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CASE REPORT

국소성 융모막암종 분화를 동반한 S상결장의 원발성 선암종

오숙경, 김형욱, 강대환, 최철웅, 최유이, 임홍규, 구자준, 최성열[1]
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Primary Adenocarcinoma with Focal Choriocarcinomatous Differentiation in the Sigmoid Colon

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Primary colorectal choriocarcinoma is a rare neoplasm. Only 19 cases have been reported worldwide, most of which involved adenocarcinomas. The prognosis is usually poor, and the standard therapy for this tumor has not been established. A 61-year-old woman presented with constipation and lower abdominal discomfort. She was diagnosed with primary adenocarcinoma with focal choriocarcinomatous differentiation in the sigmoid colon and liver metastasis. Because the serum beta-human chorionic gonadotropin level was not significantly elevated, and because only focal choriocarcinomatous differentiation was diagnosed, we selected the chemotherapy regimen that is used for the treatment of metastatic colorectal adenocarcinoma. The patient survived for 13 months after the initial diagnosis. This is the first case in Korea to assess the suppressive effects of the standard chemotherapy for colorectal adenocarcinoma against coexisting colorectal choriocarcinoma and adenocarcinoma. **(Korean J Gastroenterol 2015;66:291-296)**

Key Words: Adenocarcinoma; Choriocarcinoma; Colon; Drug therapy

INTRODUCTION

Choriocarcinoma is a malignant form of trophoblastic cancer that arises in the placenta. It can be subclassified as a gestational or non-gestational tumors. Gestational tumors arise in the testis or ovary, whereas non-gestational, extra-gonadal choriocarcinomas are rare tumors that can develop in the mediastinum, lung, stomach, pancreas, cervix, ureter, or colon. Primary colorectal choriocarcinoma is an even rarer tumor; only 16 cases have been published in the English medical literature, and only three cases have been reported in Korea.[1-19] Most of these tumors were associated with adenocarcinoma. We report a case involving a 61-year-old woman diagnosed with primary adenocarcinoma with focal choriocarcinomatous differentiation in the sigmoid colon. Based on this case, we also examine the clinical features, pathogenesis, and treatment of colorectal choriocarcinoma through a review of the literature.

CASE REPORT

A 61-year-old woman presented with a one month history of constipation and lower abdominal discomfort. Her medical history included hypertension. Colonoscopy showed se-

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vere stenosis and an ulcerative mass encircling the sigmoid colon (Fig. 1). Abdominal CT revealed an ulcero-infiltrating mass in the sigmoid colon and liver metastasis (Fig. 2A, B). Histologically, the tumor had two components: moderately differentiated adenocarcinoma, and syncytiotrophoblast-like tumor cells with highly pleomorphic, bizarre nuclei and abundant eosinophilic cytoplasm (Fig. 3A). The two components were either intimately admixed or separate from each other (Fig. 3B). The latter component showed positive immunohistochemical staining for beta-human chorionic gonadotropin (beta-hCG), a marker of choriocarcinoma (Fig. 3C). Accordingly, a diagnosis of moderately differentiated adenocarcinoma with focal choriocarcinomatous differentiation was made.

The CEA and CA 19-9 levels were markedly elevated at 1,700.34 ng/mL (normal range < 5 ng/mL) and 1,525.2 U/mL (normal range < 39 U/mL), respectively. The alpha-fetoprotein level was within the normal range. The plasma beta-hCG level was elevated to 35.2 mIU/mL (normal range < 5 mIU/mL). A self-expandable metal stent (SEMS, 8 cm, uncovered; M.I.Tech, Seoul, Korea) was inserted to relieve the symptoms associated with the obstruction. Because the serum beta-hCG level was not significantly elevated and because choriocarcinoma was confirmed in the focal part of the tumor, we selected the chemotherapy regimen used to treat metastatic colorectal adenocarcinoma rather than that used for choriocarcinoma. The patient was treated with systemic bevacizumab with leucovorin, fluorouracil, and irinotecan (FOLFIRI) chemotherapy every two weeks, and each cycle

