Медиастинальная тератома с эмбриональной тканью поджелудочной железы, незидиобластозом и очаговой гиперплазией нейроэндокринных клеток. Наблюдение из практики

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Представлен клинический случай редкой и трудной, с точки зрения диагностики, тератомы средостения, содержащей элементы зрелой ткани поджелудочной железы с незидиобластозом и очаговой гиперплазией нейроэндокринных клеток у соматически здорового 25-летнего мужчины. Основные сложности в диагностике связаны с бессимптомным клиническим течением загрудинных тератом; как правило, это случайные находки при рентгенологических исследованиях, выполненных по поводу другого заболевания. Для этой патологии характерна выраженная морфологическая гетерогенность опухоли, что при недостаточной квалификации морфолога часто приводит к ложноположительным заключениям о наличии нейроэндокринной карциномы, а это в свою очередь — к неадекватному объему лечебных мероприятий и неверному прогнозу. Поэтому целесообразно отправлять гистологические препараты на верификацию диагноза к специалистам учреждений, имеющих опыт морфологической дифференциальной диагностики. В данном случае ключевым является иммуногистохимическое исследование опухоли на инсулин, цитокератины, маркеры нейроэндокринной дифференцировки, а также определение индекса пролиферации Ki-67 в нескольких зонах. Описанная патология встречается крайне редко, что обусловливает многочисленные диагностические ошибки.

Ключевые слова: тератома средостения, незидиобластоз, ткань поджелудочной железы, нейроэндокринные клетки.

Mediastinal teratoma with mature fetal pancreatic tissue, nesidioblastosis and focal hyperplasia of neuroendocrine cells. A case report

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We present a clinical case of rare and poorly diagnosable mediastinal teratoma containing elements of mature pancreas tissue, nesidioblastosis, and focal hyperplasia of neuroendocrine cells in a somatically healthy 25-year-old male. The main diagnostic difficulties are associated with the asymptomatic clinical course of mediastinal teratomas that are usually incidentally discovered during X-ray for other conditions. The pathology is characterized by pronounced morphological heterogeneity of the tumor; if the morphologist is not sufficiently qualified, this often results in a false-positive conclusion of neuroendocrine carcinoma, which, in turn, leads to an inadequate amount of treatment and a wrong prognosis in the patient. Therefore, for verification of the diagnosis, histological specimens should be examined by experts of institutions experienced in morphological differential diagnosis. In this case, an immunohistochemical study of the tumor for insulin, cytokeratins, and markers of neuroendocrine differentiation as well as measurement of the proliferation index Ki-67 in several areas are the key tests. This pathology is extremely rare, which leads to numerous misdiagnoses.

Keywords: mediastinal teratoma, nesidioblastosis, pancreatic tissue, neuroendocrine cells.

Differential diagnosis of mediastinum neoplasms often includes thymoma, thymic neuroendocrine tumor, lymphoma, germ cell neoplasia, metastasis to lymph nodes, and teratoma [1]. Benign mediastinum teratomas are rare tumors (3 to 12% of all mediastinal tumors). They are diagnosed in patients aged 7 months to 65 years, mostly in young people, and are equally common in males and females [2—5]. Approximately 95% of teratomas occur in the anterior mediastinum, about 5% — in the posterior mediastinum [3, 5]. Most mediastinum teratomas are slow-growing tumors and are asymptomatic. The main symptoms are associated with compression of adjacent organs, such as the respiratory system, presenting with dyspnea and chest pain [4, 5]. Weichert et al. (2010) reported a rare case of mediastinal tumors in a 17-year-old male; initial biopsy of the tumor detected heterotopic pancreatic tissue. After re-examination of specimens, the diagnosis was changed to mature teratoma with pancreatic tissue [6]. In this case, there was a mature teratoma with elements of fetal pancreatic tissue, nesidioblastosis, and focal hyperplasia of neuroendocrine cells.

Clinical case

Patient *S.*, 25 years old, active in sports, informed a therapist that for the last three months, he was suffering from recurrent pain in the left side of the chest, worsening upon physical exertion and inhaling. Later on, the symptoms occurred at rest. The patient visited a chiropractor and after procedures pain intensified. X-ray examination of the chest showed mediastinal mass lesion, which was surgically removed.

Macroscopically, the mediastinal neoplasm had multilobed structure sized 13.5×7.5×3.7 cm in the brown capsule; its cross-section was yellow-gray with multiple cysts. Microscopic examination showed thymic tissue

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with cystic cavity lined with squamous epithelium; cyst wall had papillary proliferation with rosette-like complexes, which were initially considered as neuroendocrine tumor. IHC study showed that pancreatic tissue within the teratoma expressed synaptophysin, chromogranin A, CK18, Ki-67 — 8%, the reaction with CDX2 was negative. The patient was diagnosed with malignant neuroendocrine tumor and supervision of oncologist was recommended.

