Progression of choroidal metastasis of ovarian serous cystoadenocarcinoma after intravitreal bevacizumab treatment

Irene C. Kuo,1 Ruben H. Sambuelli,2 Javier Bono,1 Ricardo J. Smith,4 Victor E. Reviglio1,2,4

1Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 2Pathology Department, Cornea and Anterior Segment Research, Catholic University of Cordoba, School of Medicine, Cordoba, Argentina; 3Ophthalmology Service, Cordoba Hospital, Cordoba, Argentina; 4Instituto de la Visión Cerro de las Rosas, Sanatorio Allende, Córdoba, Argentina

Abstract

A 57-year-old woman presented to her ophthalmologist because of rapid deterioration in vision. Dilated funduscopic examination of the right eye showed an elevated, yellow-orange choroidal mass temporal to the fovea; a complete retinal detachment was present in the left eye. The patient was referred to an oncologist. Computerized tomography of the brain, thorax, abdomen, and pelvis were obtained. They revealed an 11-mm mass in the right parietal lobe, a 30-mm mass in the left temporal lobe, 23-mm mass in the right kidney, and multiple nodules in both lungs. Supported by published experience with intravitreal bevacizumab for choroidal metastasis,1 bevacizumab (Avastin; Genentech, Inc, South San Francisco, California), 1.25 mg/0.05 mL, was injected via a 25-gauge needle into the vitreous through the pars plana of the left eye using a standard sterile protocol; topical moxifloxacin 0.5% drops (Vigamox, Alcon, Fort Worth, TX) were prescribed for five days. Five days after the injection, the visual acuity was unchanged; twelve days later, visual acuity was count-fingers. The tumor mass did not show signs of regression (Figure 1C). Fluorescein angiography continued to demonstrate hyperfluorescence (Figure 1D). Based on results of sonography, computed tomography and magnetic resonance imaging, and so as to avoid complications of systemic chemotherapy, her doctors decided to initiate radiation therapy to the kidney alone. Twenty days after the intravitreal injection, the visual acuity was hand motions. Dilated funduscopic examination revealed an inferior retinal detachment; the choroidal mass was unchanged. The following day, the patient developed a total retinal detachment. Biopsy of the right kidney mass indicated that the primary tumor was (occult) ovarian serous cystadenocarcinoma (Figure 3). The patient suffered from end-state complications tumor metastasis and expired one month after the intravitreal injection.

Discussion

This report describes a patient whose choroidal metastasis from occult ovarian serous cystadenocarcinoma did not respond to intravitreal bevacizumab. This case stands in contrast to a case we described of a patient whose choroidal metastasis from colon carcinoma resolved and whose visual acuity improved markedly after intravitreal bevacizumab.2 Reasons for failure in other cases may be that ovarian tumors and their metastases are not solely dependent on vascular endothelial growth factor (VEGF) for their survival as well as may be the case in colon cancer, that VEGF is sequestered in the extracellular matrix components of ovarian tumors and therefore not biologically relevant, or that VEGF expression in metastases may be heterogeneous. When evaluated in combination with chemotherapy, bevacizumab was associated with improved long-term outcomes in other tumors, leading to approval by the United States Food and Drug Administration (FDA) for use in metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma multiforme, metastatic renal cell cancer, and recurrent breast cancer (the approval for which the Food and Drug Administration revoked in December 2011). Bevacizumab is not approved for ovarian cancer; studies are ongoing as to its role in targeted therapy for ovarian cancer and optimizing chemotherapy for ovarian cancer.2,3 Ovarian serous cystadenocarcinoma accounts for 90% of all ovarian carcinomas. Malignant epithelial ovarian cystadenocarcinomas are the only ovarian cysts associated with racial differences; women from northern and western Europe (like our patient) and North America are affected most frequently, whereas women from Asia, Africa, and Latin America are affected least frequently.4 The molecular mechanisms that govern
ovarian cancer metastasis must be understood in order to treat this disease.\textsuperscript{5-10} Multiple adhesion molecules, cytokines, growth factors and extracellular matrix components are involved in ovarian cancer cell differentiation state and metastatic potential.\textsuperscript{5-10} Since high-grade serous ovarian cancer is characterized by overexpression of VEGF, interception of this pathway can be achieved through engineered binding site molecules or through monoclonal antibodies to VEGF, the most widely studied agent being bevacizumab.\textsuperscript{11}

