Choroidal Mucinous Metastatic Adenocarcinoma from the Colon: A Diagnostic Challenge

Lina Ma Natalie Wolkow Frederick A. Jakobiec

David G. Cogan Laboratory of Ophthalmic Pathology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA

Established Facts

- The immunohistochemical marker CDX2 is often used to confirm that a metastasis is of colonic origin.

Novel Insights

- CDX2 expression may be lost in tumors that display microsatellite instability.
- The novel biomarker SATB2 is the most sensitive and specific marker for tumors of colonic origin, and its expression is often preserved in poorly differentiated tumors.

Keywords

Metastatic mucin-producing adenocarcinoma · Colon cancer · Choroidal metastatic tumor · SATB2 · Microsatellite instability · DNA mismatch repair enzyme deficiency

Abstract

An enucleated globe was submitted from an outside hospital to the Ophthalmic Pathology Laboratory for evaluation. There was a minimal amount of accompanying clinical history. Histopathologic examination revealed a mucinous adenocarcinoma of the choroid. The determination of the origin of the tumor proved to be challenging based on the lack of a definitive systemic diagnosis. Initial suspicions that the tumor may represent a breast carcinoma were disproved

when immunohistochemical biomarkers for breast carcinoma were negative. Similarly, typical markers of colon adenocarcinoma were not expressed. Positive immunostaining with a newer immunohistochemical marker, SATB2, and defects in DNA mismatch repair helped to confirm that the ocular metastasis was of colonic origin. Further clinical evaluation including imaging studies established that the patient had a primary colonic adenocarcinoma with widespread systemic metastases. The diagnostic utility and biologic significance of these latest immunohistochemical biomarkers for colon cancer are reviewed. Clinicians are encouraged to provide detailed clinical histories with the tissue specimens to enable the discovery of undetected “silent primaries” at the time an ocular metastasis develops and is discovered.

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Introduction

Although the most common malignancies of the choroid are systemic metastases [1, 2], gastrointestinal metastases to the choroid are unusual, representing only 1–4% of such tumors [2–4]. Most patients with choroidal metastases from the colon present with a known underlying history of colon cancer that has been treated with systemic therapies [4]. Only 5 cases have been reported in the literature of gastrointestinal cancer displaying choroidal metastases before the underlying primary bowel malignancy was found [4–7], of which only 1 was of colorectal origin [5]. A case of rectosigmoid adenocarcinoma presenting as a retinal metastasis has also been described [8]. In all prior cases, a systemic workup revealed the underlying malignancy.

We present a patient whose choroidal tumor was preoperatively thought to be a primary intraocular melanoma, and whose past history had allegedly included a breast carcinoma. In fact, the ocular lesion was the first manifestation of a colonic adenocarcinoma. The eye was enucleated and histopathologic examination revealed a mucinous adenocarcinoma. Characterization of the tumor was facilitated by newer immunohistochemical biomarkers for bowel malignancies, such as SATB2 and evidence of defects in the DNA mismatch repair system. The diagnostic utility and biologic mechanisms of these and other biomarkers in pinpointing the source of “silent” primaries are discussed. Clinicians are encouraged to communicate detailed histories to pathologists in order to reach a rapid interpretation and resolution of enigmatic cases.

Case Presentation

The research in this article is compliant with the Declaration of Helsinki and HIPAA regulations. An enucleated right globe was submitted to the Ophthalmic Pathology Laboratory from an outside hospital with only the following clinical history: “right eye, benign neoplasm of choroid.” Further inquiries of the local physicians disclosed that the patient was an 84-year-old Caucasian woman who had presented to an ophthalmologist with 3 months of progressively worsening blurry and distorted vision. Her past medical history was significant for atrial fibrillation, myocardial infarction, congestive heart failure, and chronic kidney disease; she was a former smoker. She had no history of cancer. Fundoscopic examination revealed a large nonpigmented choroidal mass superior to the optic disc with an overlying retinal detachment in the right eye (Fig. 1a). B-scan ultrasonography demonstrated a 20.9 × 18.4 × 8.2 mm tumor with low reflectivity and no extrascleral extension (Fig. 1b). A large choroidal melanoma was diagnosed and the patient was referred to an ophthalmic plastic surgeon for enucleation.

On gross examination, the globe measured 22 × 22 × 22 mm, with a clear cornea, and a blue-green iris with a round 4-mm pupil. There were no signs of extrascleral spread signified by pigmentary nodules. The optic nerve was unremarkable. The globe was sectioned in the horizontal plane, revealing a white, partially gelatinous, choroidal mass with necrotic nodules, measuring 16 mm in width × 6 mm in height (Fig. 1c). The adjacent retina was detached with subretinal viscid yellowish-translucent exudates. The anterior chamber, iris, and ciliary body were unremarkable. A pseudophakos with a Soemmering ring was noted and was removed. The P-O segment was submitted for processing.

