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Report

Invasive Lobular Carcinoma of the Breast with Extensive Metastases: An Autopsy Case Report

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A 79-year-old female underwent modified radical mastectomy for cancer of the left breast (stage IIIA) in 2006. Invasive lobular carcinoma was diagnosed on histopathological examination. Postoperative adjuvant therapy included oral administration of an aromatase inhibitor for 5 years and no apparent recurrence was observed at the 5th postoperative year regular checkup. However, we observed extensive gastrointestinal metastases with pleural and peritoneal dissemination 6 years and 4 months postoperatively. Nineteen months after treatment for recurrence was initiated, we were unable to control vesical bleeding due to urinary bladder metastasis and the patient died. The autopsy report suggested that the direct cause of death was postrenal failure accompanied by formation of an intravesical hematoma. In the present report, we review the relevant literature and report the clinical course of a breast cancer patient and the pathological results of her autopsy.

Key Words: invasive lobular carcinoma, extensive metastases, autopsy

Introduction

The common metastatic sites of breast cancer include the lung, bone, and liver, while gastrointestinal (GI) metastasis and peritoneal dissemination occur with low frequency. Accumulated ascites and hydronephrosis due to peritoneal dissemination are sometimes encountered in cases of invasive lobular carcinoma (ILC) in clinical practice.

Our patient had ILC leading to peritoneal dissemination, duodenal metastasis, and rectal metastasis after a postoperative lapse of 6 years and 4 months. Although we treated the patient for recurrence, vesical bleeding due to bladder metastasis could not be controlled. She died at 19 months after recurrence. After her death, her family agreed to an autopsy for future medical development. We report the details based on findings obtained from the pathological autopsy along with a relevant literature review.

Case Report

A 79-year-old female was referred to Tokyo Women's Medical University Hospital for further evaluation and treatment of a marked accumulation of ascites fluid. Her chief complaints were reduced appetite, a feeling of abdominal bloating for approximately half a year, and an urge to defecate with fecal incontinence for 1 month.

In 2006, the patient underwent modified radical

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mastectomy with axillary lymph-node dissection (lt-Bt + Ax) for stage IIIA (pT3N1M0) cancer of the left breast 6 years and 4 months ago. Histopathological examination at that time (Fig. 1) showed invasive lobular carcinoma, with skin invasion, lymphatic invasion (ly2), nuclear grade 1, estrogen-receptor-positive (ER +), progesterone-receptor-positive (PR +), a HER2 expression score of 0, and metastases to level I (10/22), and level II lymph nodes (5/5). After the operation, she received radiation therapy to the chest wall and around the collarbone. In addition, she was orally administered doses of an aromatase inhibitor (AI: anastrozole) for 5 years and oral doses of uracil-tegafur for 2 years as an adjuvant therapy.

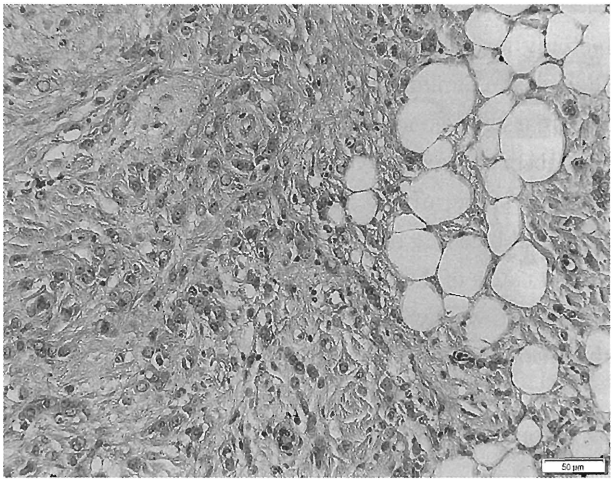

Fig. 1 Histopathological examination (H&E stain) for primary lesion in breast carcinoma, invasive lobular carcinoma; invasive proliferation in solitary diffusion and cord for atypical cells with high nucleocytoplasmic ratio was observed. Lesions are spread widely (approximately 9×4 cm).

