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CASE REPORT

A case of mediastinal teratoma with pancreatic islets accompanied by discontinuation of insulin treatment in insulin-dependent diabetes mellitus

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Abstract
A 74-year-old woman of insulin-dependent diabetes mellitus presented with gradually improvement of blood glucose control and finally discontinuation of insulin therapy, for some unknown reason. During follow-up period, she was admitted with hemoptysis. CT imaging showed a heterogeneous enhancement mass in the middle mediastinum with cyst and calcification, suggesting the diagnosis of mediastinal teratoma. Immediately after excision of the tumor, her plasma glucose levels again increased, and she required insulin therapy for glycemic control. Immunohistochemical examination showed that the tumor contained pancreatic tissue with both exocrine and endocrine components consisted with the islet cells of Langerhans with insulin-positive cells. Accordingly, we diagnosed insulin-producing mediastinal teratoma. Although hypoglycemic agents are the commonest cause of hypoglycemia in diabetic patients, an insulin-producing tumor should be considered in the patients who have dramatic improvement of diabetes mellitus, particularly after withdrawal of all hypoglycemic treatment. Mediastinal teratomas should be considered in differential diagnosis as etiology in undiagnosed case of hypoglycemia or blood glucose fluctuations.

Keywords Mediastinal teratoma · Pancreatic islets of Langerhans · Hypoglycemia · Diabetes mellitus

Introduction

Teratomas are the most common germ cell tumors of the mediastinum [1]. They arise from the multipotent germ cells in the third pharyngeal pouch that showed abnormal migration during embryonic development [2]. Therefore, they are formed by many component tissues such as stratified squamous epithelium, intestinal epithelium, fat tissue, skeletal muscle, cartilage, teeth, and bone. Pancreatic tissues are also contained frequently in mediastinal teratomas, although it is little known to the general clinicians [3, 4]. The presence of pancreatic tissues is clinically most important among other components observed in teratomas, with regard to endocrine function resulting in asymptomatic or symptomatic hypoglycemia. Here, we report a 74-year-old insulin-dependent diabetes mellitus patient who initially required insulin therapy for glycemic control, and later developed episodes of hypoglycemia which persisted even after insulin therapy was withdrawn. She was found to have insulin-producing tumor suggestive of mediastinal teratoma. After excision of the tumor, her hypoglycemic episodes ended, and her diabetes again developed and required insulin therapy.

Case report

A 74-year-old woman had diabetes mellitus at 60 years of age, and was treated with glimepiride 2 mg/day, metformin 750 mg/day, and voglibose 0.9 mg/day. Her body weight and body mass index (BMI) were 54.0 kg and 23.4 kg/m^2, respectively. She subsequently exhibited poor blood glucose control for a prolonged period. Her HbA1c levels increased to 8–9% at 66 years of age, and she began taking insulin therapy with basal and three bolus mealtime.

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Although her total dose of daily insulin requirement was 64 U per day, her diabetic control worsened, and her HbA1c levels were always 9–10%. Her fasting plasma glucose and serum C-peptide immunoreactivity (CPR) were 225 mg/dL and 0.60 ng/mL, respectively. Her urinary CPR excretion was 5.3 µg/day. She was diagnosed as insulin-dependent diabetes on the basis of these results. Anti-GAD antibody was negative. However, since around at 72 years of age, her HbA1c levels gradually decreased without the change of medication. Rapid-acting insulin at mealtime was discontinued. Despite these, she experienced frequent preprandial hypoglycemic attacks. Finally, long-acting insulin at bedtime was also discontinued, and her HbA1c levels were around 6%. She was admitted to our hospital with a sudden episode of massive hemoptysis at 74 years of age. Laboratory findings on admission are shown in Table 1. White cell count and inflammation biomarker were not increased. The levels of the tumor markers were not increased. Chest computed tomography (CT) revealed a mass of size 3 cm in the middle mediastinum with heterogeneous enhancement. The mass had polycystic portion and foci of calcification, suggesting the diagnosis of mediastinal teratoma. The tumor involved the lower lobe of the right lung. Total excision of the tumor was performed. Before surgery during admission, she presented with neurological symptoms of hypoglycemia. Her simultaneous plasma glucose level was 49 mg/dL with inappropriately high serum CPR level (4.22 ng/mL). Her urinary CPR excretion also increased to 73.3 µg/day. Thus, endogenous hyperinsulinism was considered to be the cause of her hypoglycemia. ACTH, cortisol and thyroid hormone levels were within the normal response to hypoglycemia, respectively. Anti-insulin antibodies were negative (Table 1). At surgery, the tumor extended to involve the adjacent lobe of the right lung, with adhesion to the pericardium. Partial lobectomy was also done, and a part of pericardium was excised. The tumor was size of $2.9 \times 2.5 \times 2.0$ cm (Fig. 1a). Microscopically, the tumor consisted of stratified squamous epithelium, adipose tissue, and mature cartilage, consistent with the diagnosis of a mature cystic teratoma (Fig. 1b). Pancreatic tissue was also detected. The pancreatic tissue consisted with both exocrine and endocrine components (Fig. 1c). The islet cells of Langerhans were positive for chromogranin-A (Fig. 1d), insulin (Fig. 1e), and glucagon (Fig. 1f) immunohistochemically, resembling the immature fetal pancreatic tissue.

