Asymptomatic Synchronous Quintuple Primary Cancers

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Abstract
We encountered a 46-year-old woman with synchronous quintuple primary cancers. She did not present with any symptoms, and her tumors were discovered at a gynecological screening. She had clear cell adenocarcinoma of the right ovary, moderately differentiated endometrioid adenocarcinoma of the endometrium, moderately differentiated adenocarcinoma of the ascending colon, well-differentiated adenocarcinoma of the rectum, and poorly differentiated papillary adenocarcinoma of the left lung. A fluorodeoxyglucose-positron emission tomography (FDG-PET) and other imaging techniques were extremely useful for the diagnosis of asymptomatic multiple primary cancers. Moreover, MSH2 protein expression was absent in the tumors of the ovary, endometrium, ascending colon, and rectum, while the rectal cancer also lacked MLH1 protein. These findings suggested that an abnormality of DNA mismatch repair genes was responsible for carcinogenesis.

Established Facts
• Reports about quintuple primary cancer are extremely rare. Moreover, no one reported a patient with synchronous five primary cancers in five different organs in the literature in English.

Novel Insights
• This is the first report in English of a patient with synchronous five primary cancers in five different organs.
• An abnormality of DNA mismatch repair genes (MSH2 and MLH1) was considered to be responsible for carcinogenesis.
• Fluorodeoxyglucose-positron emission tomography (FDG-PET) and other imaging techniques were extremely useful for the diagnosis of asymptomatic multiple primary cancers.

Key Words
Synchronous quintuple primary cancers · Asymptomatic · MSH2 gene · MLH1 gene · Lynch syndrome
Introduction

Multiple primary cancers commonly occur in the head and neck, upper gastrointestinal tract, and respiratory tract [1]. Among gynecological tumors, combined involvement of the ovary and endometrium is most common. When different primary tumors are found in several organs, multiple primary cancers are diagnosed and are classified according to the timing of detection as synchronous or metachronous [1]. There have been a few reports of triple or quadruple primary cancer, but reports about quintuple primary cancer are extremely rare. We encountered a patient with asymptomatic synchronous quintuple primary cancers of dissimilar histologies that had developed in five organs: ovary, endometrium, ascending colon, rectum and lung.

Case Report

The patient was a 46-year-old premenopausal Japanese woman (gravid 2, para 2). She had no relevant past history, but her father had gastric cancer and her mother had a spinal tumor. Pelvic examination conducted for cervical cancer screening 4 years earlier had revealed mild uterine enlargement and she had been followed up at a local hospital. Right ovarian enlargement was detected at periodic follow-up, and she was referred to our institution for assessment; the patient was asymptomatic at that time. At the initial examination, uterine corpus was 8 cm in diameter and adenomyosis was suspected on ultrasonography, while endometrial thickness of 12 mm was also detected. The right ovary was 9 cm in diameter and contained a solid mass with a cystic area. Cervical and endometrial cytologies were both negative. Serum tumor marker levels were 54.1 U/ml for CA125 (reference value: \( \leq 35 \) U/ml), 18.2 U/ml for CA19-9 (\( \leq 37 \) U/ml), 140.0 U/ml for CA72-4 (\( \leq 8.0 \) U/ml), and 6.6 ng/ml for CEA (\( \leq 2.5 \) ng/ml). Magnetic resonance imaging (MRI) of the pelvic cavity showed right ovarian enlargement of mixed intensity, and a predominantly solid malignancy was suspected (fig. 1c). In addition, there was endometrial thickness and a small amount of ascites (fig. 1c). Thoracoabdominal computed tomography (CT) scans revealed thickness of the intestinal wall in the ileocecal region (fig. 1b) and an irregular mass in the upper lobe of the left lung (fig. 1a). An FDG-PET scan showed various sites of abnormal accumulation that suggested malignancy, including the right ovary, ileocecal region, pelvic floor, para-aortic lymph nodes, left lung, and mediastinal lymph nodes (fig. 1d). Furthermore, colonoscopy revealed adenocarcinoma in the ascending colon (near the ileocecal valve) and rectum. However, no malignant cells were identified by bronchoscopic examination.

These findings suggested a diagnosis of synchronous quadruple primary cancers or synchronous triple primary cancers with metastasis to the lung, or even synchronous double primary cancers with metastases to the ovary and lung, and any of these possibilities was equally likely.