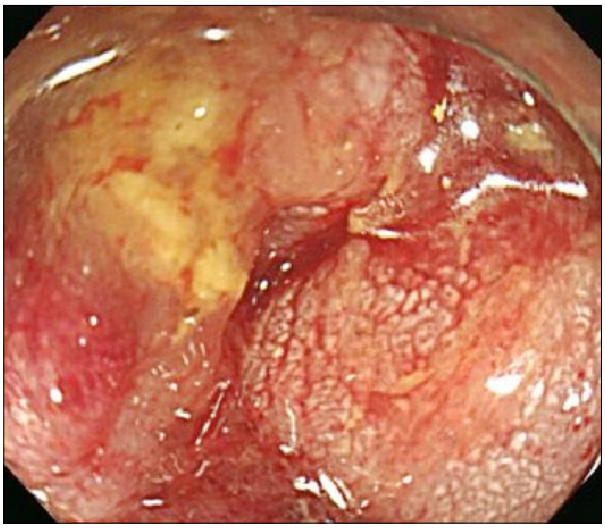

Fig. 1. Colonoscopic finding. Ulcero-infiltrating mass in the sigmoid colon (initial diagnosis).

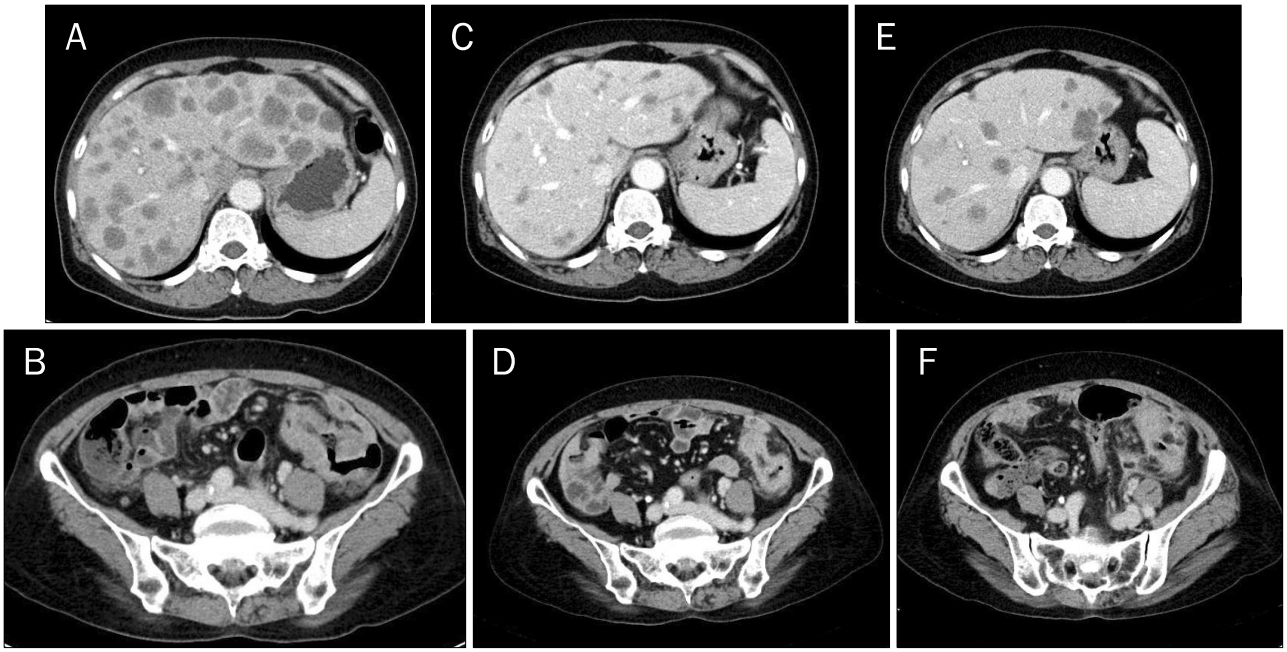

Fig. 2. Abdominal CT findings. (A, B) Multiple liver metastasis with focal wall thickening of sigmoid colon (initial diagnosis). (C, D) Interval decrease in the size of liver metastasis and sigmoid colon cancer (after 4 months of FOLFIRI with bevacizumab chemotherapy: partial response). (E, F) Interval increase in the size of liver metastasis and sigmoid colon (after 9 months of FOLFIRI with bevacizumab chemotherapy: progressive disease).

