CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 32-2018: A 36-Year-Old Pregnant Woman with Newly Diagnosed Adenocarcinoma

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PRESENTATION OF CASE

Dr. Malavika Prabhu (Obstetrics and Gynecology): A 36-year-old pregnant woman was evaluated at this hospital at 33 weeks of gestation because of newly diagnosed adenocarcinoma.

Seven months before this admission, when the patient was at her initial routine prenatal visit, transvaginal ultrasonography revealed a normal gestational sac and embryo. Thereafter, prenatal follow-up was uneventful, although she had abnormal results on a 1-hour glucose tolerance test at 27 weeks of gestation.

One week before the current evaluation, at 32 weeks of gestation, the patient had 3 days of nonradiating, severe pain in the lower back that she rated at 10 on a scale of 0 to 10, with 10 indicating the most severe pain. The pain started in the epigastric region and then migrated to the right upper quadrant and lower back. It was accompanied by severe nausea and an inability to eat any food or drink liquid without vomiting. She had night sweats and difficulty sleeping because of back pain. Four days after the pain began, the patient was admitted to the obstetrics service of another hospital.

On examination, the temperature was 36.6°C, the heart rate 96 beats per minute, the blood pressure 105/68 mm Hg, and the oxygen saturation 97% while the patient was breathing ambient air. She appeared to be uncomfortable. There was tenderness in the right upper quadrant, and the gravid uterus was soft. There was no costovertebral tenderness. The remainder of the examination was normal. The amylase and lipase levels and the white-cell differential count were normal; additional laboratory test results are shown in Table 1.

Fetal heart tones were noted on Doppler ultrasonography, and the measurements of the fetus on ultrasonography were appropriate for gestational age. The fetal biophysical profile (breathing motion, movement, tone, and amniotic-fluid volume) was reportedly normal.

Dr. Kimberly Shampain: On renal ultrasonography, the kidneys and bladder appeared normal but the liver was incidentally noted to be diffusely heterogeneous and nodular

Table 1. Laboratory Data.*

Variable	First Hospital, Reference Range	First Hospital, 8 Days before Current Evaluation	Second Hospital, Reference Range	Second Hospital, 7 Days before Current Evaluation	This Hospital, Reference Range, Adults†	This Hospital, On Admission
Hemoglobin (g/dl)	12.0–15.5	13.1	11.5–16.4	11.2	12.0–16.0	10.2
Hematocrit (%)	34.9–44.5	37.6	36.0–48.0	32.1	36.0–46.0	30.5
White-cell count (per mm^3)	4000–11,000	10,150	4000–10,000	9950	4500–11,000	14,310
Platelet count (per mm^3)	135,000–400,000	292,000	150,000–450,000	231,000	150,000–400,000	264,000
Sodium (mmol/liter)	136–145	130	136–145	131	135–145	131
Potassium (mmol/liter)	3.5–5.2	4.6	3.4–5.0	3.5	3.4–5.0	3.9
Chloride (mmol/liter)	99–109	95	98–107	95	100–108	97
Carbon dioxide (mmol/liter)	20–31	10	22–31	22	23–32	20
Urea nitrogen (mg/dl)	9–23	6	6–23	<3	8–25	4
Creatinine (mg/dl)	0.5–1.3	0.57	0.5–1.2	0.44	0.60–1.50	0.37
Glucose (mg/dl)	74–106	99	70–100	130	70–110	121
Calcium (mg/dl)	8.7–10.4	9.0	8.8–10.7	7.8	8.5–10.5	8.4
Uric acid (mg/dl)	2.6–6.0	11.9	2.4–5.7	5.0	2.3–6.6	
Albumin (g/dl)			3.5–5.2	3.1	3.3–5.0	2.7
Aspartate aminotransferase (U/liter)	6–40	47	10–50	74	10–40	103
Alanine aminotransferase (U/liter)	10–49	36	10–50	38	10–55	66
Bilirubin (mg/dl)	0–1.0	1.2	0–1.0	0.9	0–1.0	
Alkaline phosphatase (U/liter)			35–130	178	45–115	229
Lactate dehydrogenase (U/liter)	120–246	777	135–225	943		
Hepatitis A virus total antibody		Negative			Negative	
Hepatitis A virus IgG antibody				Nonreactive	Nonreactive	
Hepatitis B virus surface antibody				Nonreactive	Nonreactive	
Hepatitis B virus surface antigen		Nonreactive			Nonreactive	
Hepatitis B virus core antibody				Nonreactive	Nonreactive	
Hepatitis C virus total antibody		Nonreactive			Nonreactive	
Carcinoembryonic antigen (ng/ml)	0–5.3	60.2	0–2.5	35.5	<3.4	
CA 19–9 (U/ml)	0–55	68			<35	
Alpha-fetoprotein (ng/ml)	0–8.3	560.4	0–8.3	529.0		
CA-125 (U/ml)			0–34	361	0–35	

