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Carcinoid Tumors of the Thymus*)

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ABSTRACT

This paper reports two relatively rare cases of primary carcinoid tumors of the thymus experienced by the authors. One case is a 43-year old male who presented the Zollinger-Ellison (ZE) syndrome and received total gastrectomy and distal pancreatectomy. Mediastinal tumor was found one year and seven months post operatively, for which total extirpation was performed followed by irradiation. The histological diagnosis was primary carcinoid of the thymus. The other case is a 63-year old female, who under the diagnosis of thymus carcinoid received total removal of the tumor with postoperative irradiation in 1978. In 1984, the case developed localized recurrence of the tumor, for which excision was performed again and irradiation was repeated.

INTRODUCTION

Carcinoid tumor develops from endocrinous cells of primitive ectodermal tissue, frequently in the digestive canal and the bronchus. It is a tumor with a distinctive feature because, as a clinical symptom, it produces such hormones as ACTH and 5-HT. However, carcinoid originating in the thymus is a comparatively rare, which began to attract attention since it was reported by Rosai and Higa[12] in 1972, and more cases have gradually began to be reported. In Japan, 23 cases have been enumerated by Oguma et al[11]. Cases like ours which presented the Zollinger-Elllson syndrome are limited to the 4 cases reported by Salyer[13] and 1 case reported by Mayo Clinic[16]. Moreover, ours is the first case in Japan. This paper presents with a discussion of literature rare cases experienced by the authors which presented very interesting symptoms.

REPORT OF TWO CASES

Case 1: A 43-year old male, a salaried man. Family history was unremarkable, but the case had a history of Zollinger-Ellison syndrome. He had undergone partial gastrectomy under the diagnosis of hemorrhagic gastric ulcer at another hospital in October 1982, but owing to hemorrhage from the residual stomach postoperatively, he was referred to our clinic and underwent tolal gastrectomy here as an emergency operation. However, because gastrin in blood showed the high value of 4,156 pg/ml and ZE syndrome was suspected, percutaneous transportal blood sampling was done to determine the gastrin level of draining veins from pancreas and distal pancreatectomy was performed under the diagnosis of gastrinoma of the pancreas, which revealed multiple tumor. Although immunohistochemical study was difficult from the resected specimen, gastrin producing tumor was strongly suspected from the clinical course. The gastrin value returned to normal level of 23 pg/ml postoperatively and the patient was discharged.

As history of present illness, the patient developed cough and facial edema in May 1984 and was seen at a neighborhood hospital. Chest roentgenogram taken at the hospital showed an abnormality and the patient was admitted to our department with the diagnosis of mediastinal tumor. At admission, height was 168 cm and weight was 65.6 kg. There was no

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anemia or jaundice, and no abnormality was found on physical examination. Neither were there any chest pain due to the tumor nor any symptoms suggestive of hormone production such as sweats, flushing and diarrhea.

Laboratory studies showed mild anemia but no abnormality of liver function or renal function and no electrolyte imbalance. Fasting blood sugar showed the low value of 60 mg/dl, but no hypoglycemic attack was evident clinically and blood insulin level was normal. Blood CEA also showed normal level. (Table 1 and 2)

Table 1. Laboratory data on admission (Case 1)

WBC 7400/mm^3	RBC 399×10^4/mm^3
Hgb 8.8 g/dl	Hct 29.6%
Plt 44×10^4/mm^3	
T. Bil 0.3 mg/dl	D. Bil 0.1 mg/dl
GOT 16 U/liter	GPT 29 U/liter
LDH 264 U/liter	Choline. E 258 U/liter
Al. Phos. 46 U/liter	LAP 32 U/liter
γ-GTP 37 U/liter	T. Cholest. 184 mg/dl
Amylase 92 U	FBS 60 mg/dl
BUN 11 mg/dl	Creat. 1.2 mg/dl
Na 143 mEq/liter	K 4.4 mEq/liter
Cl 105 mEq/liter	Ca 4.5 mEq/liter
inorg. P 3.3 mg/dl	CEA less than 1 ng/ml

Table 2. Hormone values (Case 1)

Preoperative values:	
gastrin	2,700 pg/ml
insulin	6.8 ug/ml
glucagon	54 pg/ml
Postoperative values:	
gastrin	2,900 pg/ml
PTH-C	0.5 ng/ml
ACTH	16 pg/ml
TSH	1.1 μU/ml
GH	1.1 ng/ml

Chest roentgenography revealed a well-defined abnormal shadow 10 cm in diameter in the upper anterior mediastinum, which protruded into the right thoracic cavity (Fig. 1). Scintigram using ^{67}Ga-citrate showed uptake consistent with tumor, but uptake was absent at other sites.

