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CASE REPORT

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Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein

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Abstract A 56-year-old man was admitted to our hospital because of consciousness disturbance. Abdominal computed tomography revealed a large low-density tumor in the left lobe of the liver. He presented with marked leukocytosis and hypercalcemia with high levels of serum granulocyte-colony-stimulating factor (G-CSF) and parathyroid hormone-related protein (PTH-rP). A diagnosis of cholangiocellular carcinoma (CCC) of the liver was confirmed by histological examination of an autopsy specimen. The tumor cells showed positivity for both G-CSF and PTH-rP with immunohistochemical staining. These results suggest that the tumor was producing both G-CSF and PTH-rP. This paraneoplastic G-CSF and PTH-rP production caused by CCC is very rare. Such cases must be followed up carefully, since tumors associated with paraneoplastic syndrome progress rapidly, resulting in a poor prognosis.

Key words Granulocyte-colony-stimulating factor (G-CSF) · Parathyroid hormone-related protein (PTH-rP) · Cholangiocellular carcinoma (CCC) · Leukocytosis · Hypercalcemia · Immunohistochemistry

Introduction

Paraneoplastic syndrome is sometimes seen in advanced malignancies.[1,2] A genetic disorder on some genes causes a possible overproduction of some substances. A genetic disorder occurring on a gene which is associated with a physiologically important substance causes paraneoplastic syndrome. The frequencies of this syndrome are different in different cancers.

Cholangiocellular carcinoma (CCC) is well known as a malignancy which has a poor prognosis, but the tumor is rarely associated with paraneoplastic syndrome. However, granulocyte-colony-stimulating factor (G-CSF) was reported to be produced by tumor cells in many cases of CCC, suggesting that the tumor occasionally has a potential for paraneoplastic leukocytosis.[3]

We experienced a case of CCC presenting with both leukocytosis and hypercalemia. Because the present case of CCC accompanied by paraneoplastic syndrome is very rare, we report our immunohistochemical investigations of the production of both G-CSF and parathyroid hormone-related protein (PTH-rP) by the tumor.

Case report

A 56-year-old Japanese man was admitted to our hospital suffering from consciousness disturbance. The patient had a history of a laparoscopic cholecystectomy for cholecystolithiasis 3 years earlier. His height was 165 cm and his weight was 67 kg. His body temperature was 38.4°C and his blood pressure was 108/66 mmHg. Neither anemia nor icterus was observed in his conjunctiva. An abdominal tumor was palpable 5 cm into the epigastric region and felt elastic-hard. No paralysis or pathological reflex was recognized upon neurological examination.

Laboratory data showed an elevation of serum lactate dehydrogenese and biliary enzymes. Marked leukocytosis and an increased level of serum calcium were also observed. Serum levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were elevated to 1807 U/ml (normal, <37 U/ml) and 5.2 ng/ml (normal, <2.5 ng/ml), respectively, while serum alpha fetoprotein (AFP) was at a normal level (Table 1). Abdominal computed tomography (CT) revealed a large low-density tumor in the left lobe of the liver (Fig. 1).

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Table 1. Laboratory data on admission

WBC	74 300/μl	γ-GTP	99 IU/l
(granulocyte 95%)		Ca	10.4 mg/dl
RBC	345×10^4/μl	P	2.6 mg/dl
Hb	10.1 g/dl	CRP	9.7 mg/dl
Plt	17.8×10^4/μl		
		AFP	2.1 ng/ml (normal <10)
T-protein	6.7 g/dl	CEA	5.2 ng/ml (normal <5)
Albumin	2.7 g/dl	CA19-9	1807 U/ml (normal <37)
T-bilirubin	1.1 mg/dl		
AST	34 IU/l	G-CSF	264 pg/ml (normal 5.8–27.5)
ALT	25 IU/l	PTH	<10 pg/ml
LDH	507 IU/l	PTH-rP	147 pmol/l (normal 13.8–55.3)
ALP	1041 IU/l	IL-6	63.6 pg/ml (normal <4.0)

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Plt, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; CRP, C-reactive protein; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; G-CSF, granulocyte-colony-stimulating factor; PTH, parathyroid hormone; PTH-rP, parathyroid hormone-related protein; Il-6, interleukin-6

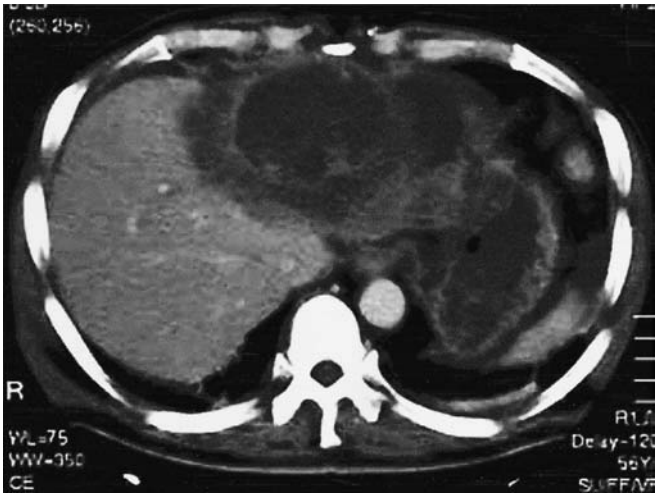

Fig. 1. Abdominal computed tomography shows a large low-density tumor in the left lobe of the liver