After informed consent was obtained from the patient and her family, laparotomy was performed. Simple total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node sampling, ileocecal resection, and lower anterior resection were performed. Subsequently, endoscopic upper lobectomy of the left lung and mediastinal lymph node sampling were also done at a later date.

The intraperitoneal findings included a small amount of ascites, but no dissemination of tumor cells. The right ovary contained a solid tumor of 8 cm in diameter and the capsule was intact. Histologically, atypical cells (mainly clear cells and some eosinophilic cells) formed a solid mass and clear cell adenocarcinoma was diagnosed (fig. 2a, b). The uterus showed endometrial thickness, mainly complex atypical endometrial hyperplasia on histological examination, but moderately differentiated endometrioid adenocarcinoma was also noted (fig. 2c, d). Muscle invasion was extremely shallow without any vascular invasion. Adenomyosis was also present in the uterine walls. In the proximal ascending colon, there was a large tumor of 45 mm in diameter that showed macroscopic serosal infiltration and that had ruptured into the peritoneal cavity. This tumor was histologically a moderately differentiated adenocarcinoma that showed marked venous invasion and lymphatic invasion (fig. 2e, f). Similar tumor cells were also found in the peri-ileocecal mesenteric lymph nodes and para-aortic lymph nodes. In consideration of the above findings, metastases from ascending colon carcinoma were suggested. The rectum contained a small tumor (7 mm in diameter) confined to the submucosa, which was classified histologically as well-differentiated adenocarcinoma with mild vascular invasion (fig. 2g, h). Immunohistochemical expression of cytokeratin 7 (CK7) and cytokeratin 20 (CK20) in each of the cancer tissues were as follows: CK7 was positive but CK20 was negative in endometrial cancer; both CK7 and CK20 were positive in ovarian cancer; CK7 was negative, but CK20 was positive in colon cancer and rectal cancer, respectively. Moreover, the left lung contained a relatively large tumor (3 cm in diameter) located immediately beneath the pleura with pleural invasion. Histologically, this tumor was a poorly differentiated papillary adenocarcinoma with marked vascular invasion. Numerous metastases to the mediastinal lymph node were also noted, and were found to be of pulmonary origin because of positive immunostaining for TTF-1 (thyroid transcription factor 1), which is expressed specifically by lung cancer (fig. 2i–k).

All of the above-mentioned cancers were considered to be primary tumors, so a diagnosis of synchronous quintuple primary cancers was made. Her tumors were classified as stage Ia for ovarian cancer, stage Ib for endometrial cancer, stage IIIb for colon cancer, stage I for rectal cancer, and stage IIIa for lung cancer. For the ovarian and endometrial cancers, higher stages were also possible, the origin of the adenocarcinoma cells in her ascitic fluid was unclear although cytologic examination of ascites was positive. In addition, our pathological diagnosis, which was five primary cancers in five different organs, was confirmed in a pathological review by independent expert pathologists in the scientific meeting of the Japan Society of Gynecologic Oncology.

After consent was obtained from the patient and her family, formalin-fixed paraffin-embedded sections of the surgical specimens were examined immunohistochemically for abnormalities in the expression of MLH1 and MSH2 (DNA mismatch repair genes). Immunohistochemical staining was done by the avidin/
biotin complex method with horseradish peroxidase-labeled antibodies, and the primary antibodies used were mouse anti-MLH1 monoclonal antibody (554073 BD Parmingen™, BD Bioscience, Franklin Lakes, N.J., USA) and mouse anti-MSH2 monoclonal antibody (556349 BD Parmingen™, BD Bioscience). MLH1 and MSH2 are both proteins expressed in the nucleus, so immunohistochemical staining was judged to be positive for MLH1 and MSH2 expression when the nuclei of tumor cells showed strong staining. The results showed that expression of MLH1 was absent in the rectal cancer, although its expression was normal in the other cancers (fig. 3a–e). For MSH2, expression was noted in normal tissues, but its expression was absent in the ovarian, endometrial, colon, and rectal cancers. However, the lung cancer did not show decreased expression of MSH2 (fig. 3f–j). All immunohistochemical studies were approved by our Institutional Review Board.

Based on these results, genetic analysis was strongly recommended to the patient and her family including microsatellite instability assay of tumor tissues and germline mutation analysis of MLH1 and MSH2 genes of her and her family members’ lymphocytes. However, this recommendation was regretfully refused by both her and her family.