There are no apparent recurrent findings at the 5th year postoperative check-up. The patient had no other relevant history and the family history was unremarkable.

Present History on Admission: We observed a tense abdomen, which may have been due to ascites. On rectal examination, we palpated a hard and narrowed rectal mucosal surface.

Blood Test Findings on Admission: Hemoglobin was 10.6 g/dL and albumin was 3.3 g/dL. Liver and renal functions were almost normal. The tumor markers were increased in carcinoembryonic antigen (CEA) at 28.0 ng/mL and NCC-ST-439 at 40.2 U/mL. Cancer antigen 15-3 (CA15-3) was 15.2 U/mL, below the reference level (Table 1).

PET-CT Examination: Diffuse fluorodeoxyglucose (FDG) accumulation was observed along the wall of the ascending colon and rectum. In addition, slight FDG accumulation was observed in the pleural and ascites fluids (Fig. 2).

Upper GI Endoscopic Findings: We observed a markedly thick and rigid wall at the gastric corpus and antrum. In addition, there was edema of the wall and erosion at the mucosal surface at the duodenal crus (Fig. 3a, 3b). A biopsy taken from the mucosal surface showed only inflammatory changes, but that taken from the site of duodenal erosion showed a small number of atypical cells in distended submucosal lymphatics. In addition, immunostaining revealed that the atypical cells were positive for ER.

Table 1 Blood chemical tests

TP	g/dL	6.6	WBC	/μL	5,240	
Alb	g/dL	3.3	RBC	$\times 10^6$/μL	3.57	
Cre	mg/dL	0.79	Hb	g/dL	10.6	
BUN	mg/dL	11.3	Ht	%	31.4	
AST	U/L	38	Plt	$\times 10^4$/μL	29.2	
ALT	U/L	23				
LDH	U/L	214	Tumor marker			Standerd value
ALP	U/L	268	CEA	ng/mL	28.0	≤5.0
T-Bill	mg/dL	0.5	CA15-3	U/mL	15.2	<25
γ-GTP	U/L	10	NCC-ST-439	U/mL	40.2	<7.0
Amy	U/L	54				
Na	mEq/L	140				
K	mEq/L	3.4				
Cl	mEq/L	103				