Because the corrected value of serum calcium was unexpectedly high at 11.7 mg/dl and no abnormality was found on head magnetic resonance imaging (MRI), we suspected that hypercalcemia had caused his consciousness disturbance, and that the leukocytosis and hypercalcemia were paraneoplastic phenomena. Accordingly, we examined the serum levels of G-CSF and PTH-rP and confirmed that both were significantly high at 264 pg/ml (normal 5.8–27.5 pg/ml) and 147 pmol/l (normal 13.8–55.3 pmol/l), respectively (Table 1).

Elcatonin and pemidronate disodium were administered for the consciousness disturbance caused by hypercalcemia. After the treatment, the serum calcium level was reduced and the patient recovered from his consciousness disturbance. However, the tumor was growing, and the number of white blood cells increased to 118 000/μl. The patient died of abdominal bleeding due to rupture of the tumor 5 days after admission.

Histological examination of autopsy specimens showed a poorly differentiated carcinoma consisting of groups and sheets of small cells with very little cytoplasm. In some parts, the tumor cells formed glandular duct-like structures. All parts of the tumor cells were positive for cytokeratin (CK) 19, CK 20, and CA19-9, and negative for antihuman hepatocyte antigen (data not shown). Abundant granulocyte infiltration was also seen in the tumor sections (Fig. 2).

The present case was difficult to distinguish from metastatic liver cancer. However, several examinations detected no lesions in the pancreas, lung, stomach, colon, or brain. Therefore, we believe that the present case was compatible with CCC of the liver. The tumor cells were also positive for both G-CSF and PTH-rP in an immunohistochemical staining, suggesting that the tumor was producing both G-CSF and PTH-rP (Fig. 3).

Discussion

We have described a very rare case of CCC that produced both G-CSF and PTH-rP. In particular, this paraneoplastic syndrome is exceptionally rare in adenocarcinoma compared with its presence in squamous cell carcinoma. The production of both G-CSF and PTH-rP has been reported in some cancers, including lung cancer,[4] bladder cancer,[5–8] and esophageal cancer,[9] but only one case has previously been reported in a patient with CCC.[10] However, the histological findings of that case presented a squamous cell type of CCC.

G-CSF is thought to be an autocrine growth factor. G-CSF produced by tumor cells acts on the tumor, resulting in an up-regulation of tumor progression.[11–13] Therefore, paraneoplastic G-CSF-producing cancer generally has a poor prognosis. In G-CSF-producing tumors, granulocytes are often seen within the tumor section. Sasaki et al.[3] reported that expressions of G-CSF and granulocyte macrophage colony-stimulating factor (GM-CSF) are responsible for granulocyte infiltration in CCC. Because the liver is one of the major hematopoietic organs in the fetal devel-

