the IS/OS line at an earlier stage by the pathological changes in a typical case of AZOOR. We should note that care should be taken in evaluation of the COST line because its visibility is dependent on the intensity and direction of the laser light that reaches the photoreceptor layer. However, in patients with AZOOR, the COST line and the foveal bulge observed by OCT could help as indicators of early cone photoreceptor dysfunction in cases with minimal ophthalmoscopic and angiographic abnormalities.

Kazushige Tsunoda, MD
Kaoru Fujinami, MD
Yozo Miyake, MD

Author Affiliations: National Institute of Sensory Organs, Tokyo (Drs Tsunoda and Fujinami), and Aichi Medical University, Aichi (Dr Miyake), Japan.

Correspondence: Dr Tsunoda, Laboratory of Visual Physiology, National Institute of Sensory Organs, 2-5-1 Higashigaoka, Meguroku, Tokyo 1528902, Japan (tsunodakazushige@kankakuki.go.jp).

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Figure 2. Findings in patient 2. A, Fundus photograph of the right eye showing a normal appearance. B, Goldmann kinetic perimetry showing a blind spot enlargement and central scotoma in the right eye. Optical coherence tomographic images horizontally profiled along the foveola (C), and magnified optical coherence tomographic images in the region of the visual field abnormality (D). In both eyes, the inner segment–outer segment (IS/OS) junction is clearly observed. In the right eye, the cone OS tip (COST) line is partially observed but appeared more indistinct than in the left eye. The foveal bulge (asterisk) cannot be seen in the right eye.


Adult Ovarian Retinoblastoma Genomic Profile Distinct From Prior Childhood Eye Tumor

We report the first case of a woman, previously cured of childhood intraocular retinoblastoma, who developed tumor in the ovary with histological and genomic characteristics suggesting an independent retinoblastoma, not a metastasis.
Report of a Case. Bilateral Retinoblastoma. In a 10-month-old girl with esotropia for 6 months, the right eye was classified as group IVb (Reese-Ellsworth classification)/group D (International Intraocular Retinoblastoma Classification) and the left eye was classified as group Vb/group D.1 There was no extraocular disease on computed tomography or bone marrow and cerebrospinal fluid examinations. She was cured by irradiation of the right eye and enucleation of the left eye. There was no tumor extension into the choroid or optic nerve.

Ovarian Tumor. At age 19 years, she had constipation and abdominal distention, with a large abdominal mass on computed tomography (Figure 1A and B). After an open biopsy, she underwent laparotomy for resection of a left ovarian tumor and fallopian tube, mesentery, and lymph nodes, which were involved by tumor, and drainage of 5 L of ascites containing no tumor cells. The variagated, white-tan-pink, bosselated, 24 × 19 × 15-cm ovarian tumor contained solid, cystic, and gelatinous areas separated by fibrous septae. Small, round, blue cells with molded round-to-ovoid nuclei and scant eosinophilic cytoplasm were arranged in nests and lobules (Figure 1C), amidst uninvolved ovarian stroma and follicles (Figure 1D) that were positive for vimentin (Figure 1E) and ovarian markers. There was no teratoma. Mitotic figures and apoptotic bodies were common (Figure 1F). The concurrent presence of Homer Wright (Figure 1G) and Flexner-Wintersteiner (Figure 1H) rosettes was pathognomonic for retinoblastoma. Tumor cells stained positively for CD56, MIB-1, and synaptophysin (Figure 1I-K) but did not colocalize with ovarian markers.

Postoperatively, her tumor recurred rapidly, but she responded to 4-cycle carboplatin-etoposide chemotherapy. She received etoposide-melphalan conditioning and autologous stem cell rescue of bone marrow, but she relapsed and died 9 months later.

Molecular Analyses. The patient was heterozygous in blood and homozygous in the eye and ovarian tumors for a C to G point mutation causing an immediate nonsense codon in exon 23 of the RB1 gene (TAC→TAG, Tyr790X).

The DNA from the ovarian and eye tumors was tested by quantitative multiplex polymerase chain reaction2 for copy number changes in the KIF14, DEK, E2F3, and MYCN oncogenes and the CDH11 tumor suppressor gene, which constitute post-RB1 mutations in retinoblastoma.

Figure 1. Radiological and pathological imaging. A, Coronal computed tomographic image of the abdomen showing a large pelvic tumor (arrowhead) extending into the abdomen with marked ascites. B, Axial computed tomographic image showing cystic (double arrowheads) and solid (single arrowhead) areas in the pelvic tumor. C, Section of the ovarian mass showing the small blue cell tumor, with a normal ovarian follicle in the lower right corner (hematoxylin-eosin). D, Ovarian follicle (hematoxylin-eosin). E, Immunohistochemistry of the normal ovary showing vimentin positivity (inhibin, desmin, calretinin, actin, and pancytokeratin positivity not shown). F, Magnification of the small blue cell tumor (hematoxylin-eosin). Homer Wright rosettes (G) and Flexner-Wintersteiner rosettes (H) in the ovarian tumor (hematoxylin-eosin). Immunohistochemistry of the ovarian tumor showing CD56 positivity (I), a high MIB-1 index (J), and synaptophysin positivity (K) (also positive for neuron-specific enolase but negative for chromogranin, desmin, CD99, pancytokeratin, S-100 protein, HMB45, epithelial membrane antigen, and CEA-P, not shown).
tumorigenesis.\textsuperscript{2,3} ACVRL1 and RLBP1 were used as 2-copy controls (Figure 2), normal blood was used as a negative control, and a retinoblastoma with known gains and loss was used as a positive control. Distinct profiles were observed: the eye tumor showed gain of KIF14 (mean copy number, 2.77) and MYCN (mean copy number, 4.80) with single-copy CDH11 (mean copy number, 1.04), whereas the ovarian tumor showed no KIF14 gain, amplification of MYCN (mean copy number, 19.50), and 2-copy CDH11 (mean copy number, 2.21) (Figure 2). DEK and E2F3 were not gained in either tumor.

Comment. We consider 2 possible explanations for our observation of retinoblastoma manifesting in the ovary: late metastasis or independent malignant transformation. Late metastasis is unlikely 18 years after cured retinoblastoma. Metastasis usually occurs in the first few years after diagnosis. Ovaries are extremely rare sites, reported in only 1 other case after 2 years.\textsuperscript{4} Malignant transformation of retinal cells within an ovarian teratoma 15 years after cured retinoblastoma has been reported, but without the molecular characterization we show.\textsuperscript{5}

Our patient had no teratoma. She developed an ovarian tumor with histological (Figure 1) and molecular (Figure 2) features of retinoblastoma. Ovarian markers were observed only in uninvolved ovarian tissue, while the proliferative tumor stained for retinoblastoma markers and displayed Homer Wright and Flexner-Wintersteiner rosettes, pathognomonic for retinoblastoma. The eye and ovarian tumors both shared the same first (M1) and second (M2) RB1 mutations, likely from loss of the normal RB1 allele and reduplication of the mutated allele (loss of heterozygosity), which is observed in 52\% of retinoblastoma cases.\textsuperscript{6}

The different pattern of post-RB1 mutational events in the ovarian tumor suggests a separate clonal origin from the eye tumor. Common for retinoblastoma, the eye tumor displayed gains of KIF14 and MYCN with loss of 1 copy of CDH11.\textsuperscript{7} The ovarian tumor showed only MYCN gains.
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 RB1 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).

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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.3,5 Herein, we illustrate a case of a more recently recognized paraneoplastic retinopathy, termed acute exudative polymorphous paraneoplastic vitelliform maculopathy (AEPPVM).

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-