Metastatic Amelanotic Melanoma of the Jejunum Diagnosed on Capsule Endoscopy

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Gastrointestinal (GI) metastasis of malignant melanomas from known primary tumors is a common autopsy finding (50–60%). However, early detection of small bowel melanomas remains a challenge for both radiologists and clinicians. Capsule endoscopy (CE) may be able to detect the presence of small bowel metastases in patients with melanomas more reliably than conventional investigative techniques. We report a case of small bowel metastatic amelanotic melanoma found on CE. A brief review of the literature focusing on the diagnostic yield of CE is also given.

Case Report

An 81-year-old white male presented with a 1-week history of intractable nausea and vomiting. He denied having abdominal pain, hematemesis, melena, hematochezia, or weight loss. The patient's medical history was remarkable for iron-deficiency anemia, hypertension, dyslipidemia, and a remote history of a cutaneous melanoma on the right side of the neck, which was resected in 2004. Pathologic examination of this melanoma showed a lesion that was 2.4 mm in thickness (stage II, T3bN0M0). Physical examination revealed pale conjunctiva and palms. Laboratory data were significant for a hematocrit level of 27.2; carcinoembryonic antigen, lactate dehydrogenase, and electrolyte levels were normal.

Due to his history of melanoma and iron-deficiency anemia, the patient had had an extensive work-up performed in the past—including repeated computed tomography (CT) scans of the neck, chest, and abdomen, all of which had normal findings. He also had 2 esophagogastroduodenoscopies and a colonoscopy, all of which had normal findings. The patient was started on intravenous iron for management of his anemia. Given his prior negative work-up, a CE was performed; this procedure showed an actively bleeding, ulcerated, small bowel mass (Figure 1). The capsule was retained. Enteroscopy or surgery was recommended.

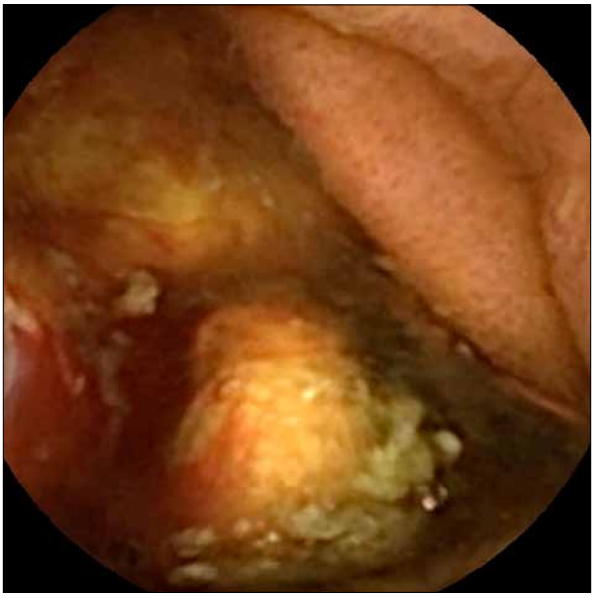

Figure 1. Capsule endoscope in the small intestine showing active bleeding.

On surgical exploration, a large (7 cm × 9 cm), irregular, multilobed, midjejunal mass was found; this mass extended into the mesentery. Immunohistochemical staining with S-100 and human melanoma black 45 antibody was positive in tumor cells (Figures 2A and 2B). No nodal metastasis was seen. Histopathology showed an amelanotic malignant melanoma invading the muscularis propria and subserosal tissue without involvement of the visceral peritoneum. A positron emission tomography (PET) scan showed a solitary hepatic metastasis, which was destroyed with CT-guided radioablation (Figure 3).

