Malignant Carcinoid Tumor of the Appendix with Liver and Lung Metastasis : Report of a Case with a High Level of Serum Carcinoembryonic Antigen†

PLERNPIT PANOMREONGSAK, M.D.*,
SANYA SUKPANICHNANT, M.D.*,
YUDHTANA SATTAWATTHAMRONG, M.D.**,
CHUMPOL WONGWANIT, M.D.***,
CHALENGPOJ STHAPANACHAI, M.D.*,
KLEOPHANT THAKERNGPOL, B.Sc., M.Sc.*,
PHUNSUP WONGSURAKIAT, M.D.**,
PRASERT SEESILLAPACHAI, M.D.***

Abstract

We report elevated serum carcinoembryonic antigen (CEA) in a case of malignant carcinoid tumor of the appendix with liver and lung metastasis. A 55-year-old Thai man was found to have multiple nodules in the liver by ultrasonography. Serum CEA was 7,387.9 ng/mL (normal 0 - 4.1 ng/mL) leading to a clinical impression of colonic carcinoma with liver metastasis. During the investigation, he developed acute abdomen caused by ruptured acute appendicitis. Malignant carcinoid tumor of the appendix, 1 cm in diameter and located proximal to the ruptured acute appendicitis, was identified. The tumor cells showed trabecular or insular growth pattern, some nuclear pleomorphism but typically fine nuclear chromatin, frequent mitoses and focal necrosis. They were immunoreactive for antibody to chromogranin, neuron-specific enolase, CEA, and cytokeratin. Tumor metastases were discovered in the liver, right lung, mediastinal and right supraclavicular lymph nodes. Electron microscopic study demonstrated pleomorphic neurosecretory granules of the midgut type of carcinoid tumor.

Key word : Carcinoid, Appendix, Liver, Lung, Metastasis, CEA, Immunohistochemistry, Electron Microscopy

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Carcinoid tumor, the most common tumor of the appendix, does not metastasize frequently [1,2]. Only a small number of such cases have been reported[3,4] and it is rare for a case complicated with ruptured appendicitis[5]. Carcinoembryonic antigen (CEA), a 180,000-200,000 daltons glycoprotein initially found in the extract of colonic adenocarcinoma, has been measured in the serum and used

* Department of Pathology,
** Department of Medicine,
*** Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
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as a tumor marker for monitoring colonic cancer. However, the elevated serum CEA has been discovered in other tumors of either epithelial or non-epithelial types including those of gastrointestinal tract other than colon, breast, lung, ovary, thyroid and even hematologic malignancy(6). More recently, the immunoreactivity with antibody to CEA has been confirmed among the tumor cells of several types of aforementioned tumors. It has been reported in goblet cell carcinoid tumor but not in classic carcinoid tumor(7).

We describe here a case of malignant carcinoid tumor of the appendix with distant metastasis. The patient was complicated by ruptured appendicitis. A high level of serum CEA was detected during investigation and the tumor cells were immunoreactive for antibody (Ab) to CEA.

CASE REPORT

A 55-year-old obese Thai man (body weight of 90 Kg) presented at Siriraj Hospital, Bangkok, Thailand, in April 1997 with vague abdominal pain and constipation. He was found to have hepatomegaly, ascites, mild jaundice, pitting edema of both legs, and spider nevi on the anterior chest wall. The clinical impression was cirrhosis of the liver. He had had a history of alcoholic ingestion for 20 years but he abstained 5 years prior to this illness. No history of diabetes and hypertension was noted. The ultrasonography of the liver demonstrated multiple non-homogeneous echogeneic masses in both lobes of the liver, indicative of liver metastasis. The level of serum CEA was 7,387.9 ng/mL (normal 0-4.1 ng/mL) and that of serum alpha-fetoprotein was 2.1 IU/mL (normal 0-5.3 IU/mL). Due to the high level of serum CEA, the most suspected primary tumor was adenocarcinoma of the colon. The computerized tomographic (CT) scan of the abdomen revealed only multiple tumor nodules in the liver and ascites. The patient then developed acute abdominal pain which was caused by ruptured appendicitis. Due to the difficulty in distinction between primary and secondary peritonitis, partly due to the patient's obesity, his condition prior to the exploratory laparotomy was devastated by generalized peritonitis. Appendectomy and liver biopsy were performed. Apart from the metastatic tumor in the liver and ruptured appendicitis, no tumor was discovered elsewhere in the abdomen. After the operation, he was placed in the intensive care unit and suffered from cardiopulmonary failure. The chest radiograph revealed right pleural effusion and an ill-defined mass at the right middle lobe. Thoracocentesis and collection of sputum via the endotracheal tube were performed. A biopsy of the left supraclavicular lymph node was also performed after it was detected following the chest radiography. The patient died on the twentieth day after the operation from multiple organ failure. An autopsy was performed. Formalin-fixed and paraffin-embedded tissues were cut and stained with hematoxylin and eosin (H&E). Histochemical stains including mucicarmine, Grimelius, Masson Fontana, periodic acid-Schiff (PAS) and reticulin stains were performed. Immunoperoxidase staining using labeled streptavidin-biotin technique with Ab to chromogranin, synaptophysin, CEA, neuron-specific enolase (NSE), S-100 protein, AE1/AE3 cytokeratins, and alpha-fetoprotein as primary autibody was performed.