However, data from studies of bevacizumab as concurrent therapy followed by maintenance therapy with bevacizumab or placebo for serous ovarian carcinoma suggest that VEGF blockade may have greater impact in preventing tumor regrowth, or in the management of recurrent disease, rather than augmentation of primary chemotherapy.\textsuperscript{12} One reason may be that ovarian tumors are avascular tumors that derive sufficient oxygen and nutrients by simple passive diffusion.\textsuperscript{13} To help explain the variable effect of intravitreal bevacizumab in different choroidal metastases, perhaps VEGF expression in metastases is heterogeneous among multiple metastases.\textsuperscript{13} Yet another possible reason for failure of bevacizumab to induce regression is that VEGF in a tumor may be sequestered in extracellular matrix components. VEGF can bind to a number of other circulating proteins, not just to VEGF receptors, but presumably, only the VEGF-receptor compound is biologically relevant.\textsuperscript{13} This notion is supported by pharmacokinetic findings regarding the spatial distribution of VEGF isoforms and their interactions with heparan sulfate in the extracellular matrix and metalloproteinases which cleave and induce the VEGF-mediated tumorigenesis.\textsuperscript{14-20} In individual case reports, intravitreal bevacizumab has been described as leading to the regression of choroidal melanoma,\textsuperscript{21,22} regression of iris metastasis from small-cell lung cancer,\textsuperscript{23} and regression of symptomatic circumscribed choroidal hemangioma with subretinal fluid.\textsuperscript{24} To our knowledge, there has been no report of the effect of intravitreal injection of bevacizumab on a choroidal metastasis from ovarian carcinoma. In recent years with a better understanding of the role of angiogenesis, many cancer therapies have targeted specific mechanisms of tumor growth and metastasis. However, it is challenging to predict the effects of VEGF-neutralizing agents,\textsuperscript{25-28} since angiogenic tumors can adapt to the presence of neovascularization inhibitors by acquiring the means to evade the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure1.png}
\caption{Fundus photographs and selected fluorescein angiograms of the right eye. A) Prior to injection of bevacizumab, an elevated yellow-orange choroidal mass in the temporal posterior pole is noted (asterisk); B) fluorescein angiogram shows leakage associated with the choroidal mass (asterisk); C) the mass is unchanged twelve days after bevacizumab treatment (asterisk); D) hyperfluorescence (pooling) on fluorescein angiogram twelve days after treatment (asterisk).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure2.png}
\caption{Computed tomographic (CT) scans of abdomen and thorax. A) unenhanced CT scan of the abdomen shows a mass lesion in the kidney; B) unenhanced CT scan of the thorax shows lesions in the lungs and mediastinum.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure3.png}
\caption{Biopsy of renal metastasis. A) Cell are pleiomorphic and hyperchromatic. They have high nuclear-cytoplasmic ratio and numerous mitoses (hematoxylin and eosin stain). B) Tissue stains for cytokeratin 7, a basic cytokeratin found in many glandular and transitional epithelia and their neoplasms.}
\end{figure}
blockade of angiogenesis pathways. Both tumor progression and mortality may follow a period of therapeutic response, while the tumor develops an adaptive response that mediates tissue matrix invasion. In contrast, patients like the one described here, in whom there seems to be no therapeutic response at all, may have tumors possessing an intrinsic resistance to angiogenesis inhibitors.

Conclusions

In conclusion, intravitreal bevacizumab had no effect on the choroidal lesion or on recovery of visual acuity in this case of choroidal metastasis from ovarian carcinoma. It is possible that the effect of bevacizumab on a choroidal metastasis is correlated with its effect on the primary tumor (bevacizumab not being the first-line treatment for ovarian carcinoma) or that expression of VEGF is heterogeneous or sequestered so as not to be biologically relevant. Longer follow up is required in cases where intravitreal bevaci- zumab has been reported to lead to regression of choroidal metastasis. These results may help guide practitioners as to which cases to choose intravitreal bevacizumab injections.