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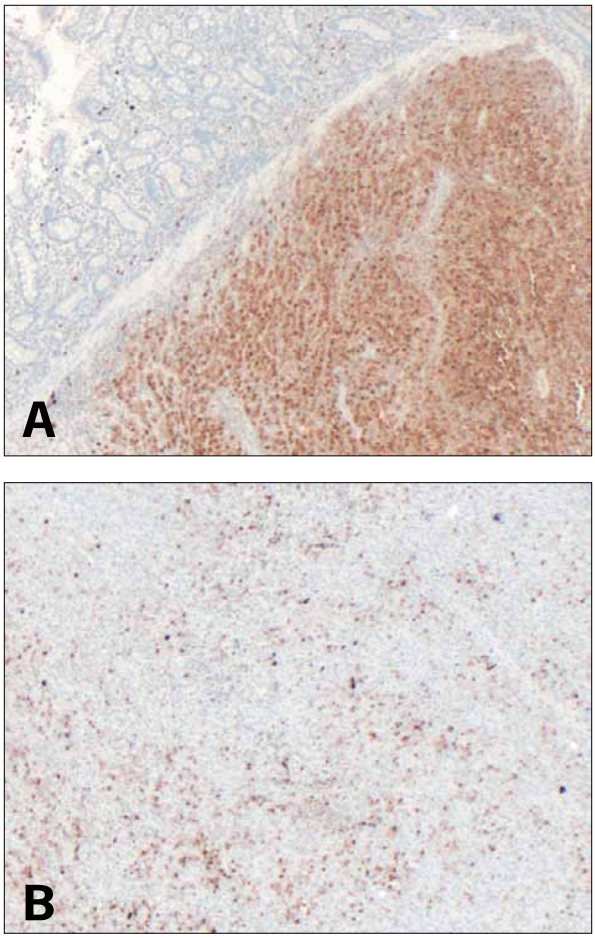

Figure 2. S-100 immunostaining showing pigmented cells (25× magnification). This marker is relatively nonspecific but is rather sensitive for melanomas (**A**). View showing scattered cells positive for the human melanoma black 45 antibody (brown cells are positive), a marker commonly seen in melanomas (25× magnification; **B**).

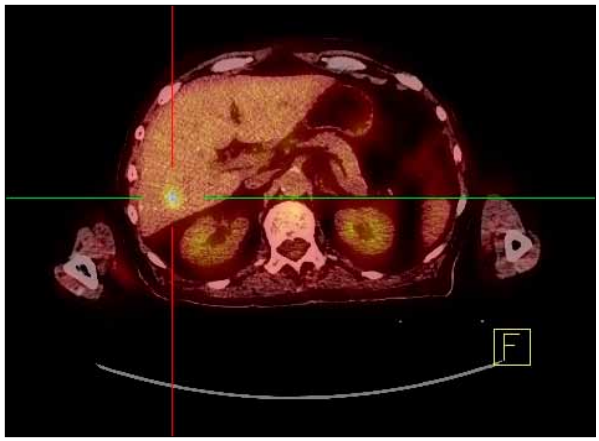

Figure 3. Positron emission tomography–computed tomography scan showing the intrahepatic lesion.

Discussion

Small bowel tumors are rare, accounting for only 3–6% of all GI tumors.[1] Melanomas of the GI tract are either primary or metastatic. Primary tumors are extremely rare. According to some researchers, primary melanoma of the GI tract does not exist as a separate clinical entity but rather represents metastatic lesions from unknown or regressed primary cutaneous melanomas.[2,3] Therefore, establishing the exact origin (primary or secondary) of a small bowel melanoma can be difficult or impossible and remains a challenge for both clinicians and radiologists.