Immediately after surgery, her hyperglycemia of around 300–400 mg/dL was observed, and she began to take basal and three bolus insulin therapies. Her fasting plasma glucose and serum CPR after surgery were 181 mg/dL and 0.55 ng/mL, respectively. Her endogenous insulin secretion was very low and comparable with insulin-dependent diabetes mellitus. Figure 2 shows the HbA1c levels and the total dose of daily insulin requirement before and after surgery. At the time of this writing, approximately 2 years after surgery, she has no signs of tumor recurrence or unusual instability of her plasma glucose levels.

Table 1 Preoperative laboratory data

CBC	
WBC	7600/µL
RBC	425×10^4/µL
Hb	13.1 g/dL
Ht	39.0%
Plts	24.2×10^4/µL
Biochemistry	
CRP	0.52 mg/dL
TP	7.1 g/dL
T-Bil	0.47 mg/dL
AST	10 IU/L
ALT	15 IU/L
LDH	182 IU/L
ALP	313 IU/L
r-GTP	17 IU/L
CK	67 IU/L
LDL-C	78 mg/dL
TG	73 mg/dL
HDL-C	52 mg/dL
Na	135 mEq/L
K	4.9 mEq/L
Cl	98 mEq/L
BUN	17.3 mg/dL
Cr	0.74 mg/dL
FPG	82 mg/dL
HbA1c	5.4%
GAD antibody	< 0.3 U/mL
Anti-insulin antibody	< 125.0 nU/mL
CEA	0.8 ng/mL
AFP	1.8 ng/mL
hCG	1.4 mIU/mL
Endocrinological examination on hypoglycemic attack	
FPG	49 mg/dL
CPR	4.22 ng/mL
ACTH	37.2 pg/mL
Cortisol	15.3 µg/dL
TSH	0.58 µIU/mL
FT3	3.32 pg/mL
FT4	1.25 ng/dL
GH	1.13 ng/mL
IGF-1	165.2 ng/mL