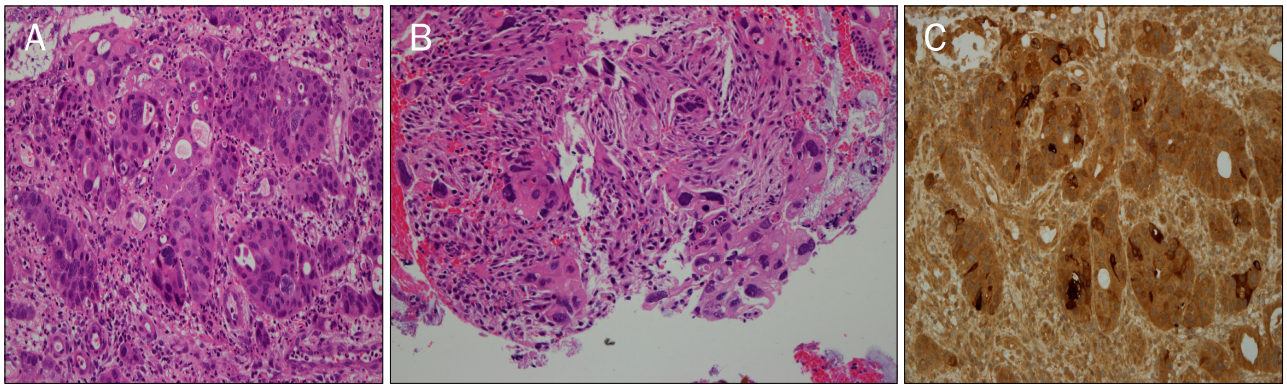

Fig. 3. Pathologic findings of the sigmoid colon biopsy. (A) Moderately differentiated adenocarcinoma is along with syncytiotrophoblastic giant cells giant cells (H&E, ×200). (B) Anaplastic tumor cells have eosinophilic abundant cytoplasm with hyperchromatic and pleomorphic nuclei, forming giant cells (H&E, ×200). (C) These anaplastic tumor cells show cytoplasmic positivity for beta-human chorionic gonadotropin staining (immunohistochemical staining, ×200).

was administered for two days. The patient's symptoms improved, and she had no constipation or abdominal discomfort. After three months of treatment with six courses of chemotherapy, abdominal CT revealed that the size of ulcero-infiltrating mass in the sigmoid colon and the round hypodense masses in the liver had markedly decreased (Fig. 2C, D). The CEA and CA 19-9 levels decreased to 94.1 ng/mL and 303.8 U/mL, respectively, and the beta-hCG level was within the normal range, 0.5 mIU/mL. These findings were indicative of a partial response according to the Response Evaluation Criteria in Solid Tumors. However, nine months after completion of the 15 courses of chemotherapy, the patient presented with intermittent abdominal discomfort, and imaging studies revealed rapidly progressive abdominal tumors. Abdominal CT showed an interval increase with a mass at the sigmoid colon and liver metastasis (Fig. 2E, F). The CEA and CA 19-9 levels were elevated to 730.5 ng/mL and 3,675.4 U/mL, respectively, and the beta-hCG level were at 5.5 mIU/mL. These findings were indicative of progressive disease according to the Response Evaluation Criteria in Solid Tumors. Thereafter, we inserted a second SEMS (8 cm, uncovered; M.I.Tech), and changed the chemotherapy regimen to leucovorin, fluorouracil, and oxaliplatin (FOLFOX) on days 1-2, administered every two weeks. However, despite three courses of treatment with this chemotherapy regimen, the symptoms persisted. Abdominal CT revealed that an abscess had developed in the sigmoid colon. We therefore administered antibiotics and performed percutaneous drainage by inserting a 10.2-F pigtail catheter, followed by supportive care. However, 13 months after the initial diagnosis, the patient died of liver failure due to the hepatic metastasis.