Operation was performed on 31 May 1984. Total excision of a tumor was made by median sternotomy. The tumor, which was spherical and capsulated, was of an elastic firmness. The tumor was easily detached from the superior vena cava and the left brachiocephalic vein, but detachment from the right pleura being difficult, the pleura was excised with the tumor. The tumor measured $11\times10\times10$ cm and weight 290 g. The cut surface was greyish white and showed small necrotic foci at some sites (Fig. 2).

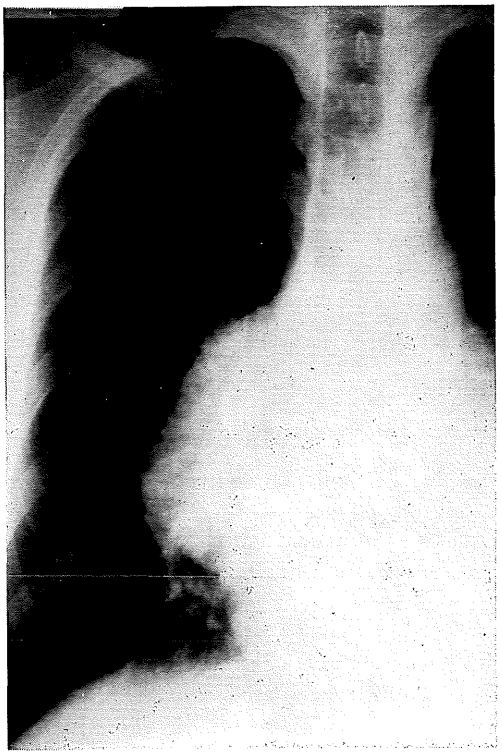

Fig. 1. Case 1 Chest roentgenography. The tumor was located in the upper anterior mediastinum. It protruded into right thoracic cavity.

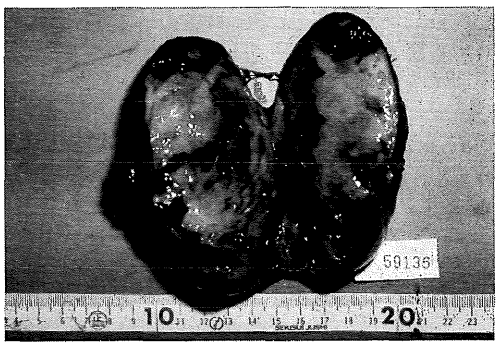

Fig. 2. Case 1 Resected specimen. The tumor measured $11\times10\times10$ cm and weight 290 g.

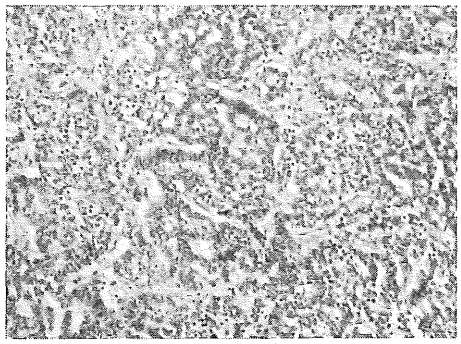

Fig. 3. Case 1 Histology of tumor. The tumor proliferated in pillar-shaped arrangement. The nucleus was rich in chromatin and roundish, and the cell body was clear. (H-E staining ×100)

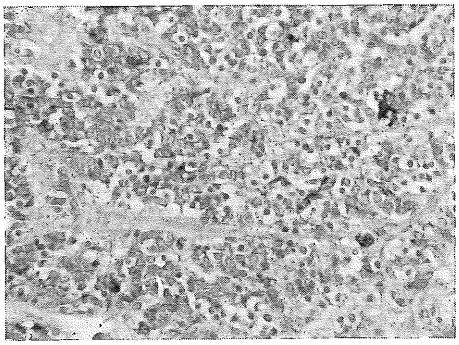

Fig. 4. Case 1 Grimelius staining of tumor Argentaffine-positive granules were stained. (H-E staining×100)