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for uric acid to micromoles per liter, multiply by 59.48. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

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and to contain numerous masses. Abdominal magnetic resonance imaging (MRI), performed without the intravenous administration of contrast material, revealed multiple lesions in the liver that were mildly hyperintense on T_2-weighted images and hypointense on T_1-weighted images; the largest lesion measured 7.4 cm by 3.9 cm, and some lesions had central necrosis (Fig. 1A).

Dr. Prabhu: Allopurinol, an injection of betamethasone acetate–betamethasone sodium phosphate, and intravenous fluids were administered. One day after admission to the first hospital, the patient was transferred to the obstetrics service of a second hospital for further evaluation. Additional imaging studies were obtained.

Dr. Shampain: Computed tomography (CT) of the chest, abdomen, and pelvis, performed after the intravenous administration of contrast material, revealed numerous hypoattenuating hepatic lesions, some with well-defined borders and others with ill-defined, irregular borders; the largest measured 8.2 cm in diameter. Multiple enlarged periaortic and portocaval lymph nodes were present (Fig. 1B).

Dr. Prabhu: Additional laboratory test results are shown in Table 1. A percutaneous liver biopsy was performed, and examination of the biopsy specimen revealed evidence suggestive of metastatic adenocarcinoma. Plans for chemotherapy were discussed, as was early fetal delivery. One week after admission to the second hospital, the patient left against medical advice. She presented to her obstetrician's office the next day, at 33 weeks of gestation, and then she was transferred to the obstetrics service of this hospital.

On evaluation at this hospital, the patient reported ongoing severe back pain. She had no vaginal bleeding or contractions. The temperature was 36.2°C, the blood pressure 114/74 mm Hg, and the oxygen saturation 97% while she was breathing ambient air. There was no abdominal tenderness, and fetal movement was detectable in the gravid uterus. The fetal heart rate was 125 beats per minute, with moderate variability and accelerations and without decelerations.

Additional history was obtained. Four years earlier, the patient had had a spontaneous abortion at 10 weeks of gestation. Medications included a prenatal vitamin with ferrous sulfate and folate. The patient had no known allergies. She was originally from Asia and lived in a suburb of Boston. She was married and was a college professor. She did not smoke tobacco, drink alcohol, or use any illicit substances. Her father had diabetes mellitus and hypertension, and her maternal grandfather had cancer, the details of which were unknown to the patient.

Management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Janet E. Murphy: I am aware of the diagnosis in this case. During the last trimester of pregnancy, this patient received a diagnosis of poorly differentiated adenocarcinoma with widespread involvement of the liver and lymph nodes. The first step in the development of an evidence-based treatment plan is to determine the site of origin of the cancer. Primary adenocarcinoma of the liver, which is typically biliary in origin, is rare. Cancer with metastasis to the liver is far more common, accounting for 95% of cases of cancer with liver involvement in the Western hemisphere.

Among women of all ages, cancer most commonly arises in the breast, lung, or colon.[1] Poorly differentiated adenocarcinoma can arise in all three of these sites. This patient was pregnant; does pregnancy alter the differential diagnosis? The most common cancers to occur during pregnancy are melanoma and breast, cervical, and hematologic cancers, which together account for 70% of all cases. Of these cancers, only breast cancer is typically adenocarcinoma.[2] In addition, the patient had widespread liver involvement. Overall, colorectal cancer is the most common cause of metastasis to the liver, owing to portal venous drainage to the liver from the large bowel. However, among women younger than 50 years of age, breast cancer is the most common cause.[3] Lung, gastric, and pancreatic cancers can also metastasize to the liver and should be considered in this case.

To determine the site of origin of the cancer in this patient, I would recommend obtaining a detailed family history, performing an immunohistochemical analysis of the liver-biopsy specimen, and then pursuing further diagnostic testing according to the index of suspicion. Such testing may include colonoscopy, diagnostic mammography, CT of the chest, and esophagogastroduodenoscopy.

