Neuroendocrine Tumors of the Liver and Pancreas Associated with Elevated Serum Prostatic Acid Phosphatase

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A 58-year-old man was revealed to have multiple liver tumors with elevated prostatic acid phosphatase (PAP) during a medical examination. The tumors were of neuroendocrine nature, but no abnormal findings were obtained in other organs in which neuroendocrine tumors develop frequently. Repeated transarterial embolization was partially effective. However, the tumors became resistant to the therapy three years later, continued growing and ruptured. Autopsy disclosed neuroendocrine tumors in the pancreas, which were immunohistologically positive for PAP. Neuroendocrine tumors of the pancreas and liver producing PAP are rare; this case is reported with a review of literature.

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Key words: carcinoid tumor, islet cell tumor, tumor marker, hepatoma

Introduction

Primary carcinoid tumor of the liver is extremely rare (1, 2). The diagnosis of primary liver carcinoid is not simple, since histological examination of the biopsy specimen does not distinguish it from a metastatic tumor, and since the possible presence of small primary carcinoids in other organs from which liver metastasis occurs frequently cannot be ruled out completely (3–5). Primary liver carcinoid is considered to arise from neuroendocrine cells (Kulchitsky cells) of the intrahepatic cholangioles and produces serotonin (3, 4). In addition to such typical carcinoids, hepatocellular carcinomas and hepatoblastomas rarely contain a carcinoid tumor component or show carcinoid features (6, 7). More intriguing are the primary hepatic tumors which do not show the morphology of carcinoids or apudoma, but nevertheless display neuroendocrine features revealed by immunohistochemical or ultrastructural studies (8). Therefore, the differential diagnosis between primary carcinoid tumor of the liver and hepatocellular carcinoma with carcinoid features is also not easy in some cases of liver tumors with neuroendocrine features.

Recently, we treated a case of multiple liver tumors of neuroendocrine nature which were associated with elevated serum prostatic acid phosphatase (PAP). The liver tumor was initially thought to be a metastatic carcinoid, but no abnormal findings were obtained in prostate, rectum and other intra-abdominal organs even with numerous diagnostic procedures including various imaging techniques and histological examination of biopsy specimens. Autopsy disclosed multiple neuroendocrine tumors in the pancreas which were immunohistologically positive for PAP. With these results, however, it seemed difficult to determine whether it was the liver or pancreas tumor which was the primary tumor. On the other hand, PAP production by a neuroendocrine tumor of the liver or pancreas is considered to be very rare, and only a few cases have been reported in which islet cell tumors and insulomas are shown to produce PAP (9–12). Here, we report this case with a review of literature on PAP-producing neuroendocrine tumors.

Case Report

A 58-year-old man was pointed out to have multiple space occupying lesions (SOLs) in the liver during a medical examination six years previously. Tumors detected with abdominal ultrasonography were 4 and 2 cm in diameter (Fig. 1). Laboratory data were: aspartate aminotransferase (AST) 7 IU/, alanine aminotransferase (ALT) 5 IU/, γ-glutamyl transpeptidase (γGTP) 19 IU/, alkaline phosphatase (Alp) 5.8 KAU, ICG 6.9%, HBsAg negative, α-fetoprotein (AFP) 2.2 ng/ml, carcinoembryonic antigen (CEA) 0.8 ng/ml, CA19-9 10 U/ml, and PAP 5.1 ng/ml (normal <2.1 ng/ml). Histological examination of biopsy specimen disclosed carcinoid features, but 5-hydroxy...
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Figure 1. Abdominal ultrasonography taken at the first admission six years ago. Space-occupying lesions (SOLs) were observed as indicated by arrows. A) SOL 2 cm in diameter. B) SOL 4 cm in diameter.

Figure 2. Abdominal angiography and CT taken at the first admission six years ago. A) Hepatic arteriography before the transarterial embolization (TAE), showing multiple tumor staining. B) Follow-up CT after the first TAE, showing lipiodol uptake by the main tumor (arrow).

Figure 3. Clinical course showing the effects of TAE and TAI on serum prostatic acid phosphatase (PAP) (upper) and Alp and γGTP (lower).

