Patients with Type 2 Diabetes Mellitus Accompanied by Elevated Serum CA19-9 Associated Not with Pancreatic Cancer but Interstitial Lung Disease

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Abstract

Introduction: CA19-9 is the most reliable tumor marker for pancreatic cancer, with \textasciitilde70–90\% sensitivity, 90\% specificity, 69\% positive predictive value, and 90\% negative predictive value. However, increased CA19-9 levels have been observed in benign conditions, pancreatitis, pulmonary disease, smoking, and hepatobiliary system disease. Numerous studies have reported that circulating CA19-9 levels are elevated during hyperglycemia in diabetes mellitus (DM) and have been associated with hemoglobin A1c (HbA1c). However, the precise mechanism behind increased serum CA19-9 levels in diabetes remains still unclear. Here, we report a case of type 2 DM (T2DM) accompanied by elevated serum CA19-9 levels due to not pancreatic cancer but interstitial pneumonitis. Case Report: The patient, a 73-year-old Japanese woman, was taking metformin (1,500 mg/day), repaglinide (1.5 mg/day), and sitagliptin (50 mg/day). Over the past year, she also took atorvastatin (5 mg/day) and azilsartan (40 mg/day). The patient had been followed up for systemic scleroderma (with low-dose steroid therapy) and mild interstitial lung disease (ILD) (without treatment) for a number of years at a different hospital. The patient’s peripheral blood laboratory findings were normal range. Her HbA1c level fluctuated between 7.0\% and 8.0\% in the past 6 months. Her CA19-9 level was fluctuated between 562.7 and 823.2 U/mL (normal \textless37), and her KL-6 level was fluctuated between 516 and 557 U/L (normal \textless500) in the past 6 months. Due to the marked increase in the CA19-9 level, an extensive screening examination was performed for malignancy, including abdominal ultrasound scan, computed tomography (CT), and magnetic resonance cholangiopancreatography, revealing no malignancy. We observed bilateral pulmonary lesions (bottom of lungs) and ground-glass opacity on the chest CT. The pancreatic monoclonal antigen type 2 (DU-PAN-2) level was \textless25 U/mL. Conclusions: In our case, CA19-9 levels were increased in association not with pancreatic cancer but with ILD. Thus, when T2DM is accompanied by elevated serum CA19-9 levels, attention needs to be paid not only to the presence of pancreatic cancer but also to the possible ILD. Especially, when diabetes and ILD are treated in different hospitals, diabetologists need to pay attention about the presence of hidden ILD besides DM.

Keywords

CA19-9 · Interstitial lung disease · Pancreatic cancer · Type 2 diabetes mellitus
Introduction

It is suggested there is a strong association between diabetes mellitus (DM) and pancreas cancer [1]. Tumor markers are clinically employed for cancer screening and monitoring. CA19-9 is the most reliable tumor marker for pancreatic cancer, with 70–90% sensitivity, 90% specificity, 69% positive predictive value, and 90% negative predictive value [1–7]. However, increased CA19-9 levels have been observed in benign conditions, pancreatitis [8], pulmonary disease [9], smoking [10], and hepatobiliary system disease [11–13]. Numerous studies have reported that circulating CA19-9 levels are elevated during hyperglycemia in DM [12–19] and have been associated with hemoglobin A1c and fasting blood plasma levels, with CA19-9 levels decreasing after improved glycemic control [16, 20]. Prolonged half-life of serum CA19-9 may contribute to the increase in serum CA19-9 levels in diabetic patients without obvious cancer [21]. However, precise mechanism behind increased serum CA19-9 levels in diabetes remains still unclear. Here, we report a case of type 2 DM (T2DM) accompanied by elevated serum CA19-9 levels due to not pancreatic cancer but interstitial pneumonitis.

Case Report

The patient, a 73-year-old Japanese woman, was taking metformin (1,500 mg/day), repaglinide (1.5 mg/day), and sitagliptin (50 mg/day). Over the past year, she also took atorvastatin (5 mg/day) and azilsartan (40 mg/day). The patient had no history of smoking and had been followed up for systemic scleroderma (with low-dose steroid therapy) and mild interstitial lung disease (ILD) (without treatment) for a number of years at a different hospital. A physical examination revealed bibasilar end inspiratory crackles.

After the attending doctor was changed to the first author this April, CA19-9 levels were measured as clinical screening for pancreatic cancer. Also, Krebs von den Lungen-6 (KL-6) levels were measured because sitagliptin was reported to cause ILD [22]. Her CA19-9 level was 562.7 U/mL (normal <37) on July 1, 2021, 823.2 U/mL on July 29, 815 U/mL on September 30, 805 U/mL on October 28, and 819.2 U/mL on November 25, respectively (Table 3). Her KL-6 level was 543 U/L (normal <500) on April 6, 501 U/L on September 30, 557 U/L on October 28, and 516 U/L on November 25, respectively (Table 3). Therefore, sitagliptin was terminated due to high level of KL-6 on April 6. However, we did not see improvement of KL-6 levels after cessation of sitagliptin suggesting that sitagliptin had nothing to do with KL-6 elevation in this patient.

Due to the marked increase in the CA19-9 level, an extensive screening examination was performed for malignancy, including abdominal ultrasound scan (July 8), abdominal computed tomography (CT) (August 7), and magnetic resonance cholangiopancreatography (August 5). Those examinations were not diagnosed with any malignancy by a diagnostic radiologist. We observed bilateral pulmonary lesions (bottom of lungs) and ground-glass opacity on the chest CT (Fig. 1). Those findings of the chest CT have not changed in the last 6 months.

