Elevated Serum Interleukin-6 Levels in Patients with Pancreatic Cancer

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The vast majority of pancreatic cancer patients have advanced disease at the time of diagnosis and they eventually become so emaciated that death primarily occurs from cancer cachexia. Cancer cachexia may be mediated by certain cytokines such as interleukin-6. In this study, we measured serum interleukin-6 levels in 55 patients with histologically proven pancreatic cancer and investigated their relationships to the clinical status of pancreatic cancer. A control population of 20 normal healthy adults and 25 chronic pancreatitis patients with comparable gender and age distribution characteristics was also studied. Serum interleukin-6 levels were measured using a quantitative sandwich enzyme-linked immunosorbent assay. Thirty pancreatic cancer patients (54.5%) had detectable levels, although interleukin-6 levels were detectable in only one healthy control and in two chronic pancreatitis patients. The specificity of serum interleukin-6 in this population was 93.3%, resulting in high diagnostic accuracy (72.0%). Among the pancreatic cancer patients, the detection rates of serum interleukin-6 levels increased significantly with the disease extent (p < 0.01). Moreover, a significant difference was also found in the detection rates between the 30 pancreatic cancer patients with body weight loss (76.7%) and the remaining 25 patients without weight loss (28.0%, p < 0.01). These results may provide new insight into both diagnosis and treatment of pancreatic cancer, because the diagnostic accuracy of serum interleukin-6 was high and because anti-interleukin-6 therapeutics could improve symptoms in pancreatic cancer patients with high interleukin-6 levels.

Key words: interleukin-6 – pancreatic cancer – cachexia

INTRODUCTION

Pancreatic cancer (PC) has the poorest prognosis of any form of cancer (1,2). Only surgical resection of the primary tumor provides any possibility of cure. However, this is rarely achieved in practice because it is not easy to diagnose asymptomatic patients with resectable tumors. In fact, at the time of diagnosis, most PC patients have advanced disease and have several symptoms such as severe pain and weight loss (2). With progression of the disease, they eventually become so emaciated that death primarily occurs from cancer cachexia.

Cancer cachexia is a syndrome of progressive wasting that, it has been suggested, is mediated by certain cytokines such as tumor necrosis factor, leukemia-inhibitory factor, interferon-γ and interleukin-6 (IL-6) (3–6). IL-6 is produced by a variety of cell types including tumor cells, and elevated levels have been reported in patients with several kinds of malignant disease such as lung cancer, renal cell carcinoma and ovarian cancer (7–12). To date, however, serum IL-6 levels in PC patients have not been fully investigated. In this study, we measured serum IL-6 levels in PC patients and investigated their relationships with the clinical status of PC.

SUBJECTS AND METHODS

Fifty-five patients (male:female ratio 38:17, age 61.2 ± 7.3 years) with histologically proven PC, who had not previously received any anti-tumor treatment, were studied. Each patient underwent staging in accordance with the TNM classification of the Union International Contra Cancrum (UICC) criteria. A control
population of 20 normal healthy adults and 25 chronic pancreatitis (CP) patients, with comparable gender (male:female ratios 14:6 and 17:8 respectively) and age (60.2 ± 6.5 and 61.6 ± 6.8 years respectively) distribution characteristics, was also studied. In the CP patients, serum and urine amylase were almost twice the normal maximum value at the time of examination (13). None of the patients was pyrexial, showed clinical evidence of infection or inflammation, or was jaundiced.

All serum samples were obtained at the time of diagnosis, stored at -70°C and assayed simultaneously. Serum IL-6 levels were measured using a quantitative sandwich enzyme-linked immunosorbent assay according to the kit procedure (R & D Systems, Minneapolis, MN). The limit of detection of the assay was 3 pg/ml and lower levels were considered undetectable. The assay was performed by one of the authors (N.K.) unfamiliar with the clinical status of the patients. The chi2 test was used to analyze the results. All p values were two-sided and p < 0.05 was considered significant.

RESULTS

The serum levels of IL-6 in healthy controls, CP patients and PC patients are shown in Fig. 1. Thirty of 55 PC patients (54.5%) had detectable levels, one patient showing an IL-6 level as high as 156 pg/ml. In contrast, IL-6 levels were detectable in only one of 20 healthy controls (5.0%) and in two of 25 CP patients (8.0%). There was a significant difference in detection rates of IL-6 between PC patients and the latter two control groups (p < 0.01). The specificity of serum IL-6 in this population was 93.3% (42/45), resulting in high diagnostic accuracy (72.0%; 72/100). A highly significant correlation between IL-6 and C-reactive protein (CRP) levels was observed (r = 0.66, p < 0.01).