indol acetic acid (5-HIAA) was 1.9 ng/day (normal 0.8–4.5) and symptoms and signs suggestive of excessive serotonin production were not observed. Prostate, colon and rectum gave no histological evidence of malignancy. Computerized tomography (CT), magnetic resonance imaging (MRI), galium-scin-
tigraphy and 123I-metaiodobenzylguanidine (MIBG) scintigraphy gave no abnormal findings in other organs. Angiography disclosed multiple hypervascular liver tumors and transarterial embolization (TAE) using 1.5 ml lipiodol, 20 mg adriamycin, and spongel was carried out. The follow-up CT confirmed lipiodol uptake by the tumor (Fig. 2). The number and size of liver tumors analyzed by ultrasonography, CT and angiography decreased significantly (photographs, not shown), and PAP decreased from 5.4 to 3.3 ng/ml (Fig. 3). Then, close surveil-
lance with ultrasonography and CT was instituted, and TAE was repeated on tumor recurrence (Fig. 3). The therapeutic effects well correlated with decreases in serum PAP (Fig. 3). Serum level of serotonin and gastrin four years earlier was 0.27 µg/ml (normal <0.25) and 54.5 pg/ml (normal 30–150), respec-
tively. Urine 5-HIAA was 3.1 ng/day. Three years previously, bone pain appeared, and bone scintigraphy disclosed multiple metastasis to vertebrae and ribs. Two years previously, transarterial injection (TAI) using lipiodol and adriamycin was performed because no feeding arteries were accessible. The TAI was not effective and the size and number of liver tumors increased in parallel with the serum levels of PAP (Fig. 3). Prostate-specific antigen (PSA) was 1.3 ng/ml (normal <3.0). One year earlier, PAP was elevated to 642 ng/ml, while PSA was 1.7 ng/ml. Six months previously, he became drowsy and flapping tremor appeared. Blood counts were; red blood cell (RBC) 279×10^6/µl, hemoglobin (Hb) 7.9 g/dl, white blood cell
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WBC 6,900/µl, and platelet 35.9×10⁴/ml. Total protein (TP) was 6.5 g/dl, while albumin (Alb) was 2.3 g/dl. Serum globulin was increased, but electrophoresis of patient’s serum gave no findings suggestive of the presence of myeloma protein. Other laboratory data were; AST 36 IU/l, ALT 22 IU/l, lactate dehydrogenase (LDH) 160 IU/l, γGTP 337 IU/l, Alp 2,000 U/l (normal 74–223), total bilirubin (T.Bil) 1.0 mg/dl, amylase 444 U/dl (normal 60–190), blood urea nitrogen (BUN) 32 mg/dl, creatinine 1.2 mg/dl, corrected calcium (cCa) 9.5 mg/dl, inorganic phosphate 3.8 mg/dl, glucose 165 mg/dl, Fe 37 µg/dl, HCV Ab negative, PAP 709 U/l, serum NH₃ 200 µg/dl. One week earlier, pneumonia was recognized and respiratory and cardiac arrest occurred, likely due to airway obstruction.

On autopsy, several tumors, measuring up to 2 cm in diameter, were recognized in the body and tail of the pancreas (Fig. 4). Tumor cells, which had abundant eosinophilic and granular cytoplasm and relatively uniform oval nuclei, were arranged in trabecular structure. These cells were positively stained by Grimelius method, and were immunohistologically positive for neuron specific enolase (NSE) and chromogranin A (Fig. 5). PAP was positively stained as shown in Fig. 5C. However, insulin, glucagon, somatostatin, pancreatic polypeptide, vasoactive intestinal peptide (VIP), gastrin and serotonin were undetectable. By electron microscopy, numerous uniform, membrane bounded, electron-dense granules, measuring about 200–300 nm in diameter were found in the cytoplasm (photographs, not shown). The liver (6,400 g) was markedly enlarged, with numerous tumor nodules, measuring up to 8x6 cm in size (Fig. 4). The immunohistochemical nature of the tumor cells was similar to that of the pancreas (Fig. 6). Metastatic vertebrae tumors (L1 to L5) were osteoblastic. Tumor nodules up to 5 mm

Figure 4. Macroscopic appearance of autopsy materials. Multiple tumors are seen in the pancreas and the liver. A) the pancreas; B) sliced surface of the pancreas; C) cut surface of the liver. Scale bars, 3 cm.

Figure 5. Histological and immunohistochemical study of the tumor of the pancreas. A) HE stain (×170); B) Grimelius staining (×170); C) PAP (×170).
Figure 6. Histological and immunohistochemical study of the tumor of the liver. A) HE stain (×226); B) Grimelius (×170); C) Chromogranin A (×170).

Discussion

In the present case multiple neuroendocrine tumors were found in the liver and pancreas, lung, bone, and lymph nodes. The incidence of primary liver carcinoid is very low, and as far as we know, only 22 cases have been reported (4, 13–21). The incidence of the primary liver cancer metastasizing to the pancreas is also very low (22). In contrast, carcinoid tumors of the intraabdominal cavity with liver metastasis are occasionally seen (23, 24). From these statistic data, the possibility that a neuroendocrine tumor had developed in the pancreas and then metastasized to the liver and other organs appears to be high. However, the incidence of primary liver tumor with carcinoid features may be higher than expected, and the metastasis of hepatocellular carcinoma to the gastrointestinal tract and pancreas is rarely seen (6–8, 22). In the present case, a pancreas tumor was not found when liver tumors were recognized. In addition, extensive metastases were found in various organs on autopsy. Therefore, the possibility that the neuroendocrine tumor had originated from the liver and then metastasized to various organs including pancreas cannot be ruled out completely.