RESULTS

The appendix showed a ruptured site located 3 cm away from the tip. The lumen proximal to the rupture was markedly narrowed by the evenly thickened light brown wall; the diameter of the appendix just proximal to the ruptured site was 1 cm. Microscopically, tumor cells were located beneath the epithelial mucosa and arranged in insular or trabecular growth pattern (Fig. 1). The nuclei were round to oval with some nuclear pleomorphism. The nuclear chromatin was fine with inconspicuous nucleoli. The cytoplasm was eosinophilic, scant to modest in amount. No goblet cells were found. Mitotic figures were frequent and minute necroses were focally seen (Fig. 2). The tumor cells occupied the whole submucosa and invaded through the whole thickness of the appendiceal wall into the mesoappendix. Small tumor emboli were identified in some venules in the mesoappendix. The ruptured site of the appendix revealed suppurative appendicitis without any tumor cells. The tumor cells contained argyrophil granules in the Grimelius stain but lacked argentaffin granules in the Masson Fontana stain. They were negative for PAS and mucicarmine stains. They showed immunoreactivity for Ab to chromogranin, NSE, CEA (Fig. 3), and AE1/AE3, but they were negative for Ab to synaptophysin, alpha-fetoprotein and S-100 protein. The electron microscopic study demonstrated pleomorphic neurosecretory granules of the midgut type of carcinoid tumor (Fig. 4).

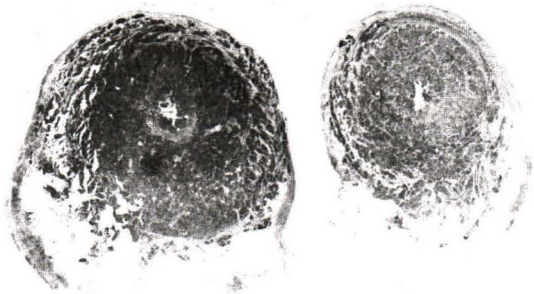

Fig. 1. Malignant carcinoid tumor of the appendix. Tumor cells are located in submucosa and extend into the mesoappendix. Note the trabecular or insular growth pattern of the tumor (H&E stain; original magnification 10x).

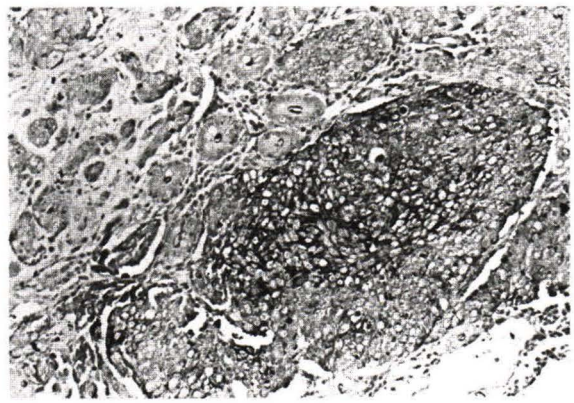

Fig. 3. Immunoreactivity to CEA in the tumor cells (original magnification 100x).

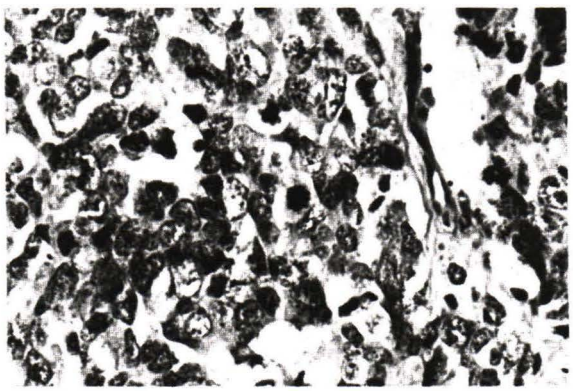

Fig. 2. Malignant carcinoid tumor, characterized by pleomorphic nuclei, frequent mitotic figures, and necrosis (H&E stain; original magnification 400x).