Dr. Dennis Sgroi (Pathology): Dr. Riley, what was your initial impression when you evaluated this patient?

Dr. Laura E. Riley: When I first met this patient, she was quite sick and in great pain. She had left another hospital in the middle of the night because she and her husband had thought that her pain was undertreated and that their goals of care were not appreciated. Although the patient had been advised to deliver the baby and then to undergo the remainder of evaluation and treatment, she and her husband were focused on identifying the primary cancer, understanding the treatment options, and obtaining adequate pain relief. Therefore, our first few days with them were spent developing a trusting relationship. The gastroenterology team reviewed the previously obtained abdominal CT scan, which showed thickening of the sigmoid colon with adjacent lymphadenopathy. Esophagoduodenoscopy and colonoscopy were performed and revealed a fungating and partially obstructing mass, measuring 5.0 cm in diameter, in the sigmoid colon. A biopsy of the mass was performed.

CLINICAL DIAGNOSIS

Pregnancy at 33 weeks 4 days of gestation and metastatic colon cancer.

DR. JANET E. MURPHY'S DIAGNOSIS

Adenocarcinoma of the sigmoid colon, stage IVB.

PATHOLOGICAL DISCUSSION

Dr. Kristen M. Basnet: On histopathological examination of sections of the colon-biopsy specimen, fragments of colonic mucosa were largely replaced by a malignant cellular proliferation that was composed of large, atypical cells with prominent nucleoli, brisk mitotic activity, and areas suggestive of possible gland formation; these findings are consistent with poorly differentiated adenocarcinoma. Immunohistochemical staining revealed preserved nuclear expression of MLH1, MSH2, MSH6, and PMS2 in the tumor cells, findings that indicate the presence of microsatellite stability and thus rule out the Lynch syndrome (Fig. 2).

We also had the opportunity to review the liver-biopsy specimen that was obtained at the second hospital. On histopathological examination of sections of the liver-biopsy specimen, multiple liver cores were heavily involved by a

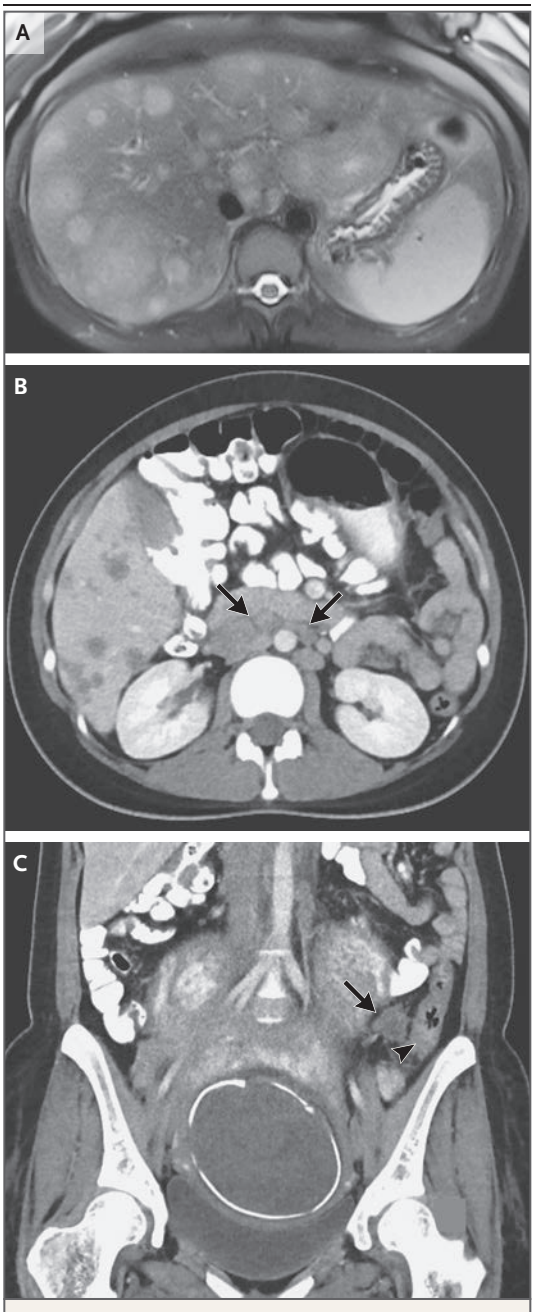

Figure 1. Abdominal Imaging Studies.
Abdominal MRI was performed without the administration of contrast material, owing to pregnancy. An axial, T_2-weighted image (Panel A) shows multiple mildly hyperintense lesions in both lobes of the liver. CT of the abdomen and pelvis was performed after the administration of contrast material. An axial image (Panel B) shows multiple enlarged periaortic lymph nodes (arrows). A coronal image (Panel C) shows thickening of the sigmoid colon (arrowhead) with adjacent lymphadenopathy (arrow). The fetus is partially visible.