Table 1. Patient’s peripheral blood laboratory findings

| Inspection items                          | Measurement value | Normal range |
|-------------------------------------------|-------------------|--------------|
| Red blood cell count                      | 431 × 10⁹/mm³     | 376–516      |
| White blood cell count                    | 11,050/mL         | 3,500–9,700  |
| Hematocrit                                | 38.8%             | 34.3–45.2    |
| Hemoglobin                                | 12.4 g/dL         | 11.2–15.2    |
| Total bilirubin                           | 0.4 mg/dL         | 0.3–1.2      |
| Aspartate aminotranserase                 | 18 U/L            | 10–40        |
| Alanine aminotransferase                  | 13 U/L            | 5–45         |
| Lactate dehydrogenase                     | 178 U/L           | 120–245      |
| Blood urea nitrogen                       | 12.2 mg/dL        | 8.0–20.0     |
| Creatinine                                | 0.68 mg/mL        | 0.46–0.82    |
| Serum sodium                              | 138 mEq/L         | 135–145      |
| Potassium                                 | 4.3 mEq/L         | 3.5–5.0      |
| Chloride                                  | 101 mEq/L         | 98–108       |
| Calcium                                   | 9.5 mg/dL         | 8.6–10.2     |
| Serum amylase                             | 113 U/L           | 39–134       |
| C-reactive protein                        | 0.06 mg/dL        | <0.30        |
| Anti-glutamic acid decarboxylase antibody | <5.0 U/mL         | <5.0         |

The patient’s peripheral blood laboratory findings were presented.
The pancreatic monoclonal antigen type 2 (DU-PAN-2) level on October 8 was <25 U/mL (normal ≤150). Those results are summarized in Table 3.

### Discussion

Patients with T2DM are at high risk for pancreatic cancer compared with individuals without T2DM [23]. An interesting and important point in this case report is the etiology of elevated CA19-9 levels. Although increased CA19-9 levels have been observed in a number of benign conditions, we confirmed that the patient was free from hypothyroidism, chronic kidney disease, pancreatitis, cigarette smoking, and hepatobiliary system disease. Her hemoglobin A1c level fluctuated between 7.0% and 8.0% in the past 6 months, and the fluctuation range was quite small.

CA19-9 is the most reliable tumor marker for pancreatic cancer, and Tanaka and colleagues [24] proposed that the cut-off value of CA19-9 should be 75 U/mL when screening patients with DM for pancreas cancer. Although CA19-9 values of our patient were consistently above 75 U/mL, we found no sign of pancreatic cancer after inspecting the abdominal ultrasound scan, CT, and magnetic resonance cholangiopancreatography. Although it was difficult to ensure that she did not have pancreatic cancer, the possibility of the disease in this patient was quite low, a judgment supported by the undetectable DU-PAN-2 level.

If this is the case, how can we explain the etiology of the elevated CA19-9 levels? CA19-9 sometimes increases in ILD, especially in advanced stages [25], and is produced in bronchial glands [26]. Our patient’s recent CA19-9 level generally continued to be flat, which was consistent with the leveling-off trend for KL-6 levels that is supposed to reflect ILD activity in the patient. In our case, CA19-9 levels were increased in association not with pancreatic cancer but with ILD.

Thus, when T2DM is accompanied by elevated serum CA19-9 levels, attention needs to be paid not only to the presence of pancreatic cancer but also to the possible ILD. Especially, when diabetes and ILD are treated in different hospitals like this patient, diabetologists need to pay attention about the presence of hidden ILD besides DM.

#### Table 2. Casual plasma glucose and glycated hemoglobin levels

| Date         | Casual plasma glucose, mg/dL | Glycated hemoglobin, % |
|--------------|------------------------------|------------------------|
| April 6, 2021| 173                          | 7                      |
| May 6        | 178                          | 7.2                    |
| June 3       | 166                          | 7.6                    |
| July 1       | 122                          | 7.6                    |
| July 29      | 199                          | 8                      |
| September 30 | 172                          | 7.5                    |
| October 28   | 117                          | 7.8                    |
| November 25  | 203                          | 7.3                    |

Casual blood glucose and glycated hemoglobin levels between April 6, 2021, and November 25, 2021, were summarized.

#### Table 3. CA19-9, KL-6, and DU-PAN-2 levels

| Date            | CA19-9, U/mL | KL-6, U/L | DU-PAN-2, U/mL |
|-----------------|--------------|-----------|----------------|
| April 6, 2021   | 543          |           |                |
| July 1          | 562.7        |           |                |
| July 29         | 823.2        |           |                |
| September 30    | 815          | 501       | <25            |
| October 8       | 805          | 557       |                |
| October 28      | 819.2        | 516       |                |
| November 25     |              |           |                |

CA19-9, KL-6, and DU-PAN-2 levels between April 6 and November 25 were summarized.

Fig. 1. Chest CT scan (August 7) of the patient. The ground-glass opacities were recognized as bilateral pulmonary lesions at the bottom of the lungs. Those findings have not changed in the last 6 months.
Statement of Ethics

The research complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki. This case report was reviewed and approved by the review board of Hidaka Hospital and conducted following the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest Statement

None of the authors have any potential conflicts of interest associated with this case presentation.

Funding Sources

No funding received.

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Author Contributions

K.K. and S.O. cared for the patient. K.K., J.O., E.Y., K.O. (Okada), K.O. (Ohshima), and S.O. attended the clinical conferences on this patient and made important suggestions for the differential diagnosis and therapeutic strategy. J.O. and S.O. revised the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the confidentiality of the participants; for example, they contain information that could compromise the privacy of research participants, but are available from the corresponding author upon reasonable request.