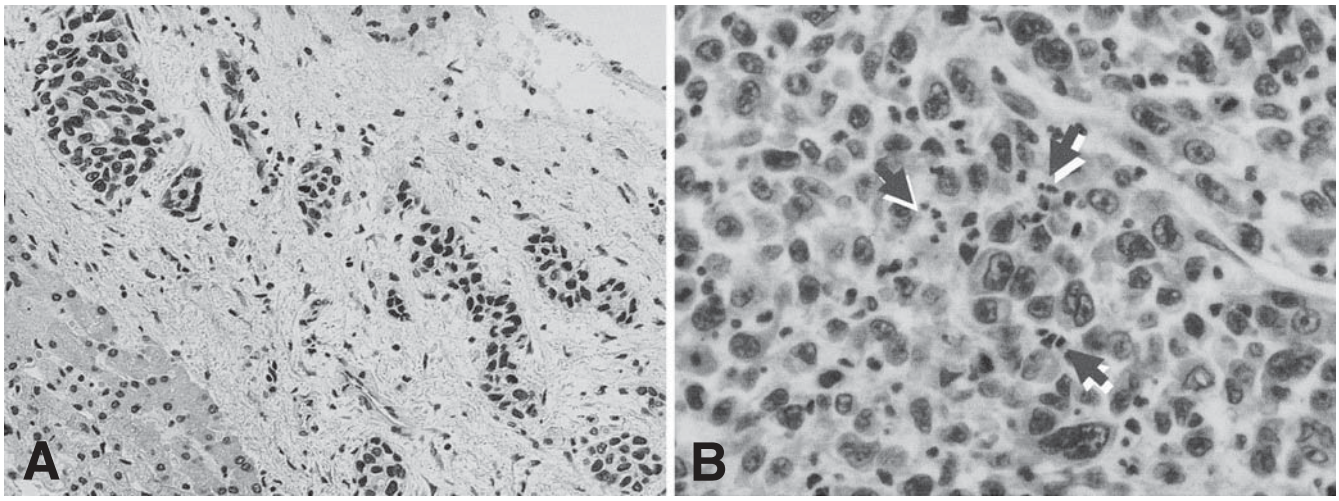

Fig. 2. **A** Histological examination of autopsy specimens showed that tumor cells in some parts formed glandular duct-like structures. This suggests that the tumor is compatible with a cholangiocellular carcinoma (×100). **B** This section shows a poorly differentiated carcinoma consisting of groups and sheets of small cells with very little cytoplasm. Abundant granulocyte infiltration (*arrows*) was also seen in the tumor section (×200)

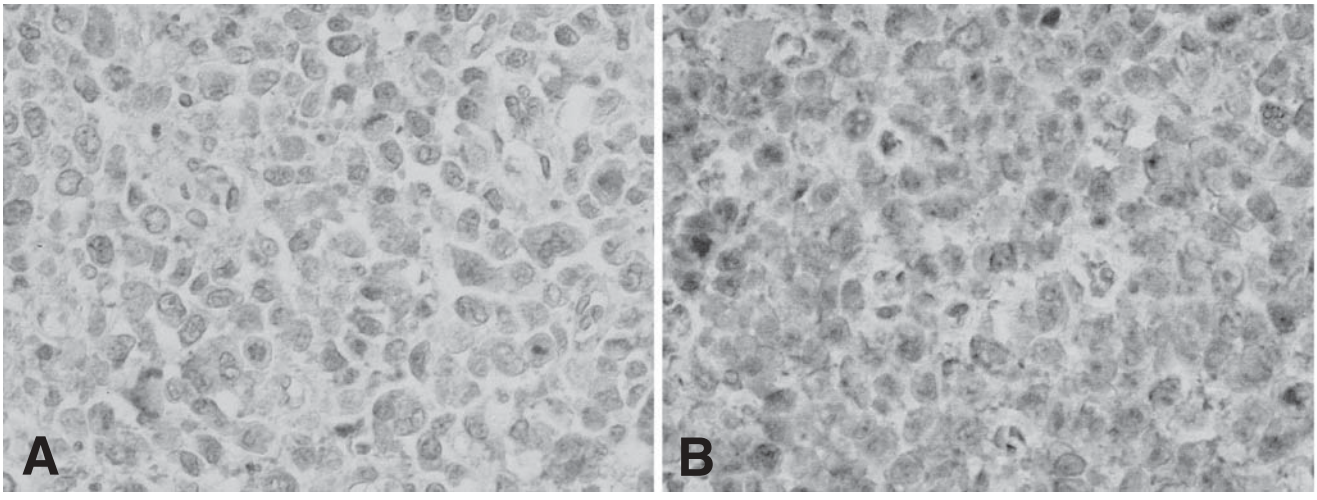

Fig. 3. The tumor cells were positive for both (**A**) G-CSF and (**B**) PTH-rP immunohistochemical staining

opmental stage, the expression of G-CSF may reflect cancer cells with hematopoietic features. This phenomenon would seem to suggest that G-CSF does not act only in the bone marrow, but the exact mechanism has not been fully elucidated. On the other hand, PTH-rP is not associated with tumor growth. However, hypercalcemia due to an overproduction of PTH-rP causes consciousness disturbance, leading to a poor prognosis.

Recent studies have shown that G-CSF and PTH-rP are responsible for paraneoplastic syndromes with leukocytosis and hypercalcemia, but the mechanisms of production of these factors by tumors have not been elucidated. PTH-rP has been reported to be associated with an induction of interleukin 6 (IL-6), which is one of the inflammatory cytokines.[14,15] Moreover, some inflammatory cytokines, including IL-6, have also been reported to be associated with G-CSF production by tumors.[16,17] These studies suggest an association between the production of PTH-rP and G-CSF via these inflammatory cytokines. The case reported here presented an increasing inflammatory reaction, with a continued high fever and a high serum level of C-reactive protein. Furthermore, the serum IL-6 level of the patient was extremely high at 63.6 pg/ml (normal <4.0 pg/ml) (see Table 1).

We have reported a case of CCC with a rare paraneoplastic syndrome. This is the first report of an adenocarcinomatous type of CCC with the production of both G-CSF and PTH-rP. The rapid institution of antihypercalcemic treatment using bisphosphonates is essential in preventing life-threatening deterioration such as

consciousness disturbance, and careful observation is paramount in such cases because the tumor progresses rapidly, resulting in a very poor prognosis.

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