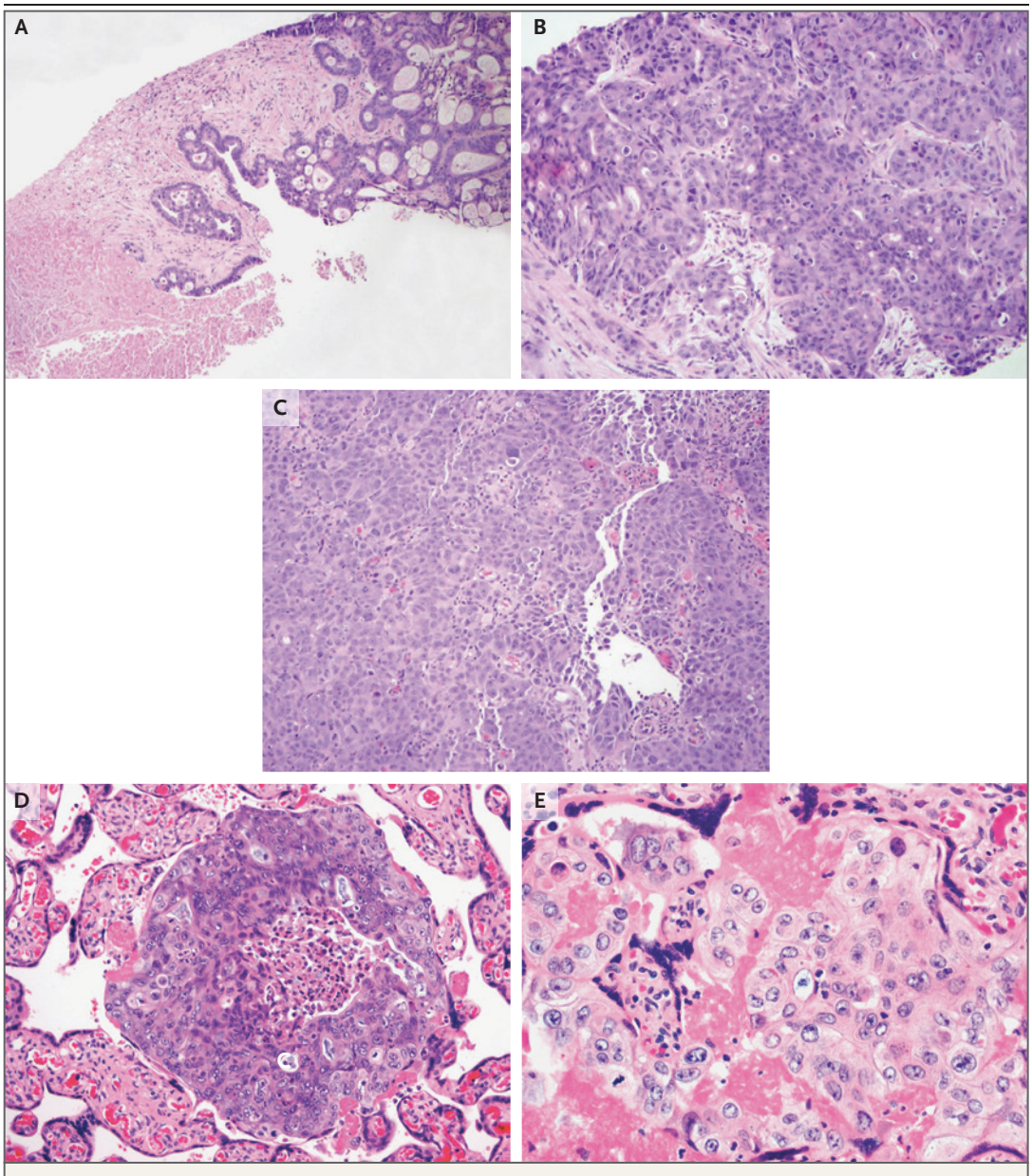

Figure 2. Biopsy Specimens of the Liver and Colon.