Among patients who are diagnosed with a cutaneous melanoma, approximately 60% have a GI metastasis, but only 1.5–4% of these metastases are diagnosed during the patient's lifetime, as evidenced by autopsy series.[4-8] Superficial spreading melanoma is the most common type of melanoma that metastasizes to the small bowel. The primary tumor is typically located in the extremities (15–57%), the trunk (13–54%), or, less frequently, in the head and neck (5–33%). Metastatic melanoma can present as 1 of 4 different morphologies: cavitary, infiltrating, exoenteric, or polypoid.[9]

The period between the diagnosis of the primary melanoma and the GI metastasis is reported to be 60–90 months.[10] Clinical signs and symptoms of GI metastases include abdominal pain, intestinal obstruction, constipation, hematemesis, melena, anemia, fatigue, weight loss, and the presence of a palpable abdominal mass. GI metastases predominantly present in 2 ways.[11,12] The most common presentation is as a submucosal implant that extends intraluminally, where it eventually leads to pain, obstruction, ulceration, and acute or chronic blood loss. The other common presentation is a polypoid lesion, which can present as an intussusception, as described in this case report.[8]

The diagnosis of small bowel melanomas remains a challenge for both clinicians and radiologists. Previously, ultrasonography, small bowel follow-through, enteroclysis, computed axial tomography scans, and CT enteroclysis were common radiographic modalities for diagnosing small bowel tumors. Conventional enteroclysis was the primary method for early detection of small bowel melanomas. CT scans have a sensitivity of 60–70% for detecting metastases.

Modalities that were previously used to investigate obscure GI bleeding (OGIB), such as push enteroscopy (PE) and intraoperative enteroscopy, are now limited to increasingly selective situations. Newer technologies, including CE and double-balloon enteroscopy (DBE), now play a major role in the evaluation of OGIB. DBE is better than CE, as biopsies can be taken under direct visualization with DBE, but CE has the advantages of being noninvasive and less expensive. CE has consistently been shown to be superior to PE and small bowel radiography for detecting small bowel

lesions. A meta-analysis of studies comparing the yield of CE to those of other diagnostic modalities in patients with OGIB showed that the yield of CE was double that of PE (63% vs 28%).[13] The same meta-analysis reported the yield of CE to be higher than the yield of small bowel radiography for clinically significant lesions (42% vs 6%).[13] Another meta-analysis of 24 studies reported the yield of CE (for all indications) to be 87%, compared to 14.8% and 9.9% for PE and small bowel series, respectively.[14]

Magnetic resonance enterography (MRE) is a relatively new modality that has emerged along with CE. No large trials have been performed to compare CE and MRE. A small study showed better diagnostic yield with CE compared to MRE (100% vs 67%) for detection of small bowel tumors, but this study was limited due to its small size.[15] CE and MRE are complementary for the evaluation of the small bowel. CE can readily depict and characterize subtle mucosal lesions, which may be missed with MRE, whereas MRE offers a rapid overview of the small bowel and provides additional mural, perienteric, and extraenteric information.

More recently, fludeoxyglucose (FDG) PET-CT has been used to identify sites of metastasis. Prakoso and colleagues compared CE and PET-CT scanning for detection of small bowel metastases.[16] They concluded that CE was better than FDG PET-CT scanning for localizing small bowel melanomas and that CE is an ideal complementary investigative modality both for patients with known metastatic melanomas who are undergoing preoperative work-ups and for patients with unexplained anemia or GI symptoms.[16] Another single-center trial showed that CE is superior to other diagnostic modalities for diagnosing small bowel tumors. In 77% of cases, CE was able to demonstrate malignancies that were not identified during the previous diagnostic work-up.[17]

The main limitation of CE is its inability to obtain biopsies or administer therapy. The most common complication of CE is capsule retention, which occurred in our patient due to an obstructive lesion. Pooled retention rates were found to be 1.4% overall and 1.2%, 2.6%, and 2.1% for CE performed in patients with OGIB, Crohn's disease, and neoplastic lesions, respectively.[18] Risk factors for capsule retention include use of nonsteroidal anti-inflammatory drugs, abdominal radiation injury, extensive Crohn's disease, and previous major abdominal surgery.[19]

Surgery is the treatment of choice for metastatic small bowel melanomas. Surgery is not a curative treatment, but it is effective in palliating symptoms and may prolong survival. The significance of complete resection on postoperative survival is well described in the literature.[11,20,21]

