CASE REPORT

Mediastinal Seminoma in a Patient with Multiple Endocrine Neoplasia Type 1

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Abstract

A patient with multiple endocrine neoplasia type 1 (MEN1) developed a mediastinal seminoma. The patient was a 46-year-old man who presented with respiratory symptoms. A diagnosis of mediastinal seminoma was pathologically confirmed and a complete remission was achieved by chemotherapy. During his hospital stay, hyperparathyroidism and multiple pancreatic tumors associated with hypergastrinemia were found. A diagnosis of MEN1 was made genetically. Although patients with MEN1 manifest a variety of neoplastic disorders, no cases of concurrent seminoma and MEN1 have previously been reported. In addition, no etiological relationship between seminoma and MEN1 has yet been reported.

Key words: mediastinal tumor, germ cell tumor, gastrinoma, Zollinger-Ellison syndrome, hyperparathyroidism, MEN1 gene

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome characterized by a predisposition to hyperplastic and neoplastic disorders arising predominantly from endocrine organs such as the parathyroid, anterior pituitary and endocrine pancreas (1). Most subjects with MEN1 harbor a germline mutation in the MEN1 gene, which encodes a 610 amino-acid nuclear protein menin. Less frequent manifestations of MEN1 include adrenal cortex adenoma, foregut carcinoid tumor and cutaneous tumors such as facial angiofibromas and lipomas (2). Germ cell tumors occur most commonly in the gonads, but infrequently appear in other locations such as the mediastinum, retroperitoneum, pineal gland and sacral area and 2-5% of the germ cell tumors are of extragonadal origin (3). Mediastinal seminoma is a relatively rare neoplasm primarily affecting men in their third decade of life, although they can also occur in younger or older individuals. The incidence of mediastinal seminoma has been estimated to be a quarter of that of primary mediastinal germ cell tumors (4, 5). Although patients with MEN1 manifest a variety of neoplastic disorders, the concomitance of seminoma with MEN1 has not yet been previously reported.

This report describes a patient with MEN1 who developed a mediastinal seminoma. The diagnosis of MEN1 was made incidentally during the diagnosis and treatment of the seminoma.

Case Report

The patient was a 46-year-old Japanese man. He had a history of nephrolithiasis and a recurrent duodenal ulcer beginning at 36 and 40 years of age, respectively. His father had died of Zollinger-Ellison syndrome at the age of 36.

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Figure 1. Transcutaneous biopsy specimens obtained from the mediastinal tumor indicated two cell types, including placental alkaline phosphatase-positive seminoma cells and lymphocytic infiltration. (a) Hematoxylin and Eosin staining 100×, (b) stained with placental alkaline phosphatase monoclonal antibody 100×, (c) stained with chromogranin A monoclonal antibody 100×.

Neoplastic lesions were found in parathyroid, pancreas, adrenal gland, and anterior pituitary during his father's autopsy.

In 2006, the patient visited another hospital because of hemosputum and a low grade fever. Enhanced contrast chest CT revealed a 95×75×145 mm large heterogeneous irregular mass encompassing the pulmonary artery and the ascending aorta, narrowing the superior vena cava, radiologically consistent with an anterior mediastinal tumor. In addition, CT imaging incidentally detected multiple pancreas tumors. An ultrasound-guided transthoracic biopsy of the mediastinal tumor was performed and a pathological examination revealed extensive infiltration by large cell with clear cytoplasm, a hypodense nucleus and a few atypical mitoses consistent with a typical seminoma cell. Tumor nests were outlined by fibrous bands infiltrated by lymphocytes. Immunostaining for placental alkaline phosphatase, a specific marker for seminoma cells, was positive, while chromogranin A was negative (Fig. 1). The patient was referred to Shinshu University Hospital in July 2006.

A physical examination showed the patient to be 173 cm tall and he weighed 51 kg. There was a prominent distension of the bilateral cervical veins. Following the pathological diagnosis of extragonadal seminoma, chemotherapy with bleomycin, etoposide and cisplatin was initiated in August 2006. A complete remission was achieved after repeating 3 series of the regimen, as shown in Fig. 2 (horizontal and coronal section CT, before and after chemotherapy).