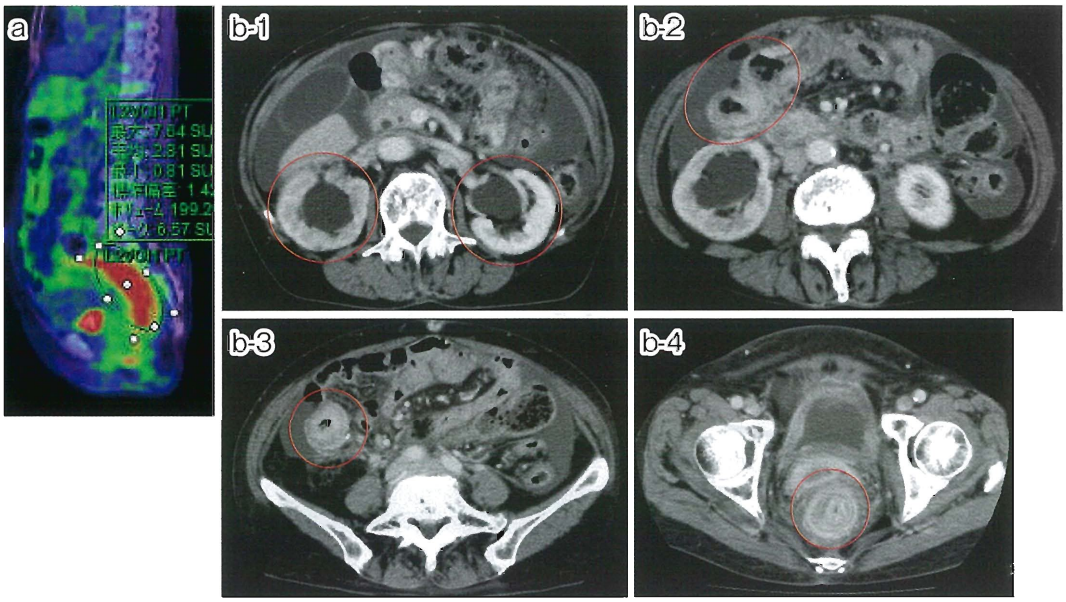

Fig. 2 PET-CT examination at the time of recurrence
a. A diffuse increase in accumulation of FDG is observed along the rectal wall. Minor accumulation of FDG is observed in both the pleural and peritoneal fluid.
b. A CT image shows hydronephrosis on both sides (b-1) and marked thickening of duodenum (b-2), ascending colon (b-3), and rectal walls (b-4).

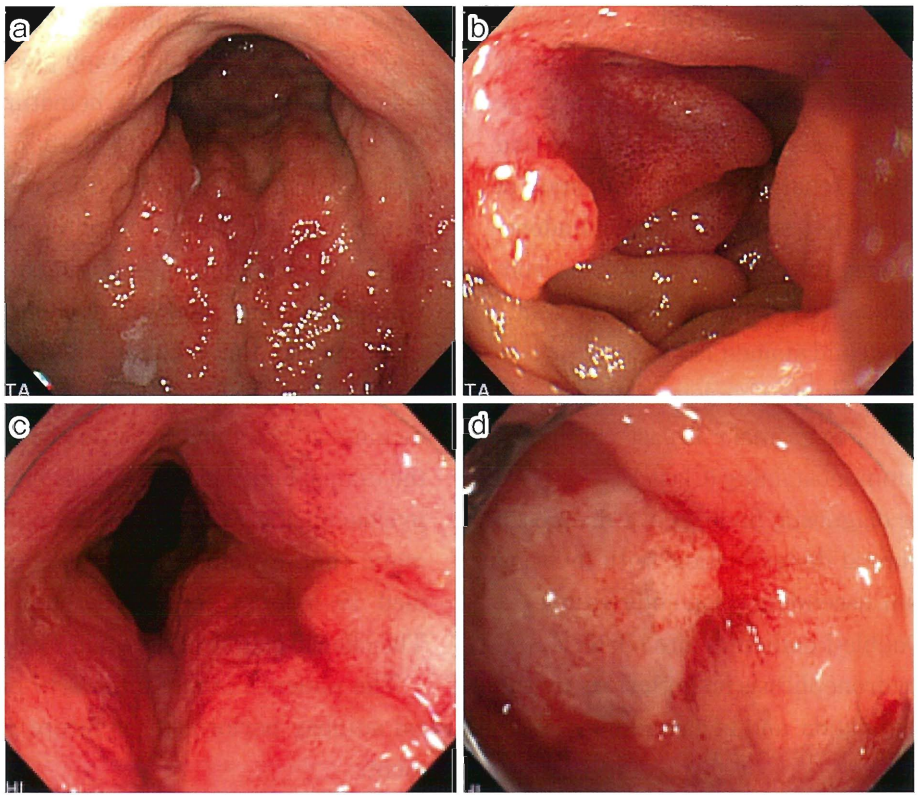

Fig. 3 Upper and lower GI endoscopy at the time of recurrence
a. Wall thickening at the gastric corpus and antrum.
b. Wall thickening and erosion are observed in the second portion of the duodenum.
c. The whole rectum is rigid with mucousal edema.
d. Multiple ulcers in the sigmoid colon are shown.