Systemic chemotherapy and immunotherapy have a limited role in these patients. Dacarbazine has been used in the past with little or no benefit. Ipilimumab (Yervoy, Bristol-Myers Squibb), a cytotoxic T-lymphocyte antigen 4 receptor blocker, has been recently approved by the US Food and Drug Administration (FDA). Ipilimumab is the first agent that has increased median survival, from 6.4 months to 10 months.[22] Another agent, vemurafenib (Zelboraf, Hoffmann-La Roche), which targets the *BRAF* mutation, was approved in August 2011 for treatment of unresectable or metastatic melanoma with the *BRAF* v600E mutation, which is detected by an FDA-approved test.

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Review

Capsule Endoscopy for Management of Small Bowel Melanoma—Is It Time Yet?

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The global burden of melanoma is increasing. Currently, 132,000 cases of melanoma are diagnosed each year worldwide.[1] In Australia, which has the highest incidence of melanoma in the world, more than 11,000 new cases are diagnosed every year.[2] The number of cases doubled in the 20 years from 1986 to 2006.[2] In 2007, a total of 1,279 Australians died from melanoma, making this cancer responsible for 3.2% of all cancer deaths.[2] Overall, 1 in 19 Australians will be diagnosed with melanoma before the age of 85 years. The risk of melanoma is higher among men than women (1 in 15 vs 1 in 24, respectively).[2] Melanoma is now the third most common form of cancer in both Australian men (behind prostate cancer and colon cancer) and Australian women (behind breast cancer and colon cancer), and melanoma comprises 10% of all cancers.[2] It is the most common cancer in young Australians (aged 15–44 years), and it kills more young Australians than any other single cancer.[2] Although melanoma makes up only 2.3% of all skin cancers, it is responsible for 75% of skin cancer deaths.[2]

In the United States, the incidence of melanoma is about one third as high as in Australia, but this incidence has also been increasing over the past 30 years.[3,4] Between 1992 and 2004, the rate of diagnosis rose by 3.1% annually.[5] An estimated 123,590 new cases of melanoma were diagnosed in the United States in 2011, resulting in 8,790 deaths.[3] As in Australia, melanoma is the most common form of cancer for young adults in the United States.[6] Of particular concern is the rise seen among women aged 15–29 years, in whom the torso is the most common location of the tumor. This finding has been attributed to high-risk tanning behaviors.[7] Melanoma is 10 times more common in whites than in African Americans, Latinos, and Asians, but it is frequently fatal in these ethnic groups.[3,5] One American dies of melanoma almost every hour (every 62 minutes).[3]

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European figures also show an increasing incidence of melanoma.[8,9] The highest rates have been reported in Scandinavia, where 15 patients are diagnosed per 100,000 individuals per year. This finding is due to the high-risk skin type of this population.

The rates of melanoma in Mediterranean countries are lower, at 5–7 cases per 100,000 individuals per year.[10] Data from Asia, the Middle East, and Africa are limited but indicate low rates of melanoma in these areas.[8]

The risk of developing melanoma depends on a combination of genetic and environmental factors. A personal or family history of melanoma increases this risk significantly, as does the presence of atypical or numerous moles (more than 50), immunosuppression, and/or a history of other skin cancers.[3] Other factors that make melanoma more likely include sun sensitivity (characterized by sunburning easily, difficulty tanning, and natural blond or red hair color), excessive sun exposure, and use of tanning booths; this recreational sun exposure is the main reason for the rising incidence of melanoma, particularly among patients with fair skin, who have a higher risk overall.[1] Depletion of the ozone layer, with its protective function as a filter for ultraviolet radiation, may also be contributing to the rising rates of melanoma. Estimates suggest that a 10% decrease in ozone levels will result in an additional 4,500 cases of melanoma.[1]