Biochemical and endocrine examinations were performed during the patients hospital stay. The results are summarized in Table 1. The patient had mild hypergastrinemia and hypercalcemia and was suspected of having MEN1. Subsequent genetic testing revealed a heterozygous 9-base pair deletion in exon 3 of the MEN1 gene (p.R171_V173del), which is a disease-causing mutation (6). Diagnosis of MEN1 was thus genetically confirmed. However, the loss of heterozygosity (LOH) in MEN 1 could not be confirmed based on investigations using the transthoracic biopsy materials of mediastinal seminoma due to an insufficient amount of DNA contained in these materials.

Chemotherapy had no effect on the size of the pancreatic tumors. A distal pancreatectomy and pancreaticoduodenectomy was performed in December 2006. The pathological examination of the resected tumors showed them to be well-differentiated endocrine carcinoma. The serum level of gastrin was reduced from 6,600-7,000 pg/mL to 15-38 pg/mL after the surgery.

A total parathyroidectomy with autotransplantation was also performed in May 2007. The pathological diagnosis was parathyroid hyperplasia and surgery was performed in order to lower the levels of parathyroid hormone and bring the serum calcium levels to within the normal range.

Discussion

This report documents a patient with a mediastinal seminoma who was diagnosed to have MEN1 during the examination. There have been no case reports of coincident of
Figure 2. Enhanced contrast chest CT revealed a mass encompassing the aortic arch and the pulmonary artery, radiologically consistent with a mediastinal tumor (arrows a, b). A complete remission was achieved after chemotherapy (arrows c, d). a, c: horizontal section, b, d: coronal section.

Seminoma and MEN1. Hyperparathyroidism-jaw tumor syndrome, another type of familial hyperparathyroidism, has been shown to exhibit seminoma (7). This fact suggests an underlying pathophysiological relationship between MEN1 and seminoma. In this case, the molecular background of the tumor development and its etiological relationship to MEN1 remained unknown since no genetic analysis of the seminoma was performed.

Germ cell tumors are classified as teratomas (mature, immature), seminomas, yolk sac tumors, embryonal carcinomas, choriocarcinomas, and combined germ cell tumors (8). Extragonadal seminomas are thought to be derived from aberrant primordial germ cells and account for 2-5% of adult germ cell malignant tumors (9). About half of man extragonadal seminomas develop in the mediastinum. An international analysis of extragonadal germ cell tumors showed that 83% were nonseminomatous and 16% seminomatous germ cell tumors (10, 11). There have been a number of studies on the molecular background of seminomas (12-14). Although somatic mutations of various genes and chromosome aberrations have been reported, the molecular mechanisms behind those alterations that lead to the development of seminomas remain largely unknown.

From the clinical aspect, the present case illustrated the importance of early diagnosis of MEN1. Although the patient had a clear family history of MEN1, that information was not utilized in the early recognition of the manifestation of the patient. The patient’s father had died of Zollinger-Ellison syndrome, and approximately 25% of such patients are affected with MEN1. Furthermore, an autopsy revealed presence of multiple MEN1-related tumors. These oversights may have occurred partly because there was an insufficient recognition of MEN1, which was not well known 40 years ago.

Other clues that were overlooked include a recurrent peptic ulcer and nephrolithiasis that the patient experienced for 10 years. Peptic ulcer is a common disorder, but hypergastrinemia can be a background in a subset of patients. Hypercalcemia-induced hypergastrinemia should also be recognized as a potential cause. In the present case, despite the fact that the hypercalcemia was not obvious, the serum phosphate level was apparently low, suggesting parathyroid dysfunction. Furthermore, the patient had a history of recurrent nephrolithiasis, which is also a cardinal feature of hyperparathyroidism. If the patient’s family history had been appropriately examined, it might have been possible to recognize his MEN1 much earlier.

The clinical utility of genetic testing for familial MEN1 has been established (15). The early detection of asymptomatic carriers in a family makes it possible to perform focused surveillance for early detection and subsequent early management of MEN1-related neoplastic diseases. In addition, non-carriers identified by genetic testing can avoid further costly surveillance. Psychosocial support is essential for MEN1 family members who plan to undergo presymptomatic genetic testing. In this case, the Division of Clinical and
Molecular Genetics in our hospital performed genetic counseling before and after testing for his family members. In conclusion, a patient was observed with extragonadal seminoma and MEN1. This is the first case of such a concomitance. The etiological correlation between the two disorders could not, however, be elucidated.

References


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