DISCUSSION

Choriocarcinoma progresses rapidly and is associated with a poor prognosis. These features are thought to result from the tumor's derivation from chorionic tissue, which normally invades and destroys the adjacent tissue, and this behavior persists after malignant transformation. For this reason, hematogenous and lymphatic metastasis is common at the time of the initial diagnosis.[8] The stomach is the most common site of choriocarcinoma in the gastrointestinal tract, and primary choriocarcinoma of the colon is extremely rare.[16] Only 20 cases of colorectal choriocarcinoma (including the case described here) have been reported worldwide (Table 1).[1-19] In the literature, primary colorectal choriocarcinoma was associated with adenocarcinoma in all except four cases,[6,12,15,17] in which only choriocarcinoma was noted and was accompanied by metastatic tumors at the time of diagnosis in 16 of 20 cases (80%). The median survival period was eight months (range, 0.5-60 months).

The most reasonable pathogenesis of primary choriocarcinoma is dedifferentiation or retrodifferentiation of a carcinoma. This hypothesis is based on the premise that an adenocarcinoma can dedifferentiate into a choriocarcinoma, both functionally and morphologically.

Verbeek et al.[13] reported a genetic evolution model, which showed that genes located on the X chromosome may be involved in the phenotypic switch from adenocarcinoma to choriocarcinomatous differentiation.

Table 1. Clinical Features of Colorectal Choriocarcinoma through Literature Review

Case	Sex/Age (yr)	Primary colon tumor location	Primary colon tumor histology	Metastatic tumor location	Metastatic tumor histology	Serum beta-hCG (mIU/mL)	Treatment	Survival (mo)
Park[1] 1980	F/49	Sigmoid	A+C	Liver, lung	C	Not checked	Palliative resection	4
Nguyen[2] 1982	M/74	Sigmoid	A+C	Liver	C	400 -before op	Laparotomy	3
Ordóñez[3] 1984	F/35	Ascending	A+C	Liver, lung	C	1,612 -after op	Right hemicolectomy	2
Kubosawa[4] 1984	F/50	Sigmoid	A+C	Liver, lung	C	230,000 -before op	Hartmann's procedure	4
Metz[5] 1985	F/42	Sigmoid	A+C	Liver, lung, spleen	C	154,000	Laparotomy	1
Lind[6] 1986	M/42	Ascending	C	Liver, lung, spleen	C	610,000	Palliative resection	1
Ostör[7] 1993	F/28	Rectum	A+C	Liver	C	16,500 -before op	Anterial resection, EMA/CO	1
Tokisue[8] 1996	F/29	Rectum	A+C	Lung, brain, vagina	Not checked	49,000 -before CTx	EMA, anterial resection, EMA+cisplatin+doxorubicin	10
Oh[9] 1997	M/69	Sigmoid	A+C	Liver, lung, thyroid brain, hyphopharynx	C	78 -after op	Colectomy, MTX+vincristine+VP16+leukovorin	15
Kim[10] 1997	M/59	Cecum	A+C	Not checked	Not checked	Not checked	Not checked	Not checked
Kiran[11] 2001	M/68	Rectum	A+C	Liver	Not checked	700,000	Hartmann's procedure	Not checked
Le[12] 2003	M/73	Ascending Descending	C	Lung, brain, kidney, pancreas	Not checked	146,000	No	15 days
Verbeek[13] 2004	F/54	Rectum	A+C	Liver, lung	Not checked	6,831 -after op	Palliative resection, cisplatin+etoposide+ifosfamide	8
Jeong[14] 2007	M/52	Rectum	A+C	Liver, lung	Not checked	4,224 -after op	Low anterial resection, bleomycin+etoposide+cisplatin	47days
Froylich[15] 2010	F/57	Descending	C	Lung, bone, brain	C	13,000 -after op	Colectomy, VP16+ifosfamide+cisplatin	16
Harada[16] 2012	F/58	Sigmoid	A+C	No	No	2,420 -before op	Hartmann's procedure, EMA, UFT/leucovorin	60
Jiang[17] 2013	M/38	Ascending	C	Liver	Not checked	10,000 -after op	Colectomy, bleomycin+etoposide+cisplatin	6
Maehira[18] 2013	M/68	Sigmoid	A+C	Liver	Not checked	1.4 ng/mL -after op	Sigmoidectomy, FOLFOX, FOLFIRI+bevacizumab	9
Mardi[19] 2014	F/54	Rectum	A+C	No	No	4,568	Radical resection, 5-FU, leucovorin	50 days
Present case	F/61	Sigmoid	A+C	Liver	Not checked	35	FOLFIRI+bevacizumab, FOLFOX	13