Tumor cells of the present case which were stained positive for NSE and chromogranin A had neuro-secretory granules (2, 17). However, peptide hormones such as insulin, glucagon and gastrin were not detected in the tumor cells. 5-HIAA and serotonin were not significantly increased and symptoms and signs of carcinoid syndrome were not seen (25). In contrast, PAP was immunohistologically stained, indicating that PAP production by the neuroendocrine tumors of the pancreas and the liver was the cause of markedly elevated serum PAP (Figs. 3 and 5) (26–28). PAP production by neuroendocrine tumors reported in the past literature is summarized in Table 1 (29, 30). PAP production is rare in carcinoid tumors of the stomach which are of foregut origin; it is seen in approximately 10–20% of carcinoid tumors of the small intestine which are of midgut origin, and is frequent in the carcinoid tumors of the rectum which are of hindgut origin (9, 12). As far as we know, PAP production has not been reported in primary liver carcinoid and in non-endocrine apudoma of the pancreas (3, 10, 23, 28). In contrast, PAP production has been reported in two cases of islet cell tumor of the pancreas, insulinoma and in occasional cells in normal Langerhans islets (12–14). Therefore, if the primary site of the PAP-producing neuroendocrine tumor in the present case was the pancreas, the tumor cells may have originated from insulin-producing cells, occasional cells of normal Langerhans islets or their ancestral cells (12, 29, 31).

PAP is a sensitive but not a specific marker of prostatic carcinoma (12, 32), and high serum PAP associated with normal PSA is characteristic of neuroendocrine tumors of non-prostate origin (9). Whether PAP production is one of the characteristics of islet cell tumors is of interest, since measuring serum PAP may be useful for the differential diagnosis. Early diagnosis of non-functioning pancreas tumors is very difficult even with CT, MRI and endoscopic ultrasonography (33). Localization of islet cell tumors by catheterization of the pancreatic vein or with radioiodinated analogues of somatostatin may not be applicable to all of the patients suspected of neuroendocrine tumors (34, 35). In contrast, measurement of serum PAP is a routine clinical test which can be applicable to...
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Table 1. Neuroendocrine Tumors Producing Prostatic Acid Phosphatase (PAP)

<table>
<thead>
<tr>
<th>Neuroendocrine tumor</th>
<th>PAP-positive/total (%)</th>
<th>References</th>
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<tbody>
<tr>
<td>Foregut Pancreas</td>
<td>1/1 (100%)</td>
<td>Mick 1972 (13)</td>
</tr>
<tr>
<td>Islet cell tumor 1)</td>
<td>1/1 (100%)</td>
<td>Choe 1978 (14)</td>
</tr>
<tr>
<td>Islet cell tumor 2)</td>
<td>6/10 (60%)</td>
<td>Jöbsis 1981 (12)</td>
</tr>
<tr>
<td>Insuloma</td>
<td>0/3 (0%)</td>
<td>Fishleder 1981 (28)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1/13 (8%)</td>
<td>Sobin 1986 (9)</td>
</tr>
<tr>
<td>Non-endocrine apudoma</td>
<td>NS2/6 (?)</td>
<td>Andreola 1990 (3)</td>
</tr>
<tr>
<td>Midgut Liver</td>
<td>0/2 (0%)</td>
<td>Azumi 1991 (10)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1/10 (10%)</td>
<td>Jöbsis 1981 (12)</td>
</tr>
<tr>
<td>Colon</td>
<td>2/8 (25%)</td>
<td>Sobin 1986 (9)</td>
</tr>
<tr>
<td>Appendix</td>
<td>5/25 (19%)</td>
<td>Sobin 1986 (9)</td>
</tr>
<tr>
<td>Ovary</td>
<td>5/5 (100%)</td>
<td>Sidhu 1993 (29)</td>
</tr>
<tr>
<td>Hindgut Rectum</td>
<td>29/35 (82%)</td>
<td>Federspiel 1990 (30)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1/1 (100%)</td>
<td>Azumi 1984 (26)</td>
</tr>
<tr>
<td>Others Lung</td>
<td>0/16 (0%)</td>
<td>Azumi 1991 (10)</td>
</tr>
</tbody>
</table>

1) with liver metastasis, 2) not studied, 3)stromal carcinoid.

References

26) Azumi N, Shibuya H, Ishikura M. Primary prostatic carcinoid tumor with normal PSA may be characteristic of endocrine apudoma of the pancreas in addition to rectal and ovarian carcinoid tumors (26, 28, 30). Apparently, however, further studies are necessary to determine whether measuring serum PAP is useful for the differential diagnosis among neuroendocrine tumors of the liver and pancreas and islet cell tumors of the pancreas.

References
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