Peritoneal malignant mesothelioma with epithelioid type, demonstrating high serum and ascitic KL-6 levels: immunohistochemical analyses

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Abstract

We report a case of KL-6 producing peritoneal malignant mesothelioma. A 56-year-old woman was referred to our hospital on November 2005 with severe abdominal distention. Peritoneal malignant mesothelioma with epithelioid type was diagnosed by clinical symptoms, laboratory investigations, imaging studies, and immunohistochemical examination of known tumor markers. In addition, high serum and ascitic KL-6 levels were observed and the immunostaining of the tumor for KL-6 was evident. We thus consider KL-6 to be a potential novel marker for peritoneal malignant mesothelioma with epithelioid type.

Introduction

Malignant mesothelioma is an aggressive neoplasm of serosal surfaces, i.e., pleura (65-70%), peritoneum (30%), tunica vaginalis testes, and pericardium (1-2%).1 Peritoneal malignant mesothelioma is clearly confined to the peritoneal cavity lined by visceral and parietal peritoneum. The risk of peritoneal mesothelioma increases with age and always without known exposure to asbestos. She had no history of pain, abdominal mass, significant weight loss, dyspnea, cough, chest pain, or constitutional symptoms. In addition, she had no other relevant past medical and surgical history or no significant drug history. Her travel, family and social histories were unremarkable.

On presentation, she was non-anemic, non-icteric, her blood pressure was 139/84 mmHg, heart rate 87 beats/min and temperature 36.8°C. Peripheral lymph nodes were not palpable. The physical examination revealed that she abdomen was soft and non-tender but much distended. No masses were palpable, but massive ascites was pointed out. Laboratory analysis revealed thrombocytopenia, hypoalbuminemia and elevated C-reactive protein. The white blood cell count, erythrocyte count, renal function tests and level of serum electrolytes were normal. Liver function test yielded elevated level of ALP (292 IU/L) and LDH (159 IU/L). However, AST, ALT, γ-GTP, AMY levels were normal. Serum total cholesterol and triglycerides were also normal. The level of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen19-9 (CA19-9), carbohydrate antigen125 (CA125), and CYFRA in serum were found to be within normal limit. Serum KL-6 was examined for early detection of interstitial pneumonia which might be a potential adverse effect of chemotherapy. It was unexpectedly elevated at 9000 IU/mL (normal up to 500 IU/mL). CT scans revealed thickened greater omentum with massive ascites (Figure 1A) but no lung tumor or interstitial pneumonia. PDG-PET scan demonstrated positivity in the peritoneum (Figure 1B) and negativity in the ovary. Diagnostic paracentesis yielded yellow exudative fluid (Protein 5.2 g/dL, 1.036 specific gravity (normal up to 1.016) and showed 3610 total cells with predominance of mononuclear cells. CA125 and KL-6 in ascites fluid was 86 U/L and 7500 U/mL, respectively. The level of hyaluronic acid in serum and peritoneal fluid was at 60 ng/mL and 11,900 ng/mL, respectively. Cytological examination suggested the possibility of peritoneal mesothelioma, but it was insufficient for the diagnosis. Diagnostic laparoscopy along with peritoneal biopsy was performed to obtain histopathological and immunohistochemical analysis for establishing the definitive diagnosis. Laparoscopy showed multiple yellowish small nodular lesions of the peritoneal surface and the thickened greater omentum. Hematoxylin and Eosin (H&E) stain at low magnification revealed sheet like epithelioid tumor cells with mononuclear and bland in appearance (Figure 2A) and higher magnification showed oval shaped mesothelioma cells, with indistinct border, moderate cytoplasm, and prominent nuclei with inconspicuous nucleoli (Figure 2B). Microscopic features were consistent with peritoneal mesothelioma with epithelioid type. In addition, immunohistochemical stains were performed with the avidin-biotin peroxidase complex (ABC) method (LSAB kit; Dako, Carpinteria, CA) using antibodies against AE1/AE3, cytokeratin 5/6 (CK5/6), epithelial

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Asbestos is the major carcinogen associated with malignant mesothelioma. However, half of the patients with malignant mesothelioma of the peritoneum have not exposed to asbestos, as in this case. Despite recent progress of multidisciplinary therapy including surgery, chemotherapy, radiotherapy, and gene therapy, the median survival is 10 months and relative 5-year survival is 16%. The important differential diagnosis of malignant mesothelioma of the peritoneum includes serous carcinoma of the peritoneum and metastatic serous carcinomas of the ovary. Immunohistochemical panels are important to establish the differential diagnosis. Malignant mesothelioma is characterized by the presence of positive staining for calretinine, EMA, CK5/6, WT1, D2-40, mesothelin and the absence of staining for CEA, CA19-9, Ber-EP4, MOC-31, or TTF-1. To the best of our knowledge, this is the first case report of KL-6 producing peritoneal malignant mesothelioma. KL-6 has been the established serum and immunohistochemical marker for diagnosing interstitial lung diseases and is widely applied to clinical practice. In addition, immunohistochemical assessment of KL-6 has been increasingly applied to diagnose various types of neoplasms, including gastrointestinal, hepatic, pancreatic, and ovarian cancers. Especially, it has been an excellent immunohistochemical biomarker in association with a micropapillary pattern in breast, urinary bladder, and gastric carcinomas and it stains linearly along the surface of the cancer cells without staining of the cytoplasm, manifesting inside out pattern.

In our case, there was distinct surface positivity with fuzzy and fluffy pattern for KL-6 of the mesothelioma cells. Several ultrastructural studies have shown that the mesothelioma cells exhibited long, occasionally branching surface microvilli. This finding has been considered as the most remarkable and reliable morphological feature of malignant mesothelioma cells. Although we did not perform electron microscopic studies of mesothelioma cells, there may be a possibility that fuzzy and fluffy surface staining for KL-6 may indicate the surface microvilli. A recent study has identified serum soluble mesothelin-related protein (SMR) could be a useful marker for malignant mesothelioma. Fukuda et al. improved its diagnostic performance by combing serum SMR and CEA. Our present study has shown that serum KL-6 can be regarded as a potential tumor marker in peritoneal malignant mesothelioma with epithelioid type. Serum KL-6 levels should be evaluated in screening for malignant mesothelioma among those who had been exposed to asbestos in future studies. As for KL-6 as a serum tumor marker, it has been useful in diagnosing several types of cancers. Kohno et al. have first reported its usefulness in diagnosing lung adenocarcinoma, pancreatic cancer, and breast cancer. They also emphasized that its elevation correlated with tumor progression. A recent large scale case-control study has further confirmed that serum KL-6 is associated with subsequent lung cancer among patients with interstitial lung disease. Recent studies have strengthened its diagnostic value in breast cancer and hepatocellular carcinoma. Although further work is needed, our findings support a potential role of serum, ascitic, and immunohistochemical evaluation with KL-6 for tumor etiology and early diagnosis in peritoneal malignant mesothelioma. Therefore, the utility of KL-6 for monitoring tumor progression should be established by studying more accumulated cases in future.

Conclusions

In summary, we are the first to describe the serum examination and immunohistochemi-
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