dimaras, PhD
Abha Gupta, MD
Diane Rushlow, BS
Carol Swallow, MD, PhD
Michael Crump, MD
William Halliday, MD
John J. Doyle, MD
Paul Babyn, MD
Elise Héon, MD
Brenda L. Gallie, MD
Helen S. L. Chan, MB, BS

Author Affiliations: Division of Hematology/Oncology (Drs Soh, Dimaras, Gupta, Doyle, and Chan) and Departments of Pediatrics (Drs Soh, Dimaras, Gupta, Doyle, and Chan), Pathology (Dr Halliday), Diagnostic Imaging (Dr Babyn), and Ophthalmology/Visual Sciences (Drs Héon and Gallie), The Hospital for Sick Children, Retinoblastoma Solutions (Ms Rushlow and Dr Gallie) and Divisions of Hematology/Oncology (Dr Crump) and Applied Molecular Oncology (Dr Gallie), Princess Margaret Hospital/University Health Network, and Department of Surgery, Mount Sinai Hospital (Dr Swallow), University of Toronto, Toronto, Ontario, Canada.

Correspondence: Dr Chan, Division of Hematology/Oncology, The Hospital for Sick Children, 555 University Ave, Toronto, ON M5G 1X8, Canada (hslchan@attglobal.net).

Financial Disclosure: None reported.

Funding/Support: This work was supported in part by a grant from the Ontario Institute for Cancer Research and The Terry Fox Research Institute (Drs Gallie and Chan), by the Canadian Retinoblastoma Society, by the Royal Arch Masons of Canada (Dr Gallie), and in part by the Ontario Ministry of Health and Long-Term Care.

Disclaimer: The views expressed do not necessarily reflect those of the Ontario Ministry of Health and Long-Term Care.

1. Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am.* 2005;18(1):41-53, viii.
2. Bowles E, Corson TW, Bayani J, et al. Profiling genomic copy number changes in retinoblastoma beyond loss of *RBI*. *Genes Chromosomes Cancer.* 2007;46(2):118-129.
3. Corson TW, Gallie BL. One hit, two hits, three hits, more? genomic changes in the development of retinoblastoma. *Genes Chromosomes Cancer.* 2007;46(7):617-634.

4. Moshfeghi DM, Wilson MW, Haik BG, Hill DA, Rodriguez-Galindo C, Pratt CB. Retinoblastoma metastatic to the ovary in a patient with Waardenburg syndrome. *Am J Ophthalmol.* 2002;133(5):716-718.
5. Schroder W. Similar histological patterns in a bilateral malignant teratoma of the ovary and a previous retinoblastoma in a girl. *Onkologie.* 1991;14(5):437-439. doi:10.1159/000217021.
6. Richter S, Vandezande K, Chen N, et al. Sensitive and efficient detection of *RBI* gene mutations enhances care for families with retinoblastoma. *Am J Hum Genet.* 2003;72(2):253-269.
7. Seeger RC, Brodeur GM, Sather H, et al. Association of multiple copies of the *N-myc* oncogene with rapid progression of neuroblastomas. *N Engl J Med.* 1985;313(18):1111-1116.

Acute Exudative Polymorphous Paraneoplastic Vitelliform Maculopathy in a Patient With Carcinoma, Not Melanoma

Paraneoplastic retinopathy occurs when autoantibodies against cancer cross-react with normal retinal antigens and lead to retinal degeneration and subsequent vision loss.¹ Two main categories of paraneoplastic retinopathies have been described, including cancer-associated retinopathy and melanoma-associated retinopathy.² Cancer-associated retinopathy is found most often in patients with small cell lung carcinoma and affects both rod and cone function, while melanoma-associated retinopathy occurs with metastatic cutaneous or uveal melanoma and affects primarily rod function.¹ Autoantibodies against recoverin and bipolar cells are typically found in cancer-associated retinopathy and melanoma-associated retinopathy, respectively, although other retinal antigens have also been described.^{1,3} Herein, we illustrate a case of a more recently recognized paraneoplastic retinopathy, termed *acute exudative polymorphous paraneoplastic vitelliform maculopathy* (AEPVPM).