Hematoxylin and eosin staining of the liver-biopsy specimen (Panels A and B) shows multiple liver cores that are heavily involved by a malignant gland-forming proliferation and are surrounded by fibrosis and abundant necrosis; these findings are consistent with moderately differentiated metastatic adenocarcinoma. Hematoxylin and eosin staining of the colon-biopsy specimen (Panels C, D, and E) shows fragments of colonic mucosa that are replaced by a malignant cellular proliferation with areas suggestive of gland formation; these findings are consistent with poorly differentiated adenocarcinoma.

malignant gland-forming proliferation and were surrounded by fibrosis and abundant necrosis; these findings are consistent with moderately differentiated metastatic adenocarcinoma. Immunohistochemical staining revealed that the tumor cells were positive for CK7, CK20, CDX2, and SMAD4 (retained), markers that are highly suggestive of colon cancer. The cells were negative for TTF1, PAX8, arginase-1, and GATA3, and these results effectively rule out cancer with a

site of origin outside the gastrointestinal tract, such as lung or gynecologic cancer (Fig. 2).

DISCUSSION OF OBSTETRIC MANAGEMENT

Dr. Riley: Once the primary cancer was identified, we tried to balance the patient's autonomy with what had become a small window of opportunity for treatment. It was the team's impression that treatment would be less complicated if the patient delivered the baby and received chemotherapy after delivery. Because the gestational age was now almost 34 weeks, the results of fetal testing had been reassuring, and betamethasone had been administered to assist in the progression of fetal lung maturity, the neonatal outcome was likely to be excellent.

Over the course of 10 days, the patient became progressively weaker, needed higher doses of narcotics to control her pain, and had increasing edema that extended from her feet to her breasts. On a daily basis, we discussed the options for treatment either with the baby in utero or after delivery, but the couple declined delivery and delayed the decision about treatment. During this time, it was difficult to manage the patient's pain while allowing her to remain alert enough to participate in the decision process. Her liver function worsened, with increasing hyperbilirubinemia, hyperammonemia, and metabolic acidosis, and we eventually focused on delivery for the baby's well-being. Ultrasonography revealed that the baby was in the breech position. Thus, a cesarean delivery was planned with input from multiple teams, including anesthesia, intensive care, and oncology. Our plan had been to perform the cesarean delivery, allow some time for recovery, and then administer chemotherapy. Even after all was planned, the couple declined delivery until 35 weeks of gestation, when it was clear that fetal compromise was imminent and the patient's ability to survive major surgery was waning.

At 35 weeks 0 days of gestation, the patient underwent a primary classic cesarean delivery, with a vertical skin incision, while she was under general anesthesia. The baby was delivered without complications. The 1-minute and 5-minute Apgar scores were 8 and 9, respectively, and the measurements of cord-blood gases were normal.

DISCUSSION OF ONCOLOGIC EPIDEMIOLOGY AND MANAGEMENT

COLORECTAL CANCER

Dr. Murphy: This patient had received a diagnosis of adenocarcinoma of the sigmoid colon with widespread metastasis to the liver and lymph nodes. Historically, colorectal cancer has been uncommon among younger people, with a median age at diagnosis of 67 years.[4] Screening with colonoscopy has lowered the overall incidence of colorectal cancer.[5] However, the incidence among younger people has increased at a pronounced rate. As compared with people born around 1950, among whom rates of colorectal cancer are the lowest, people born in 1990 have twice the risk of colon cancer (predominantly cancer involving the left side of the colon) and more than 4 times the risk of rectal cancer.[6] Data show that 11% of colon cancers and 18% of rectal cancers occur in patients 20 to 49 years of age and are considered to be young-onset cases.[6,7]

This patient had young-onset colorectal cancer, which encompasses a heterogeneous group of diseases associated with unique molecular mechanisms, clinical presentations, and prognoses. In a greater proportion of young-onset cases than of older-onset cases, the underlying cause is a known genetic syndrome, such as the Lynch syndrome and familial adenomatous polyposis. The risk of young-onset colorectal cancer is up to 4 times as high among people who have a family history of colorectal cancer, particularly in a first-degree relative, as among those who do not have a family history. This suggests that the disease is associated with complex trait genetics and epigenetic modifiers of risk.[7-10] However, in the majority of young patients with colorectal cancer, the disease is sporadic. This can lead to a delay in diagnosis, since the index of suspicion is low.[11]

Sporadic cancers involving the left side of the colon in young patients represent a unique subset of the disease. Such cancers tend to be aggressive and poorly differentiated, often with signet-ring cell differentiation. In general, they are associated with a poor prognosis.[12,13] This patient's cancer appears to be consistent with this entity.