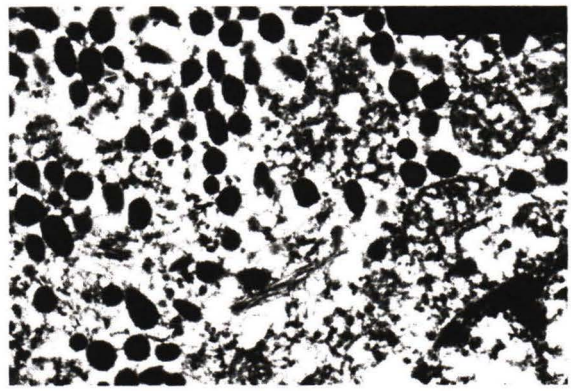

Fig. 4. Pleomorphic neurosecretory granules of midgut type in carcinoid tumor (original magnification 46,200x).

The tumor cells maintained their cytologic features and the insular or trabecular growth when presented in the biopsies of the liver and left supraclavicular lymph nodes. Clusters or aggregates of tumor cells were found in the pleural effusion and the sputum.

At autopsy, liver metastasis was confirmed (Fig. 5). Multiple tumor nodules were found in the right lung varying from peribronchial to subpleural locations. Lymphatic and vascular invasion by the tumor was noted. The right pleural cavity contained serosanguinous effusion and pleural thickening with tumor nodules. Hilar and mediastinal lymph nodes were enlarged due to metastatic tumors. The heart showed no valvular or abnormal lesions.

DISCUSSION

The present case is unusual for a carcinoid tumor of the appendix. Most of the appendiceal carcinoids are less than 2 cm in diameter and often

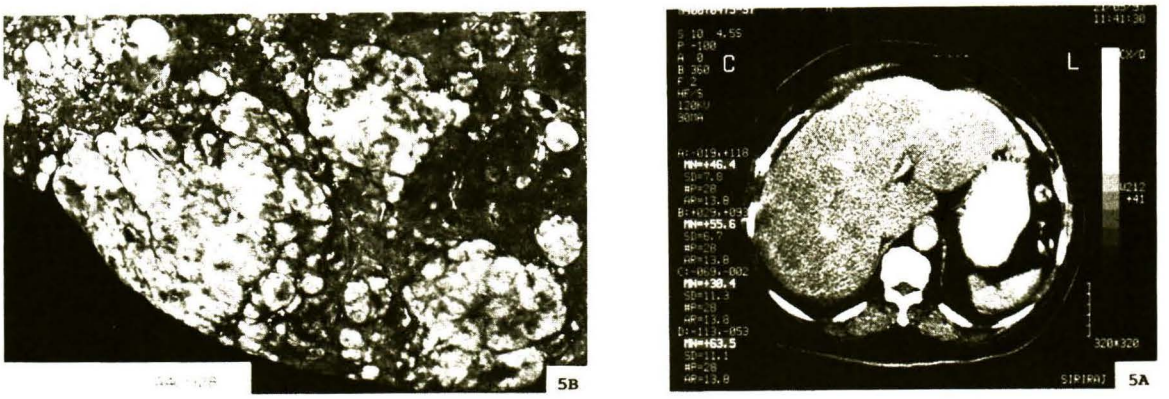

Fig. 5. Multiple tumor nodules in the liver demonstrated by CT scan (A) and gross examination at autopsy (B).

found as an incidental finding in the appendectomy specimen[1,2]. They rarely metastasize except for those larger than 2 cm in diameter. In the present case, the tumor was only 1 cm in diameter. The aggressiveness was, however, demonstrated by invasion into the mesoappendix, tumor embolization, and nuclear pleomorphism of the tumor similar to that described in atypical carcinoid of the lung. One might consider the possibility of primary atypical carcinoid of the lung with metastasis to the liver and the appendix due to the cytologic findings and the presence of argyrophil granules but lack of argentaffin granules. The positivity of immunoreactivity for chromogranin is suggestive of neuroendocrine tumor. However, the pleomorphic neurosecretory granules in the tumor indicative of a midgut type of carcinoid[8] and the typical submucosal growth of the tumor in the appendix confirmed that the tumor first arose in the appendix. Neurosecretory granules in the fore- and hind-gut types of carcinoid are round. Besides metastasis, this case was complicated by ruptured acute appendicitis, probably caused by the tumor located proximal to the ruptured site producing obstruction of the appendix[2].

The high level of serum CEA (7,387.9 ng/mL) in the present case is another unusual finding. The clinical impression prior to a definite pathologic diagnosis was colorectal carcinoma with metastasis to the liver. Due to a large tumor volume in the liver and the immunoreactivity for Ab to CEA among the tumor cells, it is conceivable that the tumor could produce and release CEA into the circulation. Arai et al reported a bronchial carcinoid tumor with a high level of serum CEA (528.6 ng/mL) and histologically strong immunoreactivity to CEA among the tumor cells[9]. They concluded that the tumor can produce CEA. Since the use of CEA as a tumor marker in monitoring colorectal carcinoma, a number of tumors with immunoreactivity for Ab to CEA have been described including lung carcinoma of both small cell and non-small cell types, gastrointestinal carcinomas other than colorectal carcinomas, breast cancer, ovarian cancer, medullary carcinoma of thyroid, leukemia and lymphoma. Goblet cell carcinoid tumor or adenocarcinoid tumor has been described to demonstrate such an immunoreactivity, however, the immunoreactivity is localized to the goblet cells. Nevertheless, up to 26 per cent of classical carcinoid tumor were found to have immunoreactivity for Ab to CEA[10].