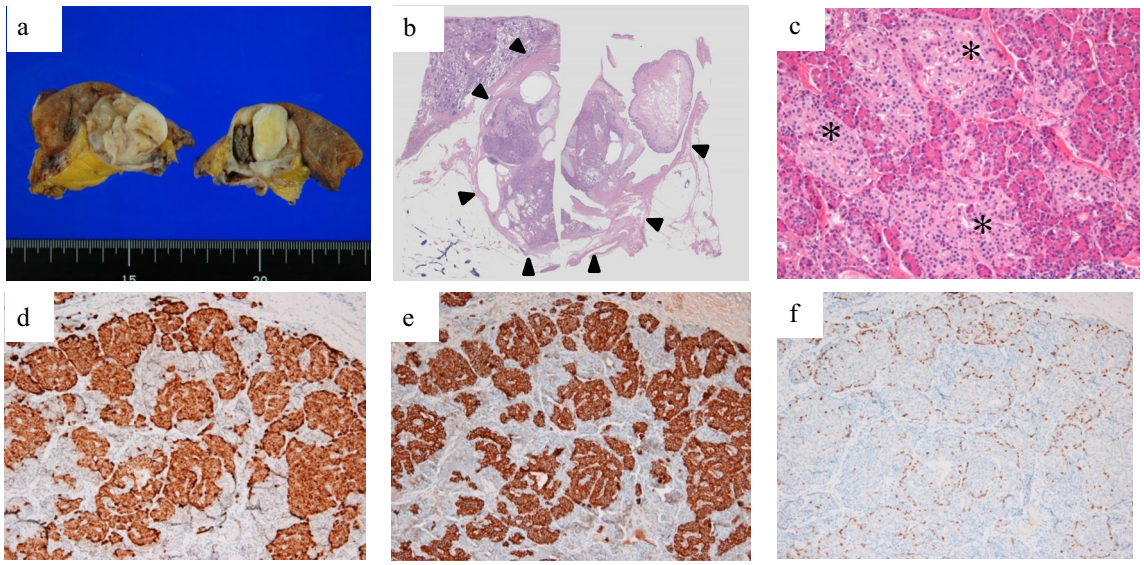

Fig. 1 Histological findings of the resected tumor. Gross cut surfaces of the tumor showed multilobular solid growth and cystic portion (**a**). Macroscopic findings (image with a loupe) of the tumor (black arrowheads) contained stratified squamous epithelium with sweat glands, adipose tissue, cartilage, and pancreatic tissue (Hematoxylin and Eosin staining, low magnification) (**b**). The tumor contained pancreatic tissue consisted with both endocrine components with islets of Langerhans (*) and exocrine components (Hematoxylin & Eosin staining, ×200 magnification) (**c**). Immunohistochemical stainings of the islet cells of Langerhans in the resected tumor were positive for chromogranin-A (**d**), insulin at center of islets (**e**), and glucagon at the periphery of islets (**f**) (×100 magnification)

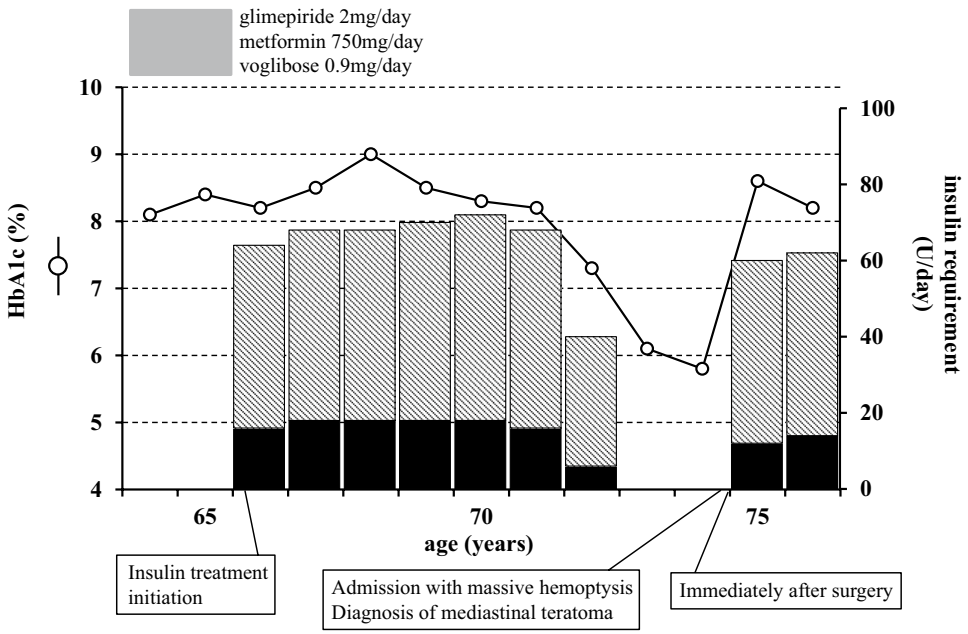

Fig. 2 Clinical course of the patient. Time line with age illustrates major events in the patients medical history. HbA1c levels and the total dose of daily insulin requirement are indicated by open dots and bar chart, respectively. The black solid bars represent daily requirement of long-acting insulin, and the hatched bars represent rapid-acting insulin

Discussion

In the mediastinum, teratomas are most frequently located in the anterior compartment [1]. About one-third of the patients remain asymptomatic [5]. Whereas, they give rise to symptoms like dyspnea, chest pain, hemoptysis, or cardiac tamponade, when they rupture into adjacent structures, such as the lung, bronchial tree, pleural space, or pericardial space [6, 7]. Intrapulmonary parenchyma invasion can cause chemical pneumonia associated with pleural effusion, while communication into the tracheobronchial tree can result in hemoptysis. Our case also presented with hemoptysis that might result from the

communication with tracheobronchial tree. In our case, the inflammatory changes with lymphocyte infiltration was shown in the resected tissue of the tumor, as observed in a previously report [8]. Thus, we speculate that pancreatic enzymes might affect inflammation in the tumor, resulting in its invasion or rupture into adjacent structures.