COLORECTAL CANCER AND PREGNANCY

Historically, colorectal cancer in pregnancy has been rare, occurring in 1 in 13,000 pregnancies.[14]

However, the convergence of two trends — the increased incidence of young-onset colorectal cancer and the increase in delayed childbearing — may place more women at risk.[15] Some symptoms of pregnancy (e.g., anemia, bloating, and a change in bowel habits) overlap with symptoms of colorectal cancer, and thus the cancer diagnosis can be delayed.[16] However, in studies involving patients with colorectal cancer, survival did not differ significantly between pregnant women and age- and stage-matched controls; this finding suggests that poor outcomes are more likely to be related to the aggressive features of sporadic, early-onset disease than to pregnancy.[17,18]

In the absence of a family history of colorectal cancer, this patient's disease was likely to be sporadic and to have an aggressive natural history, and indeed, she presented with a poorly differentiated tumor. The location of her tumor on the left side was consistent with most cases of sporadic, young-onset colon cancer. The cancer was likely to have arisen from a different genetic pathway than colorectal cancers in older patients.

Dr. Sgroi: Dr. Clark, if this patient were to opt for chemotherapy, what would be your approach to her treatment?

Dr. Jeffrey W. Clark: Data on the treatment of pregnant patients with metastatic colorectal cancer are limited. Case reports suggest that FOLFOX (fluorouracil, leucovorin [folinic acid], and oxaliplatin) chemotherapy can be administered safely until the fetus is sufficiently mature to deliver (gestational age, ≥33 weeks).[16,19] However, there is very little information on long-term outcomes among the children. In this case, the baby was delivered successfully before the patient had decided whether to undergo chemotherapy.

This patient's tumor was located on the left side, in the sigmoid colon, and was poorly differentiated; these features suggest an aggressive phenotype. Because she had numerous metastatic lesions on both lobes of the liver and had metastasis to lymph nodes, her tumor was not amenable to surgical resection and therefore was not curable. If the patient were to choose to undergo treatment, we would recommend initial FOLFOX chemotherapy, with the plan to add an anti–epidermal growth factor receptor agent such as cetuximab or panitumumab if she were to have a response to the initial cycles of treatment. This strategy is based on the fact that she had primary cancer involving the left side of the colon without *RAS* or *BRAF* mutations.[20-22] Small studies showed that FOLFOX chemotherapy was associated with an acceptable side-effect profile in patients with the same degree of liver dysfunction that was seen in this patient.[23,24] Given the hepatobiliary clearance of irinotecan, the administration of FOLFIRI (fluorouracil, leucovorin, and irinotecan) or FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) chemotherapy would be contraindicated in this patient because of the clinically significant abnormal results of liver-function tests.

In considering possible later treatment approaches if the patient's cancer were to progress after standard chemotherapy, a couple of additional points about the biology of her tumor are worth mentioning. Despite her young age, her tumor had microsatellite stability, as indicated by the preserved nuclear expression of MLH1, MSH2, MSH6, and PMS2 in tumor cells. This means that she would not be a candidate for checkpoint inhibitor immunotherapy, which was recently approved for use in patients whose tumors have microsatellite instability.[25,26] In addition, her tumor had *HER2* amplification on fluorescence in situ hybridization, a finding that is seen in approximately 4 to 5% of colorectal cancers.[27,28] Tumors with *HER2* amplification have had a response to a combination of trastuzumab (a monoclonal antibody that targets *HER2*) and lapatinib (an inhibitor of *HER2* kinase activity) and to a combination of trastuzumab and pertuzumab (a monoclonal antibody that inhibits *HER2* kinase activity in a different way) in clinical trials.[29-31]

The patient and her family were left with a very difficult decision. Her clinical status was deteriorating and she had a progressive decrease in liver function, and thus the need for a decision about therapy was urgent. She had recently given birth and had a desire to spend time with her newborn, and she was ambivalent about chemotherapy. On the basis of these considerations, a palliative care approach without specific treatment would be reasonable but would result in a very limited life expectancy. In contrast, several features of her case would support the administration of chemotherapy. First, she was young and had a strong desire to be with her baby

as long as possible. Second, she had not previously undergone chemotherapy, so her chances of having a response to initial treatment were increased. Finally, she did not have any abnormalities in organ function that would prohibit treatment.