Histologically, the tumor was found to be comprised for the most part of relatively uniform small cell which had proliferated in focal, pillar-shaped, or ribbon-shaped arrangement. The nucleus was rich in chromatin and roundish, and the cell body was clear. The interstice, which was rich in capillaries and fine, was stretched branchlike to surround the tumor cells in focal arrangement (Fig. 3).

Only a very small number of cells was found to have argentaffine-positive granules on Grimelius staining, but the presented pattern was remarkably consistent with the pattern of carcinoid of the thymus (Fig. 4).

The postoperative course was satisfactory. Because pleural infiltration was strongly suspected histologically, the superior mediastinum was irradiated with 5,000 rad by Lineac. Findings worthy of note were that before the patien's last admission to hospital, the gastrin level showed the high value of 2,700 pg/ml, which made us suspect recurrence of the tumor in the pancreas and that the gastrin value, which was 2,900 pg/ml after excision of the carcinoid of the thymus, did not decrease postoperatively. Although the patient's course is satisfactory at present four months after his discharge from hospital, an examination for gastrinoma in the pancreas will be made shortly.

Case 2 : A 63-year old female, 148 cm in height and 55 kg in weight with blood pressure of 106/60 mmHg, well-nourished and of medium build. In April 1978, the case had an abnormal shadow in the chest pointed out at her periodic examination as an atomic bomb survivor. She was hospitalized for operation under the diagnosis of mediastinal tumor. Anemia and jaundice were not found, and physical examination revealed no abnormality in the chest. Neither were any symptoms found to suspect carcinoid.

Chest roentgenography showed a tumor shadow protruding into the left thoracic cavity in the vicinity of the first arch of the shadow of the left heart (Fig. 5). Under the diagnosis of mediastinal tumor made after various examinations, excision of the tumor was performed by median sternotomy. The tumor, which was found to have developed from the left lobe of the thymus and was located below the left brachiocephalic vein, was easily detachable from the surrounding organs because adhesion was mild. The tumor was of the size of a hen's egg, capsulated and comparatively soft, and the cut surface was greyish white with cavity formation in part due to necrosis (Fig. 6). Histological diagnosis was carcinoid of the thymus. Because metastasis to the anterior mediastinal lymph nodes with anthoracosis was found, the superior mediastinum was irradiated with 3,000 rad by Lineac postoperatively, and the patient was discharged.

While the course of the patient was being followed up in the outpatient clinic after her discharge, roentgenography of the chest in January 1984 showed a mediastinal shadow protruding into the left lung field thoracic cavity and CT examination showed a picture of a tumor approximately 3 cm in diameter below the arch of aorta, and the patient was readmitted to our hospital with suspected recurrence of carcinoid (Fig. 7).

After various examinations were done, operation was performed by left thoracotomy.

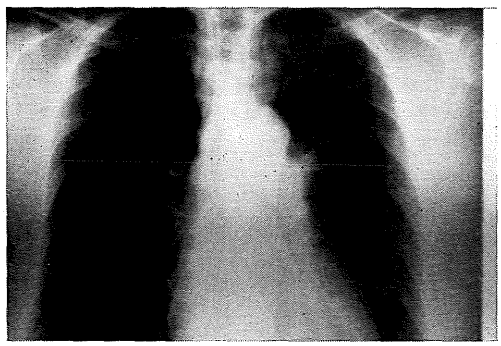

Fig. 5. Case 2 Chest roentgenography. The tumor shadow protruded into the left thoracic cavity in the vicinity of the first arch of the shadow of the left heart.

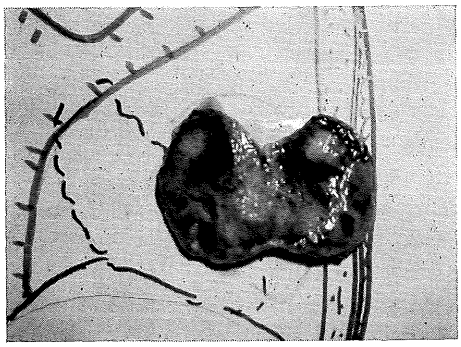

Fig. 6. Case 2 Resected specimen. The cut surface was greyish white with cavity formation.