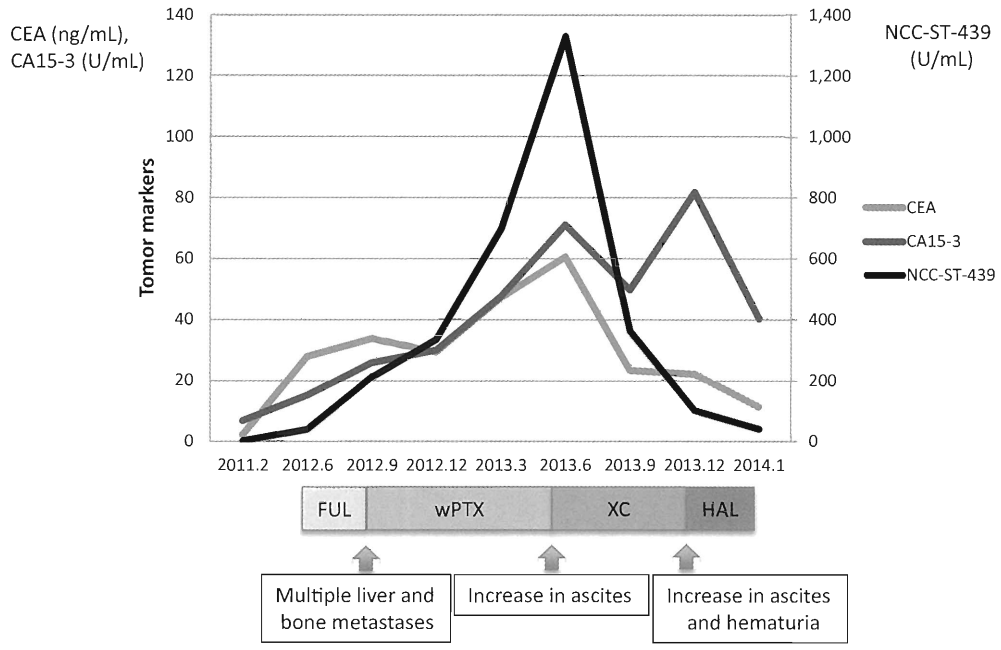

Fig. 4 The clinical course after recurrence
Treatment progress. Transition and progression of tumor markers levels.

Lower GI Endoscopic Findings: We were only able to evaluate up to the sigmoid colon, because of patient's pain threshold. The whole rectal wall was rigid with mucosal edema. We observed a large number of ulcerative lesions in the visible sigmoid colon (Fig. 3c, 3d). Histopathological examination of a biopsy taken from the rectal wall showed adenocarcinoma, which may have been a metastasis from the breast carcinoma. It was identified in the rectal mucosal interstitium and stained ER+.

Ascites Fluid Cytology: Cytology revealed cell morphology resembling primary breast carcinoma cells, with ER+ immunostaining (Class V).

Based on these diagnostic findings, we diagnosed peritoneal and pleural dissemination, with invasion into the duodenum, ascending colon and rectum.

We inserted Double-J catheters into bilateral ureters because of hydronephrosis on both sides by the peritoneum dissemination, and began administering of fulvestrant (FUL).

Because multiple liver and bone metastases developed 3 months later, we started administration of weekly paclitaxel (PTX, 64 mg/m^2) and denosumab and long stable disease (SD) was achieved. The patient's volume of ascites increased (SD for liver) after 7 months (11 months after recurrence); therefore, we switched chemotherapy to capecitabine plus cyclophosphamide (XC, X: 1,200 mg/body, C: 100 mg/body) therapy plus denosumab and long SD was achieved. The hematuria persisted and there was another increase in the volume of ascites 7 months later (18 months from recurrence); therefore we began administration of eribulin (HAL, 0.7 mg/m^2). However, it was difficult to control the vesical bleeding and the patient complained of photophobia. Immediately thereafter, the patient developed impaired consciousness. We suspected meningeal dissemination secondary to metastasis to the cranial bone along with infectious disease due to pyelonephritis. We started the patient on symptomatic therapy but it was ineffective. The patient died 19 months after recurrence was confirmed. The clinical course is shown in Fig. 4.