Histopathologic examination revealed a plateau-type choroidal tumor composed of fragmented nodules, clusters and cohesive cords of basophilic cells forming glandular structures embedded within abundant extracellular mucinous material devoid of a fibrotic stroma (Fig. 1d, e). Areas of necrosis (Fig. 1f) and many mitotic figures were appreciated (Fig. 1g, inset). Immunostaining for Ki67 revealed a proliferative index of almost 100% (Fig. 2a). Intracellular vacuoles and the extracellular mucinous material were positive with the Alcian blue (Fig. 2b, c), mucicarmine, and Gomori methenamine silver methods. MART-1 and SOX-10 immunostains were negative, ruling out melanoma. Pancytokeratin (AE1/AE3) was positive in the tumor cells (Fig. 2d), confirming that it was a carcinoma. CK7 and CK20, however, were both negative, limiting further characterization of the tumor.

The referring pathologist was contacted to discuss the intraocular findings in order to guide additional testing. Preoperatively, the tumor was suspected to be a choroidal melanoma. However, the local physician noted that the patient had recent imaging studies in which systemic metastases of unknown origin were detected. These metastases were thought to originate either from the putative choroidal melanoma, a recurrence of an earlier breast cancer that had been allegedly treated many years ago, or from a yet unidentified separate primary malignancy.

Further immunostaining with biomarkers of breast carcinoma, including mammaglobin, GCDPF-15, HER2/neu, GATA3, estrogen receptor, and progesterone receptor were negative. Markers for other malignancies, including PAX8 for ovarian and thyroid carcinomas, synaptophysin for neuroendocrine tumors, TTF-1 for lung and thyroid tumors, and WT1 were also negative. CDX2, a marker of colorectal cancer, was focally very weakly positive (Fig. 2e). The case was reviewed with several pathologists at the

Fig. 1. Choroidal metastatic colonic adenocarcinoma. **a** Fundus photography of an epipapillary creamy multinodular lesion (arrows) with surrounding retinal detachment. **b** B-scan ultrasonogram reveals low internal reflectivity and absence of extrascleral extension (arrows point to tumor). **c** Fresh, gross appearance of the cut surface of a multinodular creamy tumor. (The black arrows point to the tumor, while the white arrows point to areas of retinal detachment.) **d** A highly cellular lesion overrides the optic nerve head. The arrow indicates a lighter staining, central mucinous zone. The crossed arrow points to an exudative retinal detachment. **e** Trabeculae of tumor cells enveloped by a hematoxylinophilic mucinous matrix (M). **f** Irregular masses of tumor cells (T) separated by extracellular mucin (M). The arrow points to a focus of necrosis (N). **g** Hyperchromatic, crowded tumor cells. The inset shows a mitotic figure. **d–g** Hematoxylin and eosin; ×5 (**d**), ×600 (**e**), ×200 (**f**), ×600 (**g**).

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Fig. 2. Special stains and immunohistochemical biomarkers. **a** Ki67 is virtually 100% positive. **b** Alcian blue vividly stains the mucinous stroma (M), which envelops islands of tumor cells (T) and necrosis (N). **c** The arrows highlight intracytoplasmic mucinous vacuoles. M indicates extracellular mucin. **d** Pancytokeratin (AE1/AE3) is strikingly positive. **e** CDX2, a biomarker of colonic

carcinoma and other gastrointestinal malignancies, is weakly, focally positive. **f** SATB2, a highly specific marker for colonic carcinoma, is positive. **a, d-f** Immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain; $\times 600$. **b, c**, Alcian blue, $\times 100$ (**b**), $\times 600$ (**c**).

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Massachusetts General Hospital, who agreed only that the tumor was a poorly differentiated adenocarcinoma that could represent either a primary breast (given the alleged past history) or gastrointestinal malignancy. Immunostaining for SATB2, a newer biomarker with high sensitivity and specificity for colon cancer, and for loss of expression of DNA mismatch repair genes, MSH2, MSH6, PMS2, and MLH1 was recommended. SATB2 (Fig. 2f), MSH2, and MSH6 (Fig. 3a, b) were expressed in the tumor cells, while expression of PMS2 and MLH1 had been lost (Fig. 3c, d), confirming a likely diagnosis of a primary colon cancer.