Clinicians have long recognized that melanoma is more likely than other skin tumors to spread to other parts of the body, and melanoma is the most common tumor to metastasize to the gastrointestinal (GI) tract. When it does metastasize to the GI tract, the small bowel (SB) is involved more frequently than the stomach or the colon.[11-15] Primary SB melanoma is extremely rare.[16] The case report by Atiq and coauthors adds to previous reports of SB involvement by melanoma.[17] Importantly, this case illustrates that not all patients are symptomatic, not all melanoma lesions are pigmented, and the most common lesion is polypoid in nature.[18-20] In this particular case, the pretest probability of finding an abnormality was high since the patient had one of the most common indicators of possible SB melanoma, namely iron-deficiency anemia due to occult bleeding.[16,21-23]

Albert and colleagues recently proposed an algorithm for the detection of SB melanoma.[24] In their open, multicenter, prospective study, 390 patients with melanoma of all stages were screened for GI bleeding using fecal occult blood testing (FOBT). Those patients who were positive by FOBT underwent panendoscopy, including capsule endoscopy (CE). In addition, all patients with stage IV disease (distant metastases) were offered panendoscopy. Forty-nine of the 390 patients (12.6%) were positive by FOBT or had other evidence of GI bleeding. Thirty-eight of these patients (77.6%) agreed to

undergo endoscopic evaluation. The detection rate of SB melanoma was 28.6% in patients with stage IV disease but then dropped significantly: 1.7% in patients with stage III disease (nodal involvement) and 0% in patients with stage I/II disease. In patients who were FOBT-positive alone, SB melanoma detection rates were higher: 72.7% in patients with stage IV disease and 14.3% in patients with stage III disease. In 10 patients, SB melanoma was detected by CE. Albert and colleagues also found that a positive FOBT result was an independent, negative prognostic factor for survival in patients with stage III or IV disease.[24]

The question that always arises is whether there is any clinical benefit to the detection of SB involvement by melanoma. Approximately 84% of melanomas are diagnosed when they are still localized. Treatment at this early stage is generally successful, with a 5-year survival rate of 98%.[3] This rate falls to 62% and 16% for patients with regional and distant spread, respectively. Patients with advanced disease are more likely to have SB involvement.[24] Similarly, those with secondary tumors in the SB will often have metastases elsewhere.[25] While the prognosis in this group is generally poor, studies have shown that complete resection of metastatic melanoma can significantly improve survival and provide effective palliation.[14,15,22,23,26-28] This reasoning also applies to resection of GI disease, which is safe and can achieve prolonged remission.[29] It is therefore recommended that clinicians attempt to identify SB secondary tumors in symptomatic patients who are undergoing treatment with "curative" intent.

It is reasonable to hypothesize that finding SB melanoma at an earlier stage could improve survival. As mentioned by Atiq and coauthors in their literature review, CE is superior to other modalities for detecting SB tumors.[17] Given that the SB is the most common location for GI melanoma metastases, CE would seem to be an ideal diagnostic tool.[11-15] We have previously reported that CE is more sensitive than SB follow-through and abdominal computed tomography (CT) for detecting SB melanoma.[19] CE can also identify SB involvement that is not seen on fludeoxyglucose positron emission tomography–CT scanning, although the converse may also apply.[18]

In the case report by Atiq and colleagues, the capsule was retained.[17] However, the case report does not document whether it was found at surgery. Capsule retention is a possibility in any patient with a tumor. However, in our series, the capsule passed spontaneously in all patients.[18] Nevertheless, the possibility of capsule retention is not a contraindication to the procedure, provided the patient does not have a history of small bowel obstruction.

At present, we recommend that melanoma patients be investigated by CE for possible SB disease if they have either iron-deficiency anemia or unexplained GI symptoms or signs, provided they do not have end-stage disease that would preclude further treatment if metastases are found. Likewise, any patient with increased uptake in the abdomen on a PET-CT scan should also undergo CE. These 2 investigations should be regarded as complementary.

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