The patient's family offered to have a pathological autopsy performed for future medical development.

Pathological Autopsy Findings

1. Multiple metastases and disseminations of the breast cancer

1) Macroscopically multiple white nodules with a diameter of 3-5 mm were observed in the diaphragm, mesentery, serosa of the small intestine

and parietal peritoneum. Multiple clusters of petechial hemorrhages were scattered in the parietal peritoneum. Microscopically atypical cells proliferated invasively in the liver (15 mm in the right lobe, 7 mm in the left lobe), left adrenal gland, bilateral kidneys, spleen, uterus, rectum (Fig. 5), stomach, esophagus, tail of the pancreas, and small intestine. These atypical cells were morphologically similar to the original lesion (breast cancer, ILC) and did not contradict that they ware metastatic and a dissemination lesion of the breast cancer [cytokeratin 7(+), cytokeratin 20(+), ER(+), PR(+)]. Macroscopically, meningeal dissemination was not observed.

2) Macroscopically, metastasis into the urinary bladder and ureter and forming hematoma in the urinary bladder. Microscopically cancer cells invasively proliferated from the deep layer of the urinary bladder to the ureteral fascia, resulting in ureteral obstruction. Multiple cells were present within lymphatic ducts in the muscular layers of the bladder, suggesting lymphatic spread. In addition, a large quantity of clots in 123 g, containing multiple cancer cells, were formed in the urinary bladder (Fig. 6).

2. Disseminated intravascular coagulation (DIC)

Microscopically, microscopic fibrin thrombi were scattered in the renal glomeruli, confirming the presence of DIC.

3. Pyelonephritis

Macroscopically, a green, muddy material (large quantity in the right kidney and small quantity in the left kidney) was present in bilateral renal pelvises. Microscopically, an invasion of inflammatory cells, mainly composed of neutrophils, was found in bilateral renal pelvises and urinary tubules.

As a result of the autopsy, it was diagnosed that the direct cause of death was postrenal failure accompanied by intravesical hematoma formation.

From the above findings, we believed that the vesical bleeding developed when a bladder vessel ruptured due to bladder metastasis of breast carcinoma. This possibly led to pyelonephritis accompanied by intravesical clot formation.

Discussion

The most common metastatic sites for breast cancer are well known, and occur in the lungs, bones, and liver, while GI metastases and peritoneal dissemination are rarely encountered in clinical practice. Although Mukaiyama et al[1] noted metastasis into the GI tract and peritoneum in 31% of autopsy cases, they described that it could be diagnosed before death in only 6% of autopsy cases. They believed that this type of metastasis was rarely accompanied by clinical symptoms, including hydronephrosis, and was asymptomatic for long periods in many cases. However, in recurrent cases of ILC which is a particular class of breast carcinoma that is thought to account for approximately 5–10% of all breast carcinomas, accumulative ascites due to peritoneal dissemination and hydronephrosis are rarely encountered. The report prepared by Borst et al[2] showed that peritoneal and retroperitoneal metastatic rates in clinical cases were 3.1% in ILC compared with 0.6% in invasive ductal carcinoma (IDC), which coincided with clinical experience. McLemore et al[3] conducted a retrospective analysis of 12,001 cases that were diagnosed as metastatic breast carcinoma from 1985 to 2000 at the Mayo Clinic. They found GI tract metastasis (including peritoneal dissemination) in 73 cases, of which ILC was observed in 54%. Because ILC accounted for 12% of all initial breast carcinoma diagnoses during the same period, they reported that the frequency of GI tract metastasis was significantly higher with ILC ($p < 0.001$). This difference in metastatic sites between ILC and IDC may be attributed to the disappearance of expression of E-cadherin, an intercellular adhesion molecule[4].

The possible pathways for the distant metastasis of carcinoma include lymphatic spread, hematogenous spread, and dissemination. Although metastatic pathways to the GI tract and peritoneum of ILC have been presumed and discussed in various ways from case reports to review papers, no clear conclusions have been drawn. This point remains controversial owing to the lack of definitive evidence.