Further discussion with the outside physicians revealed the following additional history. Prior to the enucleation and the diagnosis of presumed choroidal melanoma, just a few weeks after the onset of her visual symptoms, the patient had been hospitalized for shortness of breath for an exacerbation of congestive heart failure. A CT scan demonstrated a large pericardial effusion, small bilateral pleural effusions as well as multiple new lung nodules, the largest measuring 2.3 cm, concerning for a malignancy. In subsequent weeks, concurrent with her diagnosis of presumed choroidal melanoma, a whole-body PET/CT revealed an FDG-avid mass in the right eye (Fig. 3e, arrow), as well as numerous lung, liver, mediastinal and right hilar FDG-avid masses consistent with metastases (Fig. 3f, g, arrows). One particularly large mass (7.4×5.1 cm) was seen in the right lower quadrant of the abdomen, in the area of the cecum, and was interpreted by the radiologist as the probable site of primary malignancy (Fig. 3h, arrow). Despite this new information preoperatively, the enucleation was nevertheless performed.

In the postoperative period, the patient underwent an intense, selective oncologic evaluation. Serologic studies revealed an elevated carcinoembryonic antigen level of 29.5 ng/mL (reference range ≤ 3.4 ng/mL), an elevated cancer antigen 125 level of 52 U/mL (reference range ≤ 35 U/mL), and an elevated cancer antigen 19-9 level of 110 U/mL (reference range ≤ 35 U/mL), consistent with colon cancer. Systemic treatment with Xeloda (cepecitabine) was offered, but the patient declined therapy.

Discussion

Poorly differentiated uveal carcinomatous metastases without an obvious primary tumor source pose a significant diagnostic challenge to pathologists and to treating clinicians. The work of the pathologist becomes even more difficult if a detailed clinical history is not available.

Fig. 3. Microsatellite instability markers and PET/CT scan results. **a** MSH2 expression is preserved. **b** MSH6 is also expressed. **c** PMS2 expression has been lost from the tumor cells. **d** MLH1 expression is also absent in the tumor cells. **e** PET/CT scan shows FDG-avid uptake by the right intraocular tumor, which is indicated by an arrow. **f** Several FDG-avid nodules are seen in the lung (arrows) on PET/CT scan. **g** Metastases are also seen in hilar lymph nodes (arrows) as strong FDG-avid foci on PET/CT scan. **h** A large FDG-avid mass is seen in the right lower quadrant of the abdomen (arrow), corresponding to the cecum, thought to represent a primary malignancy. **a–d** Immunoperoxidase reaction; $\times 600$.

Uveal carcinomatous metastases are the most common type of intraocular malignancy. As an estimate, they are 5–50 times as common as primary uveal melanomas [2, 3, 9–11]. Only two-thirds of patients presenting with a metastatic lesion in the uveal tract have a known underlying primary malignancy [4]. Thus, in a significant number of patients, a primary tumor must still be identified. Only in half of these cases with an unknown primary tumor will the source malignancy be identified after a thorough evaluation [4].

Gastrointestinal metastases are relatively underrepresented in the uvea [2, 4, 12]. This implies either an underlying molecular property that makes the uvea particularly attractive to breast and lung cancers, or a molecular difference between lung, breast and gastrointestinal primary tumors that allows breast and lung cancers to metastasize more readily to the uvea. Carcinoma can metastasize to the uvea from any portion of the colon, although the sigmoid colon and rectum appear to be most highly represented [2, 13]. In most cases, an underlying history of colon cancer is known [4]. Only 1 patient has been previously reported in the literature who had a choroidal metastasis from a colorectal primary without an established prior diagnosis [5]. Colon cancer is often a mucinous adenocarcinoma. It has recognizable histopathologic features that, along with selected immunohistochemical biomarkers, allow for its identification (Table 1) [14]. Positive expression of CK20 or CDX2 is commonly used to confirm a colorectal origin [14]. CK20 is an intermediate cytoplasmic filament that is expressed in glandular cells of the gastrointestinal tract, while CDX2 is a transcription factor that is expressed throughout the whole gastrointestinal tract. Positive expression of these two markers is often sufficient in confirming a diagnosis of colorectal cancer [15]. A subset of colorectal cancers, however, loses expression of these genes [16], necessitating alternative diagnostic strategies. Moreover, although very sensitive, CDX2 and CK20, are not entirely specific for colorectal carcinomas, and may be expressed by adenocarcinomas originating from other tissues [17–19].