In summary, we presented a case of malignant carcinoid tumor of the appendix with unusual manifestations including distant metastasis (despite its small size), a high level of serum CEA (misleading to the clinical impression of colorectal carcinoma), and ruptured acute appendicitis as a complication. A thorough examination of the appendix was crucial for a definite diagnosis in this case especially the histologic examination of the grossly normal portion proximal to the ruptured site of acute appendicitis. Paraffin section immunoperoxidase study demonstrated the immunoreactivity for anti-

body to CEA among the tumor cells, allowing us to establish the relationship between the tumor and the high level of serum CEA. Electron microscopic finding of pleomorphic neurosecretory granules confirmed primary carcinoid tumor of the appendix.

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เนื้องอกคาร์ศินอยด์ชนิดร้ายแรงของไส้ติ่งที่มีการแพร่กระจายไปตับและปอด: รายงานผู้ป่วยหนึ่งรายที่มีระดับซีอีเอในน้ำเลือดสูง

เพลินพิศ พนมเริงศักดิ์, พ.บ., เชลงพจน์ สถาปนไชย, พ.บ.*,*
สัญญา สุขพณิชนันท์, พ.บ., เกลียวพันธ์ เถกิงพล, ภ.ม.*,*
*ยุทธนา ศตวรรษธำรงค์, พ.บ.**, พูนทรัพย์ วงศ์สุรเกียรติ, พ.บ.**,*
*ชุมพล ว่องวานิช, พ.บ.***, ประเสริฐ สี่ศิลปชัย, พ.บ.****

รายงานระดับคาร์ศิโนเอ็มบริโอนิคแอนติเจน (ซีอีเอ) ในซีรัมสูงในเนื้องอกคาร์ศินอยด์ชนิดร้ายแรงของไส้ติ่งซึ่งแพร่กระจายไปที่ตับและปอดหนึ่งราย ผู้ป่วยชายไทยอายุ 55 ปี ถูกตรวจพบว่ามีก้อนในตับหลายก้อนโดยอัลตราซาวน์ ระดับ ซีอีเอในซีรัมสูง 7,387.9 นาโนกรัม/เดซิลิตร (ปกติ 0 – 4.1 นาโนกรัม/เดซิลิตร) ทำให้สงสัยว่าเป็นมะเร็งในลำไส้ใหญ่ซึ่งแพร่กระจายมาที่ตับ ระหว่างการสืบค้น ผู้ป่วยเกิดอาการปวดท้องเฉียบพลันจากการแตกของไส้ติ่งอักเสบเฉียบพลัน การตรวจทางพยาธิวิทยาพบเนื้องอกคาร์ศินอยด์ชนิดร้ายแรงของไส้ติ่งขนาดเส้นผ่าศูนย์กลาง 1 เซนติเมตร เหนือต่อรอยแตกของไส้ติ่งอักเสบ เซลล์เนื้องอกเรียงตัวเป็นแถวหรือกลุ่มเล็กๆ มีขนาดของนิวเคลียสแตกต่างกันบ้างโดยมีโครมาตินละเอียด พบการแบ่งตัวบ่อยและหย่อมเนื้อตาย ให้ผลบวกต่อการย้อมสำหรับโครโมแกรนิน อีโนเลสจำเพาะต่อเซลล์ประสาท ซีอีเอ และซัยโตเคอราติน พบการแพร่กระจายของเนื้องอกในตับ ปอดข้างขวา ต่อมน้ำเหลืองในช่องกลางอกและไหปลาร้า การตรวจด้วยกล้องจุลทรรศน์อิเลคตรอนพบนิวโรซีครีตอรีแกรนูลขนาดต่างๆ แสดงลักษณะจำเพาะของเนื้องอกคาร์ศินอยด์ของลำไส้ส่วนกลาง

คำสำคัญ : คาร์ศินอยด์, ไส้ติ่ง, ตับ, ปอด, การแพร่กระจายของมะเร็ง, ซีอีเอ, อิมมูโนฮิสโตเคมี, จุลทรรศน์อิเลคตรอน

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* ภาควิชาพยาธิวิทยา,
** ภาควิชาอายุรศาสตร์,
*** ภาควิชาศัลยศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700