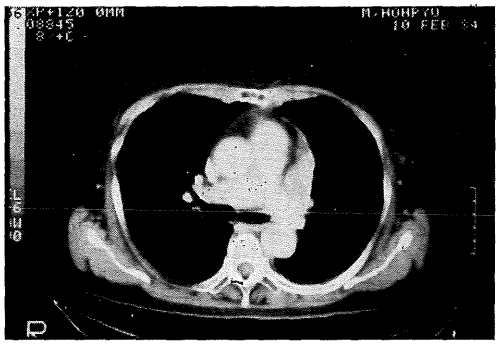

Fig. 7. Case 2 CT scanning. The recurrent tumor was showed below the aortic arch.

The tumor was found to have grown infiltrating in the pericardium, in contact with the aortic arch and the pulmonary artery and vein. Almost total excision of the tumor, including the pericardium, was done, but curative excision was not possible. The pericardium was reconstructed with the fascia of latissimus dorsi muscle. The tumor measured 5×3×1 cm and had an elastic firmness and a relatively smooth surface.

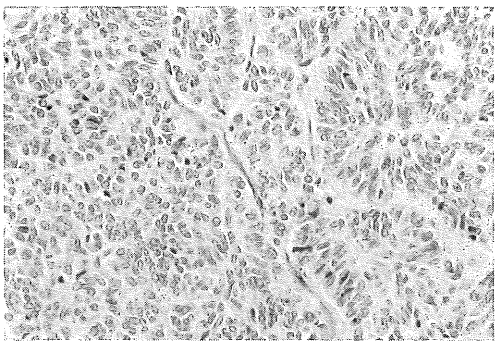

Fig. 8. Case 2 Histology of tumor. The tumor proliferated forming alveolar structure. The cells had proliferated assuming a rosette-like arrangement. (H-E staining ×400)

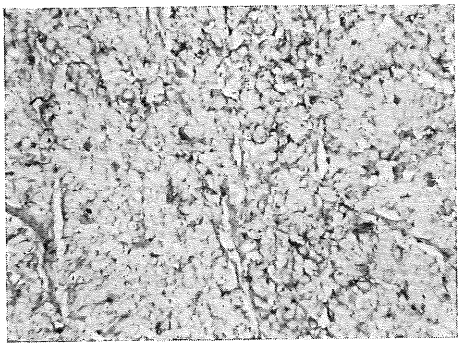

Fig. 9. Case 2 Grimelius staining. Many argentaffine-positive granules were found in the cell bodies. (H-E staining ×400)

The histological findings revealed a tumor composed of relatively uniform cells with roundish nuclei those margins were well-defined, which had proliferated forming a ribbon -shaped, alveolar structure. In part, the cells had proliferated assuming a rosette-like arrangement (Fig. 8). On Grimelius staining, numerous argentaffine-positive granules were found in the cell bodies (Fig. 9).

The patient's postoperative course was satisfactory. Because the operative findings had made it impossible to perform curative excision, the anterior mediastinum was irradiated with 5,100 rad by Lineac. Blood serotonin level, which had shown the high value of 45 μg/dl (normal: 10-30 μg/dl) preoperatively, dropped to lower than normal postoperatively (Table 3). At present six months after the operation, there is no sign of recurrence.