CDH17 and SATB2 are newer biomarkers that are more specific for colon cancer than CK20 and CDX2 [14, 17, 19, 20]. CDH17 is a cell adhesion molecule that is under the transcriptional regulation of CDX2 [17, 18]. Like CDX2, CDH17 is expressed throughout the whole gastrointestinal epithelium, but it is more specific than CDX2 [17, 18]. SATB2 is a nuclear transcription factor whose expression is restricted to the lower gastrointestinal tract; it is considered to be the most sensitive and most specific marker for colorectal adenocarcinoma [14, 17, 19, 20].

Table 1. Use of immunohistochemical biomarkers in the differential diagnosis of metastatic mucinous adenocarcinomas of the globe and ocular adnexa

Primary mucinous adenocarcinoma	Biomarkers
Breast ^a	<p><i>Expected: CK7 positive; ER positive; HER2/neu negative; CK20 negative.</i></p> <p>Helpful if positive, but is not always expressed: GATA3 (<i>this marker may also be positive in other malignancies</i>). Mammaglobin, GCDP-15 and PR. <i>These markers are more specific than GATA3, but less sensitive.</i></p> <p>Potentially misleading: WT1 may be expressed in 50%. Neuroendocrine markers (synaptophysin, chromogranin) may be expressed.</p>
Lung ^b	<p><i>Expected: CK7 positive (but sometimes expression is lost).</i></p> <p>Helpful if positive, but is not always expressed: TTF-1 (only in 50% of mucinous) – <i>very helpful if positive.</i> Napsin A (only in 30% of mucinous) – <i>very helpful if positive.</i> ALK gene rearrangements – associated with mucinous histology.</p> <p>Potentially misleading: CK20 and CDX2 may be focally positive in some cases.</p>
Ovarian (intestinal and endocervical subtypes) ^c	<p><i>Expected: CK7 positive;</i> – Intestinal subtype usually also CK20 positive; PAX8 usually focally positive – <i>very helpful if positive.</i> – Endocervical subtype typically negative or weakly positive for CK20; ER and PR are usually positive.</p> <p>Potentially misleading: WT1 usually negative in mucinous ovarian tumors; often positive in other ovarian tumors.</p>
Colon	<p><i>Expected: CK7 negative; CK20 positive (if undifferentiated, CK20 expression may be lost); SATB2 positive (this marker is very sensitive and specific to colorectal tumors).</i></p> <p>Helpful if positive, but is not always expressed: CDX2: <i>Expression typically very strong and diffuse if colon cancer; patchy, focally positive staining may also be present in upper gastrointestinal tract, pancreatic, ovarian, endometrial, cervical, urinary bladder and pulmonary tumors.</i> CD117: <i>More specific than CDX2, but expressed in tumors from all parts of gastrointestinal tract, and some pulmonary and endometrial tumors; marker not as commonly used as CDX2 and SATB2.</i> Microsatellite instability (MSI): <i>Occurs in 15% of colon cancers and sometimes in endometrial – typically MLH1 and PMS2 expression is lost; if loss of other markers, consider Lynch syndrome; MSI is associated with loss of CDX2 expression.</i></p>
Upper gastrointestinal tract or pancreaticobiliary	<p><i>Expected: Partially focally positive for CK7, CK20 and CDX2.</i></p> <p><i>Useful immunostain: Loss of SMAD4 expression favors pancreatic cancer.</i></p>

ALK, anaplastic lymphoma kinase; CDX2, caudal type homeobox 2; CK7, cytokeratin 7; CK20, cytokeratin 20; ER, estrogen receptor; GATA3, GATA binding protein 3; GCDP-15, gross cystic disease fluid protein 15; HER2/neu, human epidermal growth factor receptor 2; Napsin A, novel aspartic proteinase of the pepsin family; PAX8, paired box gene 8; PR, progesterone receptor; SATB2, special AT-rich sequence-binding protein 2; SMAD4, SMAD family member 4; TTF-1, thyroid transcription factor; WT1, Wilms tumor protein. ^a Only 5% of breast cancers are mucinous. ^b Only a small percentage of lung adenocarcinomas are mucinous. ^c There are many subtypes of ovarian carcinoma; the main subtypes to consider in the differential of mucinous adenocarcinomas are intestinal and endocervical.

Expression of SATB2 and CDH17 may be preserved even when expression of CK20 and CDX2 is lost [14, 16].

Loss of CK20 and CDX2 expression is associated with poorer tumor differentiation and defects in the expression of DNA mismatch repair genes, which results in microsatellite instability [16, 21, 22]. Microsatellites are regions of noncoding DNA that are composed of short, repeating sequences. These sequences are highly prone to mutations and errors during cellular replication, which, if left uncorrected, affect the expression of neighboring

genes, contributing to tumorigenesis. A special group of proteins, called DNA mismatch repair proteins, which include MLH1, PMS2, MSH2, and MSH6, are responsible for correcting the errors in the DNA microsatellite regions. These proteins form heterodimers, MLH1 pairing with PMS2, and MSH2 pairing with MSH6 [16, 21, 23].