Report of a Case. A 69-year-old woman noted gradually progressive blurred vision in both eyes over 2 years. Three months previously, she experienced subjective loss of peripheral vision bilaterally. Other symptoms included mild decreased night vision and photopsia. Stage I breast cancer was diagnosed 5 years prior and treated with excisional biopsy and radiotherapy. She had a second cancer, stage IV lung cancer with liver metastasis, that was diagnosed 2 years prior and was treated with chemotherapy.

On examination, best-corrected visual acuity was 20/80 OD and 20/70 OS. The anterior segment, optic disc, and retinal vessels were unremarkable bilaterally. Fundus examination revealed multiple small, round, amelanotic (vitelliform) lesions approximately 500 µm in diameter in the postequatorial region bilaterally that superficially appeared like choroidal metastasis or retinal pigment epithelial detachments (**Figure 1**). There was no vitritis. Ultrasonography showed multifocal regions of chorioretinal thickening. Optical coherence tomography revealed multiple areas of localized subretinal fluid with debris overlying flat retinal pigment epithelium (**Figure 2**). Autofluorescence disclosed hyperautofluorescence corresponding to the serous retinal detachments (Figure 1), whereas fluorescein angi-

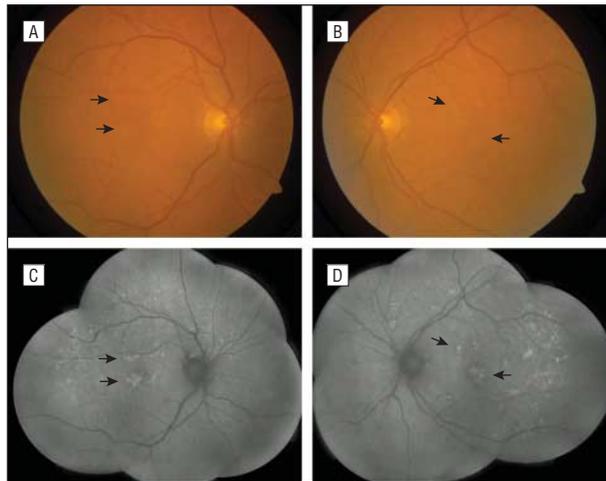


Figure 1. Fundus photographs of the right (A) and left (B) eyes show numerous subtle hypopigmented subretinal lesions (arrows) corresponding to multifocal serous detachments of the neurosensory retina. Autofluorescence of the right (C) and left (D) eyes reveals hyperautofluorescence (arrows) in the area of the serous retinal detachment.

ography demonstrated hypofluorescence of these regions with no leakage (Figure 2). The patient refused electroretinography testing.

Comment. This case illustrates an unusual cause of vision loss in a patient with systemic cancer, namely AEPPVM. This condition manifests with multiple vitelliform lesions and is considered an atypical subset of cancer-associated retinopathy or melanoma-associated retinopathy or a separate paraneoplastic entity. Several authors have associated this entity with underlying cutaneous and choroidal melanoma, but not carcinoma.³⁻⁶ Previous reports have labeled this condition as Vogt-Koyanagi-Harada-like syndrome, melanoma-associated retinopathy syndrome variant, vitelliform maculopathy with skin melanoma, vitelliform paraneoplastic retinopathy associated with melanoma, and AEPPVM.³⁻⁶ While most previously reported cases have occurred in patients with skin or eye melanoma, we are unaware of reports of this condition with carcinoma, as in our case.

Clinicians should be aware of AEPPVM. Differentiation from choroidal metastasis can be made by clinical examination and more specifically by optical coherence tomography in that the choroid is flat in AEPPVM, whereas it is elevated with choroidal metastases. In our case, optical coherence tomography showed elevated retina and flat choroid, consistent with AEPPVM. Superficially, the optical coherence tomography changes resembled pigment epithelial detachment, but close scrutiny disclosed flat retinal pigment epithelium and subretinal fluid with dense debris.

Symptoms from paraneoplastic retinopathy can occur before or after the discovery of the primary malignant neoplasm.^{1,2} Systemic evaluation for primary cancer, particularly cutaneous or uveal melanoma, is indicated. In our case, systemic evaluation showed no sign of melanoma, and the previously diagnosed carcinomas were confirmed. There is a remote possibility that our patient could have had a regressed cutaneous melanoma or undetected visceral melanoma.