beta-hCG, beta-human chorionic gonadotropin; A, adenocarcinoma; C, choriocarcinoma; op, operation; EMA/CO, etoposide, methotrexate, and actinomycin D, alternating with cyclophosphamide and vincristine; CTx, chemotherapy; MTX, methotrexate; VP16, etoposide; UFT, tegafur-uracil.

Gestational choriocarcinoma is sensitive to chemotherapy if therapy is initiated within three months.[18] The preferred regimen for the treatment of gestational choriocarcinoma was etoposide, methotrexate, and actinomycin D, alternating with cyclophosphamide and vincristine (EMA/CO). However, a standard treatment for primary colorectal choriocarcinoma has not been established. Additionally, the response of colorectal choriocarcinomas to chemotherapy is

much worse than that of gestational choriocarcinomas. In fact, most treatments are based on clinical experience, with varying methods and results (Table 1).[1-19] During the 1980s, patients were predominantly treated surgically, described in seven case reports. Of the total 20 patients, eight underwent surgery with chemotherapy for choriocarcinoma rather than chemotherapy for adenocarcinoma. In the present case, we selected colonic stent insertion combined with the chemotherapy that is used for adenocarcinoma instead of radical surgery combined with the chemotherapy used for choriocarcinoma. Because the patient was elderly, she did not want invasive surgery and we therefore chose SEMS. The serum beta-hCG level was 35 mL/IU, which was above the normal range, but this level was low compared to that observed in other cases. Additionally, the dominant histology was adenocarcinoma. Thus, we selected the standard chemotherapeutic regimens for colorectal adenocarcinoma: bevacizumab plus FOLFIRI, and later FOLFOX.

There are two reports of cases in which the treatment for adenocarcinoma in the primary tissues was effective against choriocarcinoma. Noguchi et al.[20] reported that treatment for adenocarcinoma prolonged the survival of patients with gastric choriocarcinoma. Moreover, Maehira et al.[18] performed sigmoidectomy and administered FOLFOX, and FOLFIRI plus bevacizumab with sigmoidectomy, based on an in vitro collagen gel droplet-embedded culture drug sensitivity test for colorectal choriocarcinoma, which resulted in suppression of the tumor growth for four months.

This case study has some limitations. First, we could not evaluate serial choriocarcinomatous differentiation by conducting a biopsy after disease progression. Second, we could not conduct a culture drug sensitivity test before deciding on the treatment or genetic studies for the marker of choriocarcinomatous differentiation, because these techniques are not available in our hospital and the patient refused to undergo expensive tests.

In conclusion, we report a rare case of primary adenocarcinoma with focal choriocarcinomatous differentiation in the sigmoid colon. Primary colorectal choriocarcinoma is typically accompanied by adenocarcinoma. However, the appropriate treatment of this type of tumor has not been well established. Our case differs from other cases, in which palliative resection with chemotherapy for choriocarcinoma was chosen as the treatment. However, our case indicates that the standard chemotherapy for colorectal adenocarcinoma along with non-invasive SEMS might have a suppressive effect on colorectal choriocarcinoma, with our patient surviving longer than the reported median survival period.

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