Germline mutations in the DNA mismatch repair genes underlie the Lynch syndrome, in which there is an increased incidence of colorectal cancer; epigenetic silencing inactivates expression of DNA mismatch repair

genes in 15–20% of sporadic colorectal cancers [14, 21, 23]. The epigenetic silencing typically occurs through DNA promoter hypermethylation [21, 23]. In sporadic colorectal cancers, epigenetic inactivation of the MLH1 gene leads to loss of its protein expression, as seen with immunohistochemical staining (Fig. 3d) [16, 21, 23]. In addition, immunostaining for PMS2, the heterodimer partner of MLH1, is lost (Fig. 3c), because without MLH1 as a physical partner, PMS2 is unstable and is rapidly degraded [16, 21, 23]. Loss of mismatch repair gene expression is seen only in tumor cells, while normal, surrounding stromal cells continue to express these markers and act as positive controls (Fig. 3d, e) [14, 16, 21, 23]. Immunohistochemical loss of expression of the DNA mismatch repair genes strongly correlates with the PCR evidence of microsatellite instability [21, 22]. In clinical practice, because immunohistochemical testing is easier to perform than PCR testing, immunohistochemical loss of DNA mismatch repair gene expression is commonly used as a surrogate marker for microsatellite instability. Immunohistochemical evidence of loss of DNA mismatch repair gene expression in colorectal cancer is associated with loss of CDX2 and CK20 expression, poorer tumor differentiation, older patient age, right-sided tumor location, nodal metastases and poorer survival, all encountered in our patient [16].

In the present patient, although melanoma was clinically suspected, it was easily ruled out on microscopic examination because of the presence of copious extracellular mucinous material and the absence of melanin granules, pancytokeratin expression, S100, SOX10 and MART1 negativity, and the extraordinarily high proliferation index (Ki67). Distinguishing among various mucinous adenocarcinomas became more difficult, since CK7 and CK20, which help differentiate colon from breast and lung, were both negative, and CDX2, which is often positive in colon cancer, was very weakly staining. Moreover, the patient had a supposed remote history of breast cancer, was a long-time former smoker, and had FDG-avid lesions on CT/PET scan in the lungs as well as the colon. The loss of expression of the DNA mismatch repair genes, MLH1 and PMS2, along with the strongly positive SATB2 immunostaining, allowed for confirmation of colon cancer. SATB2 has similarly been helpful in distinguishing colorectal adenocarcinomas from mucinous adenocarcinomas of other organs, including pulmonary and ovarian tumors, when standard immunohistochemical markers [24] have been insufficient (Table 1) [17, 25, 26].

One should take note that among adenocarcinomas of the breast and of the lung, mucinous adenocarcinomas

are uncommon, and often have a markedly different immunostaining pattern from nonmucinous adenocarcinomas. These expression patterns may be difficult to interpret. Certain biomarkers are highly specific for particular tumor origins, although unfortunately they are not always expressed. When expressed, strong, diffuse expression of SATB2 or CDX2 is highly suggestive of colonic adenocarcinoma. TTF1 and Napsin A expression strongly support lung adenocarcinoma. Estrogen receptor positivity points to breast or ovarian carcinoma. Finally, loss of SMAD4 is useful in identifying pancreatic adenocarcinoma (Table 1).

An interesting feature of the current choroidal tumor was that, on the preoperative imaging studies (B-scan and CT scan) as well as on gross inspection, it was plateau-shaped and multinodular, but not dome-shaped like primary ocular melanomas. Most primary ocular melanomas break through Bruch's membrane into the subretinal space to create a mushroom shape. Thickening or flattening evidenced by a choroidal mass is more consistent with metastases [4, 27], or rarely a diffuse melanoma. Ocular metastases from gastrointestinal and kidney cancers in particular tend to be thicker than those from other sites [4]. In addition, the tumor grew rapidly (confirmed by the high proliferative index), which is a feature more commonly seen in metastases than in primary ocular melanomas [4].

From the current case, a number of lessons were learned. It is apparent that the results of many diagnostic tests were not integrated into a holistic picture and that certain studies were not fully appreciated for their diagnostic value.

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Statement of Ethics

The study followed the tenets of the Declaration of Helsinki and was approved by the Massachusetts Eye and Ear Infirmary Institutional Review Board.

Disclosure Statement

The authors declare no conflicts of interest.

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