References

1. Kuo IC, Haller JA, Maffrand R, et al. Regression of a subfoveal choroidal metastasis of colorectal carcinoma after intravitreal bevacizumab treatment. Arch Ophthalmol 2008;126:1311-3.
2. Burger R, Fleming G. Phase III randomized study of carboplatin and paclitaxel versus carboplatin, paclitaxel, and concurrent bevacizumab without versus with extended bevacizumab in patients with stage III or IV ovarian epithelial or primary peritoneal cancer (GOG-0218). National Cancer Institute, trial NCT00262847. Available from: http://clinicaltrials.gov/ct2/show/register/NCT00262847. Accessed: September 2012.
3. Walker J. A phase III clinical trial of bevacizumab with IV versus IP chemotherapy in ovarian, fallopian tube, and primary peritoneal cancer NCPI-supplied agent(s): Bevacizumab (NSC #704865, IND #7021). National Cancer Institute, trial NCT00951496. Available from: http://clinicaltrials.gov/ct2/show/register/NCT00951496. Accessed: December 2012.
4. Miller BA, Kolone LN, Bernstein L, et al. Racial/ethnic patterns of cancer in the United States 1988-1992. Whashington DC: National Cancer Institute; 1996, NIH Pub. No. 96-4104.
5. Saad AF, Hu W, Sood AK. Microenvironment and pathogenesis of epithelial ovarian cancer. Horn Cancer 2010;1:277-90.
6. Choi KC, Kang SK, Tai CJ, et al. Follicle-stimulating hormone activates mitogen-activated protein kinase in preneoplastic and neoplastic ovarian surface epithelial cells. J Clin Endocrinol Metab 2002;87: 2245-53.
7. Lau MT, Wong AS, Leung PC. Gonadotropins induce tumor cell migration and invasion by increasing cyclooxygenases expression and prostaglandin E(2) production in human ovarian cancer cells. Endocrinology 2010;151: 2985-93.
8. Schifferbauer YS, Abranowitch R, Meir G, et al. Loss of ovarian function promotes angiogenesis in human ovarian carcinoma. Proc Natl Acad Sci USA 1997;94:13205-8.
9. Wang J, Luo F, Lu JJ, et al. VEGF expression and enhanced production by gonadotropins in ovarian epithelial tumors. Int J Cancer 2002;97:163-7.
10. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 1999;91:1459-67.
11. Bookman, MA. The addition of new drugs to standard therapy in the first-line treatment of ovarian cancer. Ann Oncol 2010; Suppl 7:vi111-7.
12. Burger RA, Brady ML, Bookman MA, et al. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or Fallopian tube cancer (FTC): a gynecologic oncology group study. J Clin Oncol 2010;28(suppl): abstract LBA1. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?view=abstract_detail_view&confID=74&abstractID=52788.
13. Kerbel S, Ellis LM. Molecular biology. In: Devita, Hellman & Rosenberg’s Cancer: principles & practice of oncology. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. pp 104-115.
14. Lee S, JiJani SM, Nikolova GV, et al. Processing of VEGF-A by matrix metalloproteinasues regulates bioavailability and vascular patterning in tumors. J Cell Biol 2005;169:681-91.
15. Hawinkels LJ, Zuidwijk K, Verspaget HW, et al. VEGF release by MMP-9 mediated heparan sulphate cleavage induces colorectal cancer angiogenesis. Eur J Cancer 2008;44:1904-13.
16. Ruhrberg C, Gerhardt H, Gölting M, et al. Spatially restricted patterning cues provided by heparin-binding VEGF-A control blood vessel branching morphology. Genes Dev 2002;16:2684-98.
17. Grunstein M, Masbad JJ, Hickey R, et al. Isoforms of vascular endothelial growth factor act in a coordinate fashion To recruit and expand tumor vasculature. Mol Cell Biol 2000;20:7282-91.
18. Rosenberg JM, Krum JM. New roles for VEGF in nervous tissue—beyond blood vessels. Exp Neurol 2004;187:246-53.
19. Williams RS, Annex BH. Plasticity of myocytes and capillaries: a possible coordinating role for VEGF. Circ Res 2004;95:7-8.
20. Small AR, Neagu A, Amoyt F, et al. Spatial distribution of VEGF isoforms and chemotactic signals in the vicinity of a tumor. J Theor Biol 2008;252:593-607.
21. Lima BR, Schoenfield LR, Singh AD. The impact of intravitreal bevacizumab therapy on choroidal melanoma. Am J Ophthalmol 2011;151:323-8.
22. Sharma RK, Balayia S, Chalam K. Bevacizumab suppression of establishment of micrometastases in experimental ocular melanoma. Invest Ophthalmol Vis Sci 2010;51:6906.
23. Nakashima C, Keino H, Watanabe T, et al. Intravitreal bevacizumab for iris metastasis of small-cell lung carcinoma with neovascular glaucoma. Jpn J Ophthalmol 2011;55:800-1.
24. Sagong M, Lee J, Chang W. Application of intravitreal bevacizumab for circumscribed choroidal hemangioma. Korean J Ophthalmol 2009;23:127-31.
25. Senger DR. Vascular endothelial growth factor: more than an angiogenesis factor. Mol Biol Cell 2010;21:377-9.
26. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002;20:4368-80.
27. Kowanetz M, Ferrara N. Antiangiogenic therapy in cancer: a new perspective. Clin Cancer Res 2006;12:5018-22.
28. Bertolini F, Mancuso P, Shahed Y, Kerbel RS. Molecular and cellular biomarkers for angiogenesis in clinical oncology. Drug Discov Today 2007;12:806-12.
29. Shojaei F, Ferrara N. Antiangiogenic therapy for cancer: an update. Cancer J 2007;13:345-8.
30. Miller KD, Sweeney CJ, Sledge GW Jr. Can tumor angiogenesis be inhibited without resistance? EXS 2005;2005:55-112.
31. Kerbel RS. Inhibition of tumor angiogenesis as a strategy to circumvent acquired resistance to anticancer therapeutic agents. Bioessays 1991;13:31-6.
32. Kerbel RS, Yu J, Tran J, et al. Possible mechanisms of acquired resistance to anti-angiogenic drugs: implications for the use of combination therapy approaches. Cancer Metastasis Rev 2001;20:79-86.
33. Fernando NT, Koch M, Rothrock C, et al. Tumor escape from endogenous, extracellular matrix-associated angiogenesis inhibitors by up-regulation of multiple proangiogenic factors. Clin Cancer Res 2008;14:1529-39.