In our patient, autopsy revealed a large number of disseminated nodules in the peritoneum and diffuse metastasis of the breast cancer with thickening

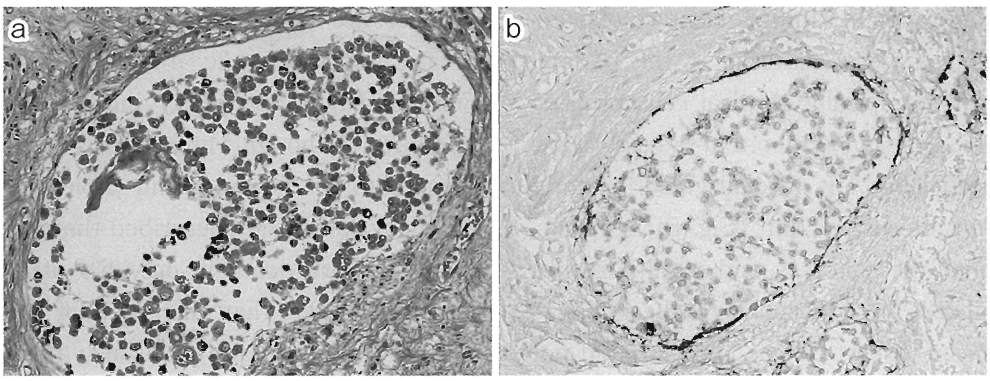

Fig. 5 Histopathological examination of the rectum on autopsy
Many cancer cells are observed within submucosal lymphatic ducts.
a. H&E stain (×40).
b. D2-40 stain (×40).

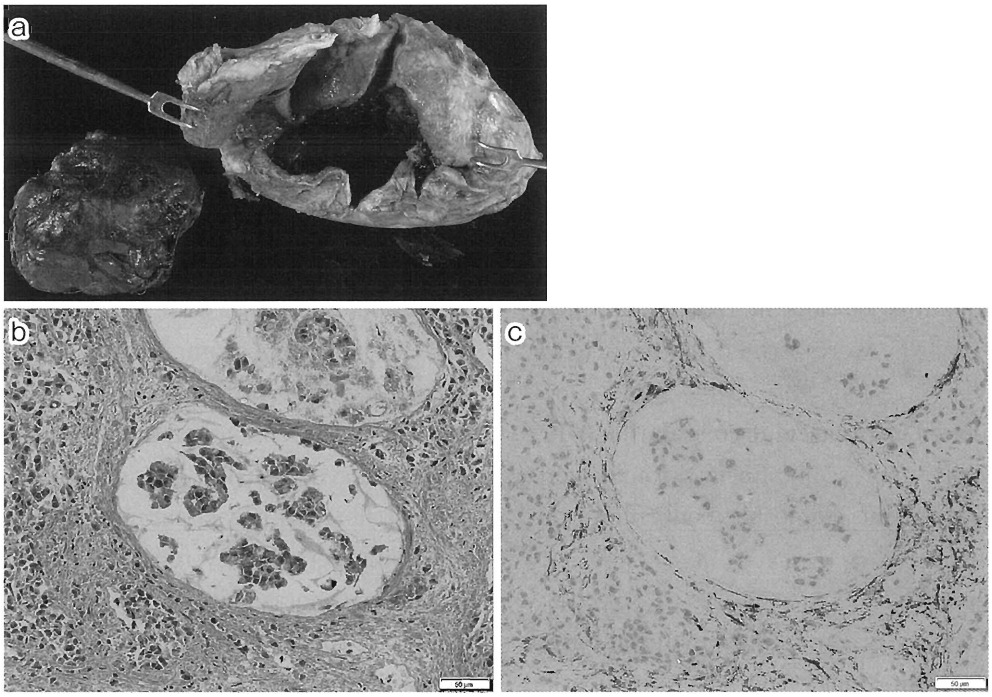

Fig. 6 The urinary bladder findings on autopsy
Many cancer cells are observed within the lymphatic ducts in the muscle layers of the urinary bladder wall.
a. The urinary bladder wall with marked thickening and clots.
b. H&E stain (×40).
c. D2-40 stain (×40).