After the operation, she underwent adjuvant therapy for lung cancer which was considered to be the most important prognostic factor among the five cancers. She received 8 cycles of adjuvant chemotherapy including paclitaxel and carboplatin. Three months after completion of adjuvant chemotherapy treatment, she relapsed with multiple metastatic tumors to the brain and thoracic bones. She underwent Gamma Knife radiosurgery for brain metastases and irradiation for thoracic bone metastases; both therapies were effective clinically. Five months later, she again relapsed with intrapulmonary metastases. Eight cycles of gemcitabine and vinorelbine were administered as a second-line chemotherapy and she showed stable disease. In addition, she was administered S-1 as a third-line chemotherapy; however, she developed progressive disease. Currently, she is receiving erlotinib monotherapy as a fourth-line chemotherapy, and she is alive with disease at 45 months after initial surgery.

**Discussion**

A thorough review of the literature reveals only 17 published cases of quintuple primary cancers (or higher tumor numbers) [2–14]. Most of these reports are related to metachronous cancers, and synchronous quintuple
Asymptomatic Synchronous Quintuple Primary Cancers

Fig. 2. Pathological features of ovarian cancer, endometrial cancer, colon cancer, rectal cancer, and lung cancer. a The right ovary contained a solid tumor of 8 cm in diameter with an intact capsule. b Histologically, atypical cells (mainly clear cells and some eosinophilic cells) formed a solid mass, and clear cell adenocarcinoma was diagnosed. The uterus showed endometrial thickness (c), mainly complex atypical endometrial hyperplasia on histological examination, but moderately differentiated endometrioid adenocarcinoma was also noted (d). Muscle invasion was extremely shallow without any vascular invasion. e In the proximal ascending colon, there was a large tumor of 45 mm in diameter that showed macroscopic serosal infiltration and had ruptured into the peritoneal cavity. f This tumor was histologically a moderately differentiated adenocarcinoma that showed marked venous invasion and lymphatic invasion. The rectum contained a small tumor (7 mm in diameter) confined to the submucosa (g), which was classified histologically as well-differentiated adenocarcinoma with mild vascular invasion (h). i The left lung contained a relatively large tumor (3 cm in diameter) located immediately beneath the pleura with pleural invasion. j Histologically, this tumor was a poorly differentiated papillary adenocarcinoma with marked vascular invasion. k It was found to be of pulmonary origin because of positive immunostaining for TTF-1 (thyroid transcription factor-1), which is expressed specifically by lung cancer.

Fig. 3. Immunohistochemical features of synchronous quintuple primary cancers. Immunostaining of MLH1 is shown in a (ovarian cancer), b (endometrial cancer), c (colon cancer), d (rectal cancer), and e (lung cancer). Expression of MLH1 was absent in the rectal cancer, although its expression was normal in the other cancers. Immunostaining of MSH2 is shown in f (ovarian cancer), g (endometrial cancer), h (colon cancer), i (rectal cancer), and j (lung cancer). Expression of MSH2 was noted in normal tissues, but it was absent in the ovarian, endometrial, colon, and rectal cancers. However, the lung cancer did not show decreased expression of MSH2.
primary cancers are limited to one case reported by Weingärtner et al. [10]. In their patient, five primary cancers (renal cancer, prostate cancer, two bladder cancers, colon cancer) were present in four different organs. Thus, we believe this is the first report in English of a patient with five primary cancers in five different organs.

Since our patient had early-onset cancer, an abnormality of DNA mismatch repair genes was suspected. As expected, MSH2 protein expression was absent in the tumors of the ovary, endometrium, ascending colon, and rectum, while the rectal cancer also lacked MLH1 protein. These findings suggested that an abnormality of DNA mismatch repair genes was responsible for carcinogenesis in these four organs. We surmise that the patient may possibly have germline mutation of the MSH2 and MLH1 genes or hypermethylation of the promoter region of the MLH1 gene [15, 16]. In contrast, an abnormality of these genes is an unlikely cause for lung cancer. Although this case did not meet the diagnostic criteria for hereditary non-polyposis colorectal cancer (Amsterdam Criteria II), an abnormality of DNA mismatch repair genes was involved in four of the five cancers. This suggests that our patient is very likely to have Lynch syndrome [17].

Since the present patient did not have any symptoms and her tumors were discovered at a gynecological examination, it can be said that this is a rare and highly suggestive case. Unfortunately, the lung cancer and colon cancer were advanced at initial detection. Furthermore, from a clinical standpoint, FDG-PET and other imaging techniques were extremely useful in the diagnosis of multiple primary cancers in this patient.

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Disclosure Statement

The authors declare no potential conflicts of interest.

References