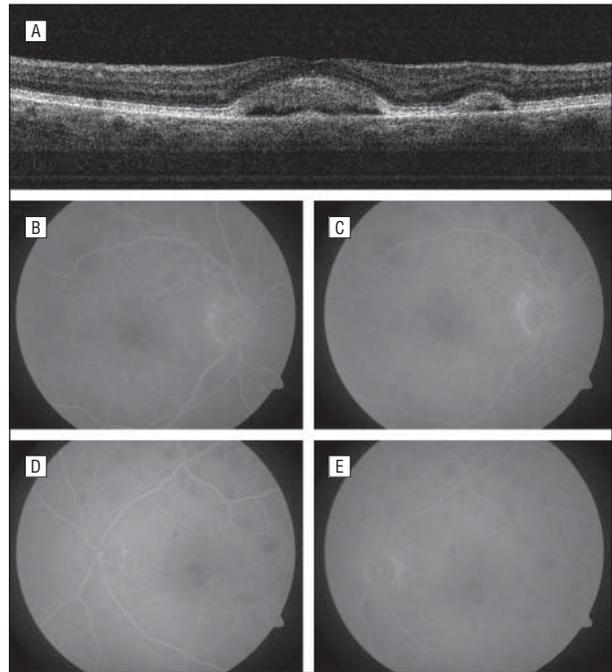


Figure 2. Optical coherence tomographic image and fluorescein angiograms. A, Optical coherence tomography shows multiple serous neurosensory retinal detachments with optically dense debris. Fluorescein angiograms show hypofluorescence of the lesion in early frames in the right (B) and left (C) eyes and late frames in the right (D) and left (E) eyes.

In summary, we describe an unusual paraneoplastic syndrome, namely AEPPVM. This condition should be recognized by clinicians, and systemic evaluation for the primary malignant neoplasm should be performed owing to the high association with cutaneous and choroidal melanoma and, now, carcinoma.¹

Lili Grunwald, MD
Brad E. Kligman, BS
Carol L. Shields, MD

Author Affiliations: Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina (Dr Grunwald); and Ocular Oncology Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania (Mr Kligman and Dr Shields).

Correspondence: Dr C. L. Shields, Ocular Oncology Service, Ste 1440, Wills Eye Institute, 840 Walnut St, Philadelphia, PA 19107 (carol.shields@shieldsoncology.com).

Financial Disclosure: None reported.

Funding/Support: This work was supported by the Eye Tumor Research Foundation, Philadelphia, Pennsylvania (Dr Shields).

1. Chan JW. Paraneoplastic retinopathies and optic neuropathies. *Surv Ophthalmol.* 2003;48(1):12-38.
2. Thirkill CE. Cancer-induced, immune-mediated ocular degenerations. *Ocul Immunol Inflamm.* 2005;13(2-3):119-131.
3. Bianciotto C, Shields CL, Thirkill CE, Materin MA, Shields JA. Paraneoplastic retinopathy with multiple detachments of the neurosensory retina and autoantibodies against interphotoreceptor retinoid binding protein (IRBP) in cutaneous melanoma. *Br J Ophthalmol.* 2010;94(12):1684-1685, 1696.
4. Borkowski LM, Grover S, Fishman GA, Jampol LM. Retinal findings in melanoma-associated retinopathy. *Am J Ophthalmol.* 2001;132(2):273-275.

5. Palmowski AM, Haus AH, Pföhler C, et al. Bilateral multifocal chorioretinopathy in a woman with cutaneous malignant melanoma. *Arch Ophthalmol*. 2002;120(12):1756-1761.
6. Sotodeh M, Paridaens D, Keunen J, van Schooneveld M, Adamus G, Baarsma S. Paraneoplastic vitelliform retinopathy associated with cutaneous or uveal melanoma and metastases. *Klin Monbl Augenheilkd*. 2005;222(11):910-914.