The options of chemotherapy and supportive care were discussed in a family meeting that involved several family members and multiple members of the health care team. The patient opted to not start chemotherapy and to see how she did clinically before reconsidering. Unfortunately, her clinical status deteriorated rapidly, and after delivery of the baby, she was admitted to the surgical intensive care unit (ICU), where her condition further deteriorated over a period of 72 hours. Several days after the family meeting, the patient and her husband made the decision to decline treatment with chemotherapy and to proceed with comfort measures only. The patient saw her baby only once and died 5 days later under in-hospital hospice care, with her husband and brother at her side.

PATHOLOGICAL DISCUSSION

Dr. Basnet: Sections of the placenta were submitted for histopathological examination. Several foci of large malignant cells were present in the space between and surrounding chorionic villi. The cells were morphologically similar to those in the adenocarcinoma of the colon. Immunohistochemical staining revealed multiple additional foci of tumor cells, which were strongly positive for CK20 and showed some positivity for SMAD4 (retained) and CDX2 (Fig. 3).

Maternal cancer is an important indication for placental examination, because malignant tumors can metastasize to the placenta. When such metastasis is present, the cancer is advanced to stage IV. In very rare cases, the tumor crosses the placenta and spreads to the fetus. The most common primary placental cancer is choriocarcinoma in situ, and the most common cancer with metastasis to the placenta is melanoma. Gastrointestinal cancer with metastasis to the placenta has been reported previously but is rare.[32]

Dr. J. Drucilla Roberts (Pathology): Because there is a small risk of transplacental involvement in the baby, how will the baby be monitored?

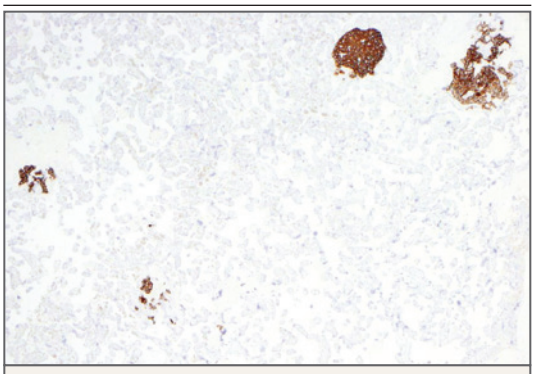

Figure 3. Specimen of the Placenta.

Immunohistochemical staining shows several foci of large malignant cells in the space between and surrounding chorionic villi. The cells are morphologically similar to those in the adenocarcinoma of the colon and are strongly positive for CK20.

Dr. Riley: The recommendation is that the baby undergo ultrasonography periodically, approximately every 6 months. When I last spoke with the father, the baby had been screened at least once and had had an extensive negative workup in the neonatal ICU.

A Physician: Why do you think the patient and her husband had such a difficult time deciding whether to deliver the baby and to initiate chemotherapy?

Dr. Riley: Perhaps the most frustrating aspect of this case, which will haunt me for a long time, is the difficulty we had in conveying all the information and the urgency of the situation to this patient and her husband. Although we tried every possible way of communicating with them and offered everything we could think of to help them make these decisions, we ultimately could not make a breakthrough until it was too late.

ANATOMICAL DIAGNOSIS

Poorly differentiated primary adenocarcinoma of the colon, with moderately differentiated metastatic adenocarcinoma in the liver and poorly differentiated metastatic carcinoma in the placenta.