Among the PC patients, the detection rates of serum IL-6 levels increased significantly with the extent of the disease (p < 0.01): the detection rates in patients with tumors of Stage II, Stage III and Stage IV (metastatic disease) were 0.0% (0/5), 35.3% (6/17) and 72.7% (24/33) respectively (Fig. 2). Regarding the histological type of PC, most PCs (92.7%; 51/55) were tubular adenocarcinoma and the remaining four were: two papillary adenocarcinoma, one adenosquamous carcinoma and one mucinous carcinoma. The four patients with PC other than tubular adenocarcinoma did not have detectable IL-6 levels although IL-6 levels were detectable in 30 (58.8%) of 51 patients with tubular adenocarcinoma.

Regarding body weight loss (WL), a significant difference was found in the detection rates between the 30 PC patients with WL (≥ 7% of total body weight less than 6 months prior to the diagnosis) and the remaining 25 patients without WL (p < 0.01, Fig. 3). Serum IL-6 was detectable in 23 (76.7%) of the former group, whereas only 7 (28.0%) of the latter group showed detectable serum IL-6.

DISCUSSION

Pancreatic cancer is one of the deadliest cancers (1,2). Because of the high mortality associated with this neoplasm, it is the fifth most common cause of cancer death in Japan. In PC patients, cancer cachexia has been listed as a major cause of death although the mechanisms that underlie this complex syndrome are not completely understood (2). However, it has recently been suggested that certain cytokines such as IL-6 play an important role in cancer cachexia (6).

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**Figure 1.** Serum IL-6 levels in healthy controls (H), patients with chronic pancreatitis (CP) and patients with pancreatic cancer (PC). The limit of detection of the assay (3 pg/ml) is indicated by the dotted line.

**Figure 2.** Relationship of serum IL-6 levels with the disease extent in patients with pancreatic cancer. The limit of detection of the assay (3 pg/ml) is indicated by the dotted line.
IL-6 is a multipotent cytokine exerting numerous biological activities and its serum levels are elevated in several kinds of malignant diseases such as lung cancer, renal cell carcinoma and ovarian cancer (7–12). Recent studies on IL-6 have revealed its biological roles in the pathogenesis and progression of neoplasms; IL-6 can act as an autocrine and/or paracrine growth factor (14,15), and it may promote tumor metastasis and invasiveness (9,12,16). Additionally, IL-6 could be implicated in some clinical manifestations such as body weight loss and fever in cancer patients (10). However, anti-IL-6 or anti-IL-6 receptor antibodies could be useful in treating patients with IL-6-producing tumors (15,17,18).

In the present study, the detection rate of IL-6 in PC patients (54.5%) was significantly higher than for healthy controls or CP patients. It is not yet clear whether the increased serum IL-6 levels in PC patients were produced by the cancer cells, because there is a possibility of IL-6 production from the tumor-associated host cells such as fibroblasts and macrophages (19–21). This point requires further confirmation using in situ hybridization and immunostaining with anti-IL-6 antibodies.

IL-6 induces the production of acute phase proteins, including CRP, by liver cells (22). It has been reported that serum CRP concentrations are correlated with serum IL-6 levels in several kinds of solid tumors such as renal cell carcinoma and lung cancer (9,11). In the current study, this close relation is also demonstrated. Recently, an increase in serum IL-6 levels has been reported in those patients with acute severe pancreatitis (13,23). However, most of our CP patients did not have detectable IL-6 levels, although, in this study, we included only CP patients who did not show marked elevation of serum and urine amylase.

In this study, we revealed a close relationship between detectable serum IL-6 levels and clinical status in a substantial proportion of PC patients. Excessive amounts of IL-6 in serum may play various roles in tumor progression, including metastasis and clinical manifestations such as weight loss, although further investigation is needed to prove that increased serum IL-6 levels are directly responsible for such clinical status (6,10,16).

Additional studies are warranted to establish whether IL-6, either alone or in concert with other cytokines, is involved in the pathophysiology of PC. However, our data may provide new insight into both diagnosis and treatment of PC, because the diagnostic accuracy of serum IL-6 was high and because anti-IL-6 therapeutics could serve as a useful tool for improving symptoms in PC patients with high IL-6 levels (15,17,18).

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References