Pancreatic tissue is frequently present in mediastinal and sacrococcygeal teratomas, although it is absent in gonadal teratomas [3, 4, 9]. The reason why mediastinal teratomas frequently contain pancreatic tissue is that the pancreatic tissue arises from a part of the foregut in the third pharyngeal pouch which is also the origin of mediastinal teratomas. In our case, her diabetic control gradually improved and showed recurrent symptomatic hypoglycemia, which returned to poor blood glucose control postoperatively. This fact implies that mediastinal teratoma in our case was producing the excess insulin. Our case had hyperinsulinemic hypoglycemia even when hypoglycemic agents was completely withdrawn. The differential diagnosis of hyperinsulinemic hypoglycemia includes insulinoma, islet-cell hyperplasia, noninsulinoma pancreatogenous hypoglycemic syndrome (NIPHS), and non-islet-cell tumor hypoglycemia (NICTH). There were no tumors on a chest–abdominal–pelvic CT scan, except for mediastinal teratoma. Our case was diagnosed as hypoglycemia by insulin-producing tumor suggestive of mediastinal teratoma, based on the exclusion of the most common causes of hypoglycemia, the demonstration of increasing serum CPR level in the presence of low level of blood glucose, and the fact that serum CPR level promptly returned to very low when hypoglycemic attack disappeared after excision of the tumor. Shoji et al. previously reported that an adult case of anterior mediastinal gastroenteric cyst containing pancreatic tissue influenced the severity of diabetes mellitus [10]. This patient presented the improvement of blood glucose control before treating the anterior mediastinal tumor, while his diabetes mellitus worsened after removal of the tumor. On CT imaging, anterior mediastinal gastroenteric cysts show the same findings as anterior mediastinal teratomas. The differential diagnosis of mediastinal teratomas from other lesions of the mediastinum like gastroenteric cyst is necessary. We should keep the diagnosis of gastroenteric cysts containing pancreatic tissue in mind. In resected tumor of our case, the density of the islets was very high, and the pancreatic endocrine tissue showed the proportion of islet of Langerhans, where β cells stained for insulin were arranged centrally, with the rim of α cells for glucagon. β cells in immature fetal pancreas are clustered in the center of islet surrounded by slightly α cells, while β cells in adult pancreas are mainly detected in the islet core, with α cells scattered throughout the islets with a prevalent peripheral localization [11, 12]. Thus, the islets in the tumor of our case were similar to immature fetal pancreas. Only a few cases of teratoma with hypoglycemic attack have been already reported, although pancreatic tissue is frequently present in mediastinal teratomas [13, 14]. Teratomas containing pancreatic tissue are almost always asymptomatic hypoglycemia and not suffer from symptomatic hypoglycemic attack. Our case is a diabetes mellitus patient with mediastinal teratoma which causes symptomatic hypoglycemia. The mechanisms linking diabetes mellitus and teratoma with pancreatic tissue are unclear. Previous reports suggested that exposure of immature β cells to glucose itself can enhance maturation of islet β cells in fetal rat islets [15]. It has been also reported that not only do immature β cells respond poorly to increased glucose levels, but also they fail to shut off insulin secretion efficiently when glucose levels are low [16]. In our case, the pancreatic tissue with a large amount of the islets resembled to immature fetal pancreas, as previously report of case of mediastinal teratoma with hypoglycemic attack [13]. Immature fetal islets have very high density of the islets, and exhibit the lack of glucose responsiveness ascribed to immaturity of glucose receptor sites on the fetal β cells and the autonomous excessive release of insulin [17]. The quantity and immaturity of fetal pancreatic islets in teratomas might link to symptomatic hypoglycemic attack. Therefore, we speculate that long period of hyperglycemia developed the maturation of the islet β cells and enhanced insulin secretary capacity in mediastinal teratomas of our case, although their cells had no feature of maturation enough to suppress insulin secretion at hypoglycemia. Further studies in larger numbers of mediastinal teratoma patients are required to investigate the endocrine function and the differentiation of pancreatic tissue in the teratomas.

In conclusion, we reported a case of teratoma contained pancreatic tissue in the anterior mediastinum. To the best of our knowledge, our case is the first report of a diabetes mellitus patient with mediastinal teratoma, which causes symptomatic hypoglycemia and discontinuation of insulin therapy. Because pancreatic tissue including the islets of Langerhans always present in mediastinal and sacrococcygeal teratoma, blood glucose levels should be measured in patients with such tumors. Hypoglycemic agents are the commonest cause of hypoglycemia in diabetic patients. However, in the patients who have dramatic improvement of diabetes mellitus, particularly after withdrawal of all hypoglycemic treatment, an insulin-producing tumor should be considered. We suggest that our case is noteworthy for predicting a clinical suspicion to identify teratomas as etiology in undiagnosed case of hypoglycemia or blood glucose fluctuations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard This article does not contain any studies with human or animal subjects performed by the any of the authors. The identity of the patient has been protected. The patient provided informed consent for this manuscript, and this submission was approved by the ethics review board in Public Central Hospital of Matto Ishikawa.

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