This case was presented at the Cancer Center Grand Rounds.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. Boere I, Lok C, Vandenbroucke T, Amant F. Cancer in pregnancy: safety and efficacy of systemic therapies. Curr Opin Oncol 2017;29:328-34.
3. de Ridder J, de Wilt JHW, Simmer F, Overbeek L, Lemmens V, Nagtegaal I. Incidence and origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients. Oncotarget 2016;7:55368-76.
4. Cancer stat facts: colorectal cancer. Bethesda, MD: National Cancer Institute (https://seer.cancer.gov/statfacts/html/colorect.html).
5. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544-73.
6. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. J Natl Cancer Inst 2017;109(8).
7. Ahnen DJ, Wade SW, Jones WF, et al. The increasing incidence of young-onset colorectal cancer: a call to action. Mayo Clin Proc 2014;89:216-24.
8. Yeo H, Betel D, Abelson JS, Zheng XE, Yantiss R, Shah MA. Early-onset colorectal cancer is distinct from traditional colorectal cancer. Clin Colorectal Cancer 2017;16(4):293-299.e6.
9. Silla IO, Rueda D, Rodríguez Y, García JL, de la Cruz Vigo F, Perea J. Early-onset colorectal cancer: a separate subset of colorectal cancer. World J Gastroenterol 2014;20:17288-96.
10. Inra JA, Syngal S. Colorectal cancer in young adults. Dig Dis Sci 2015;60:722-33.
11. Chen FW, Sundaram V, Chew TA, Ladabaum U. Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. Clin Gastroenterol Hepatol 2017;15(5):728-737.e3.
12. Kirzin S, Marisa L, Guimbaud R, et al. Sporadic early-onset colorectal cancer is a specific sub-type of cancer: a morphological, molecular and genetics study. PLoS One 2014;9(8):e103159.
13. Chang DT, Pai RK, Rybicki LA, et al. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol 2012;25:1128-39.
14. Salani R, Billingsley CC, Crafton SM. Cancer and pregnancy: an overview for obstetricians and gynecologists. Am J Obstet Gynecol 2014;211:7-14.
15. Rogers JE, Dasari A, Eng C. The treatment of colorectal cancer during pregnancy: cytotoxic chemotherapy and targeted therapy challenges. Oncologist 2016;21:563-70.
16. Vitoratos N, Salamalekis E, Makrakis E, Creatsas G. Sigmoid colon cancer during pregnancy. Eur J Obstet Gynecol Reprod Biol 2002;104:70-2.
17. Dahling MT, Xing G, Cress R, Danielsen B, Smith LH. Pregnancy-associated colon and rectal cancer: perinatal and cancer outcomes. J Matern Fetal Neonatal Med 2009;22:204-11.
18. Bernstein MA, Madoff RD, Caushaj PF. Colon and rectal cancer in pregnancy. Dis Colon Rectum 1993;36:172-8.
19. Jeppesen JB, Østerlind K. Successful twin pregnancy outcome after in utero exposure to FOLFOX for metastatic colon cancer: a case report and review of the literature. Clin Colorectal Cancer 2011;10:348-52.
20. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary tumor location on overall survival and progression-free survival in patients with metastatic colorectal cancer: analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34:Suppl:3504. abstract.
21. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017;28:1713-29.
22. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2017;3:194-201.
23. Roderburg C, do O N, Fuchs R, et al. Safe use of FOLFOX in two patients with metastatic colorectal carcinoma and severe hepatic dysfunction. Clin Colorectal Cancer 2011;10(1):E6-E9.
24. Elsoueidi R, Craig J, Mourad H, Richa EM. Safety and efficacy of FOLFOX followed by cetuximab for metastatic colorectal cancer with severe liver dysfunction. J Natl Compr Canc Netw 2014;12:155-60.
25. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.
26. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-91.
27. Richman SD, Southward K, Chambers P, et al. HER2 overexpression and amplification as a potential therapeutic target in colorectal cancer: analysis of 3256 patients enrolled in the QUASAR, FOCUS and PICCOLO colorectal cancer trials. J Pathol 2016;238:562-70.
28. Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. Mod Pathol 2015;28:1481-91.
29. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-46.
30. Hurwitz H, Singh Raghav KP, Burris HA, et al. Pertuzumab + trastuzumab for HER2-amplified/overexpressed metastatic colorectal cancer (mCRC): interim data from MyPathway. J Clin Oncol 2017;35:Suppl:676. abstract.
31. Siena S, Sartore-Bianchi A, Marsoni S, et al. Targeting the human epidermal growth factor receptor 2 (HER2) oncogene in colorectal cancer. Ann Oncol 2018;29:1108-19.
32. Pavlidis N, Pentheroudakis G. Metastatic involvement of placenta and foetus in pregnant women with cancer. Recent Results Cancer Res 2008;178:183-94.