of the gastric, duodenal, ascending colon, rectal, and bladder walls. Disseminated nodules and intestinal and bladder walls were not macroscopically continuous firmly through serosa. We postulated that there was diffuse intramural metastasis through vessels, followed by cancer progression from the metastatic site into the serosa, leading to the scattered peritoneal nodules. From the histological point of view, multiple cancer cells were observed in lymphatic ducts within the wall of rectum.

Detailed studies of an autopsy series in several countries[2)5)~8)] indicate that ILC metastasizes to the GI tract and peritoneum in association with the fusion of several micronodules. Gastrointestinal tract metastases are associated with diffuse spread, mainly to the submucosa, muscularis propria, and

serosa, and occasionally to the mucosa. In particular, gastric lesions show a linitis plastica type of wall thickening. A similar observation was found in our case.

Isolated intestinal metastasis that was not accompanied by peritoneal dissemination was reported in cases of IDC[3] as well as cancers of the other origin in Japan[9)10)] and overseas[11)12)]. The presence of diffuse intramural metastasis through vessels, as discussed above, should be considered.

McLemore et al[3] reported that drug therapy was the only factor contributing to a statistically significantly improved prognosis for the treatment of GI tract metastasis for breast carcinoma; operative therapy did not significantly contribute to improvement of prognosis. However, when the study was limited to 23 cases with GI tract metastasis for breast carcinoma without peritoneal dissemination, the mean survival times (MST) were 44 months in the operative group (12 cases) and 9 months in the nonoperative group. Further statistically significant differences were not observed in the GI tract metastatic cases of breast carcinoma without peritoneal dissemination. However, it was suggested that surgery was possible to contribute to the improvement of both prognosis and quality of life. However even if our case did not have peritoneum dissemination, we did not believe that an operation was indicated because GI tract metastasis spread very widely.

The lung, bone, and liver are known to be common metastatic sites of breast cancer. However, according the report by Mukaiyama et al[1)], metastatic investigation on autopsy showed that metastasis to lung, bone, liver, soft tissue accounted for at least 75% of metastases. Metastasis to endocrine organs including the adrenal gland, GI tract, and urogenital organs accounted for 20–40% of metastases. However they stated that the diagnostic rate before autopsy was very low, less than 5%. This report was prepared in 1989 and it may not be applicable to the current situation because of improvements in our imaging diagnostic capabilities. However, in our case, autopsy revealed multiple cancer metastases in the left adrenal gland, bilateral kidneys, spleen, uterus, esophagus, and tail of the pancreas. Though an accurate antemortem diagnosis may not have changed the prognosis of this patient, we hope our report will encourage reconsideration of the biological features of breast cancer as a systemic disease.

Acknowledgment

We are deeply thankful for family of the patient, and the patient herself who offered the present autopsy for future medical development and we pray for repose of her soul.

The authors indicated no conflicts of interest.

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広範な他臓器転移を認めた乳腺浸潤性小葉癌の1剖検例

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症例は79歳女性．左乳房の局所進行浸潤性小葉癌で手術を施行．術後補助療法として5年間のアロマターゼ阻害剤を内服し，術後5年目の定期検診では明らかな再発所見を認めていなかったが，術後6年4ヵ月に広範な消化管転移と胸膜・腹膜播種を認めた．再発治療後19ヵ月で，膀胱転移による膀胱粘膜よりの出血コントロールがつかず亡くなったが，剖検により直接死因は膀胱内血腫形成に伴う腎後性腎不全と推定された．再発治療後の経過と剖検結果を若干の文献的考察を加えて報告する．