Early Diabetes Mellitus or Hypertension Is Not Significantly Associated With Severity of Vision Loss in Nonarteritic Anterior Ischemic Optic Neuropathy

Glaucoma is a progressive optic neuropathy with features similar to nonarteritic anterior ischemic optic neuropathy (NAION), the most common optic neuropathy causing acute vision loss. Glaucoma has an annual incidence rate of 240 per capita, while NAION has an annual incidence of 2.3 per capita among individuals older than 50 years.^{1,2} Early diabetes mellitus (DM)—defined as an absence of clinically visible diabetic retinopathy—may be associated with upregulation and downregulation of intraocular interferon, interleukins, and other cytokines promoting neuroprotection.³ The initial Ocular Hypertension Treatment Study report documented a protective effect of early DM in glaucoma development, but reanalysis showed no effect.^{4,5} Studies have shown DM to be a risk factor for NAION, but it is possible that early DM could have neuroprotective effects in NAION. Hayreh and Zimmerman⁶ had documented less severe visual field loss for diabetic patients with NAION. However, 11% of their participants had juvenile diabetes, 36% had diabetic retinopathy, and the investigators had used manual kinetic perimetry. To discern the role of early DM in NAION, we have studied patients aged 50 years or older without diabetic retinopathy using automated static perimetry.

Methods. We reviewed the records of all patients with NAION evaluated by the neuro-ophthalmology service

between October 1990 and August 2009, after obtaining institutional review board approval. Criteria for NAION were similar to those used in past studies.² Patients were excluded if they had significant cataract, presumed toxic causes of NAION such as amiodarone hydrochloride or erectile dysfunction drug use, perioperative NAION, diabetic retinopathy, temporal arteritis, or other disorders that could cause the vision loss. A standardized comprehensive medical history and comprehensive neuro-ophthalmologic examination were obtained for all patients, including best-corrected visual acuity, Humphrey automated perimetry program 24-2 or 30-2 Swedish interactive thresholding algorithm fast results, and dilated ophthalmoscopy.

Patients were classified as having DM with or without hypertension or not having DM with or without hypertension. Diabetes was identified if the patient had been diagnosed by the primary care physician as having DM or if the patient had been prescribed oral hypoglycemic medications or insulin prior to NAION. Patients with hypertension had been prescribed antihypertensive medications. Usable visual fields had less than 33% fixation loss, false-negative errors, and false-positive errors. Statistical analyses were performed with SAS version 9 statistical software (SAS Institute, Inc, Cary, North Carolina). We compared categorical variables such as sex with χ^2 test, ordinal variables such as age with Wilcoxon rank sum test, and logMAR visual acuity and mean deviation on visual field with 2-sample *t* test and analyses of variance and covariance.

Results. A total of 206 patients (53 with DM [43 having hypertension] and 153 without DM [73 having hypertension]) who were aged 50 years or older (mean age, 65.1 years; male, 122 [59%]) qualified for the study. There were 176 usable visual fields (45 with DM and 131 without DM). There was no significant difference in logMAR visual acuity ($P=.77$) for DM (mean [SD], 0.81 [0.71]) and no DM (mean [SD], 0.84 [0.79]) or when

Table. LogMAR Visual Acuity and Mean Deviation of Standard Automated Perimetry

Visual Acuity or Field	Patients, No.	Visual Acuity, LogMAR/Mean Deviation of Visual Field Loss, dB, Mean (SD)	P Value
Visual acuity			
By DM only			
With DM	53	0.81 (0.71)	.77
Without DM	153	0.84 (0.79)	
By DM and HTN			
With DM, with HTN	43	0.88 (0.73)	.10
With DM, without HTN	10	0.49 (0.56)	
Without DM, with HTN	73	0.98 (0.82)	
Without DM, without HTN	80	0.72 (0.74)	
Visual field			
By DM only			
With DM	45	-18.5 (9.8)	.52
Without DM	131	-17.5 (9.1)	
By DM and HTN			
With DM, with HTN	36	-18.1 (9.5)	.34
With DM, without HTN	9	-19.9 (11.6)	
Without DM, with HTN	62	-18.9 (8.9)	
Without DM, without HTN	69	-16.2 (9.2)	

Abbreviations: DM, diabetes mellitus; HTN, hypertension.