Table 3. Change of serum serotonin values

	Preoperative	Postoperative (2 ws)	Postirradiated
serotonin values*	45.0	less than 0.1	less than 0.1

* normal value 10-30 ug/dl

Table 4. Features of patients with thymic carcinoid associated with ZE syndrome

Case	Age/Sex	Associated endocrine adenomatosis	Grossly invasive	Metastasis	Follow up data
1[13]	33 M	parathyroid hyperplasia	+	+	Died of tumor 14 yr
2[13]	38 M	parathyroid hyperplasia pituitary adenoma adrenal hyperplasia thyroid adenoma	+	+	Died of tumor 9 yr
3[13]	32 M	parathyroid hyperplasia	+	−	Died of tumor 4 yr
4[13]	46 M	parathyroid hyperplasia	−	−	no evidence of tumor 5 yr
5[16]	38 M	parathyroid hyperplasia	unknown	+	alive with residual tumor 4 yr
6*	43 M	−	+	−	no evidence of tumor 4 m

* Case 1 of this report

DISCUSSION

Ever since Oberndorfer[9] in 1907 named it "Karzinoid" in view of the unique histologic pattern it presented which resembled carcinoma, reports of cases of carcinoid have increased. In Europe and America, Rosi and Higa[12] in 1972, reported on a total of 19 cases, 11 cases they themselves experienced and 8 cases in literature. In Japan, Oguma et al.[11] in 1983 enumerated 26 cases in literature.

Carcinoid is a hormone-producing tumor those primary cells can be originated from the endocrinous cells found dispersed in organs of archenteric tissues[14]. Tumors applicable to this concept are tumors of so-called APUD concept of Pearse et al. Such tumors include the tumor group that belongs in the category of multiple endocrine adenomatosis (MEA), and association with hyperparathyroidism and Sipple's syndrome is also reported[3,5]. Our case 1 is a case associated with ZE syndrome, and it is believed to be quite possible for carcinoid of the thymus to be associated with MEA type I. However, no report has been made in Japan so far of a case combining these two, the case experienced by the authors is the first case. Salyer et al.[13] have reported four cases of these combination, and it is reported the carcinoid tumors found at Mayo Clinic up to 1980 and one was a case presenting the ZE syndrome[16]. A comparative study of other cases and our case revealed that all were males in their thirties to forties. Metastasis was found in three of the six cases, and infiltration into surrounding organs was observed in four cases including our case. Further, it was found on comparing the endocrinous lesions they were associated with, that five cases excepting our case will all associated with parathyroid hyperplasia (Table 4).

The carcinoid is a so-called functioning tumor, but the hormones it secretes are various. In case 1 which presented hypergastrinemia, the gastrin level once returned to normal following resection of the tail of the pancreatic body, but it rose to the same high level as before the operation again four months later. As gastrin-producing carcinoid tumors have been reported, our case was conjectured that carcinoid tumor of the thymus might produce gastrin, but the gastrin level did not come down postoperatively. Therefore, this can be assumed to be due to metastasis or recurrence of tumor of island of Langerhans of pancreas. Case 2 is considered to be a serotonin-producing carcinoid tumor. It is believed to be a well-known fact that carcinoid tumors produce serotonin and develop carinoid symptoms. Actually, however, only 1-3% of all carcinoid tumors are said to develop carcinoid symptoms[8,14] and only one such case of carcinoid tumor has been reported

in Japan[4]. And, no case presenting a high serotonin level preoperatively has been reported other than our case. Despite its high serotonin level, our case, like almost all the other cases, developed no carcinoid symptoms. On the other hand, it is well known that carcinoid tumors of the thymus frequently produces ACTH[1,7,15,17]. Symptoms such as facial edema and pigmentation develop, and our case 1 also had visited the hospital with the chief complaint of facial edema and the possibility of ACTH having been produced can be considered. The possibility also cannot be ruled out that the tumor compressed the superior vena cava and caused the superior vena cava syndrome to be presented[2].

The degree of malignancy of carcinoid tumors of the thymus is expressed us "potentially malignant", and it is considered to be of so-called low grade malignancy. In reality, however, many of these tumors recur and metastasize, and cases are reported whose initial symptom was metastasis to the brain. Our case 1 had developed pleural infiltration, and case 2, metastasis to lymph nodes, which, on recurrence, had metastasized more extensively to lymph nodes and developed pericardial infiltration. Not infrequently, the organ unavoidably has to be repaired by graft as in case 2[15].

As curative method, various methods including surgical treatment are tried, but no method has been established as yet. Because radiotherapy was given in many cases and there were reports of its effectiveness, we also irradiated our cases by Lineac. Although the tumor regrettably recurred in case 2, the site of recurrence was not in the field of initial irradiation so that the radiotherapy is believed to have been effective.

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