Re-examination of histological preparations and IHC study in the pathomorphology laboratory of Endocrinology Research Center identified mature teratoma in the prepared tissue specimens, which contained the following components: pancreatic tissue, mucous membrane of the intestine, and small fragment of the thymus tissue. Pancreatic tissue has lobular structure with mixed regions of acinar and insular epithelium and ductal structures. IHC study found positive reactions of cells with antibodies to chromogranin A, synaptophysin, CD56 in the insular tissue and solid areas. Reaction with antibodies to insulin was positive in the insular component and in the trabecular areas. CK19 is expressed in a large number of cells of tubular structures and ductal-insular complexes, as well as the epithelial component of preserved thymus. In the area with predominance of neuroendocrine cells, proliferation marker Ki-67 is no more than 2%, in all pancreatic structures — 8%. Conclusion: mature teratoma with elements of fetal pancreatic tissue, nesidioblastosis, and focal hyperplasia of neuroendocrine cells. Immature pancreatic tissue, as well as other embryonic tissues, can be characterized by high proliferative activity, which is not indicative of teratoma malignancy. The observed changes in the form of combination of endocrine and epithelial components are indicative of dysplastic pancreatic tissue (congenital tissue malformation) and hyperplasia **(Fig. 1)**.

Discussion

Mediastinal teratomas are usually asymptomatic and can be detected incidentally during x-ray, CT, MRI, or ultrasound examination. Surgical removal of the mediastinum is the method of choice in treatment of benign teratomas. Tumor recurrence after complete surgical resection is extremely rare [3, 5]. Several cases of mediastinal neoplasms with pancreatic tissue have been reported [1]. It is assumed that these mediastinal neoplasms represent a rare form of hyperplasia of the anterior portion of the intestinal tube [6]. In this case, mediastinal teratoma was represented by mature elements, including acinar pancreatic cells, mature islet cells, as well as specific hyperplastic nesidioblastosis. The term nesidioblastosis was proposed by Laidlaw in 1938 to denote cells that are differentiated from the ductal epithelium and form new islets [7]. Nesidioblastosis is characterized by the presence of ducts of the insular complex (budding of islet cells from the pancreatic epithelium), along with increased shape, size, and number of islet cells [8—10]. Nesidioblastosis is usually detected within the first 2 years of life. It is rare in older age groups and is usually accompanied by episodes of hyperinsulinemic hypoglycemia. In the histological diagnosis of islet cell hyperplasia, the presence of ductulo-insular complexes virtually eliminates other causes of their hyperplasia, since they are characteristic of nesidioblastosis. Resnick et al. (1994) described the cases of nesidioblastosis, which was structurally similar to fetal pancreatic tissue in the third trimester of pregnancy or neonatal period, in sacrococcygeal and anterior mediastinal teratomas. They suggested that mechanisms, controlling differentiation of neuroendocrine cells in normal pancreas, take place in teratomas as well [11]. This patient had no symptoms of hyperinsulinism or any other metabolic disorders, which were observed in other cases of mediastinal teratomas, containing pancreatic tissue [1]. This is most likely due to relatively small amount of functional neuroendocrine tissue. Since the tumor was encapsulated, it is logical to assume that secretion occurred within the cystic cavity and the secret did not get into the bloodstream.

The lack of expression of glucagon, the main contrainsular islet hormone, is an important feature of the reported case. Differentiation of islet cell subtypes during embryogenesis is regulated by complex and unexplored cascades of transcription factors. It is known that insulin and glucagon are regulated simultaneously at a certain stage of secretion. There is an evidence [12] that stem cell factor (SCF) and its receptor c-Kit play an important role in the differentiation and proliferation of islet cells. C-Kit/SCF interaction facilitates differentiation and proliferation of both types of pancreatic ductal cells [12]. Selective loss of glucagon secretion can be a key element of regulatory mechanisms, which are not yet discovered.

Conclusion

Asymptomatic clinical course of retrosternal teratomas explains detection of these tumors at the stage, when they are already quite large, which makes minimally invasive endoscopic resection impossible. Morphological differential diagnosis of teratomas is sophisticated, which leads to false positive diagnosis of neuroendocrine carcinoma. It is advisable to send histologic specimens for verification of the diagnosis to the specialists of institutions experienced in morphological differential diagnosis **(Table 1)**.

ADDITIONAL INFORMATION

Conflict of interest. All the authors declare the absence of explicit and potential conflicts of interest associated with publication of this article.

Patient's consent. Medical data are published with the written consent of the patient.

***Table 1*. Characteristic features of the mediastinal teratomas**

Parameter	Characteristics
Age	Typically up to 30 years (85% of patients)
Hereditary predisposition	None (defect of embryonic development period)
Complaints	Are often asymptomatic, accidental finding; rarely, chest pain
Diagnosis:	Clinical presentation: possible hypoglycemic syndrome Radiological diagnosis: X-ray/CT/MRI. Most often, not visualized by US. Blood test: Chromogranin A
Treatment:	Surgery : thoracoscopic approach in the case of tumors <7 cm, open surgery with sternotomy (extremely traumatic) in the case of larger tumor
Morphological verification	Tumor is heterogeneous and may comprise numerous components. IHC study for insulin, cytokeratins, and neuroendocrine differentiation markers, including assessment of Ki-67 proliferation index in different zones, is required to verify the diagnosis

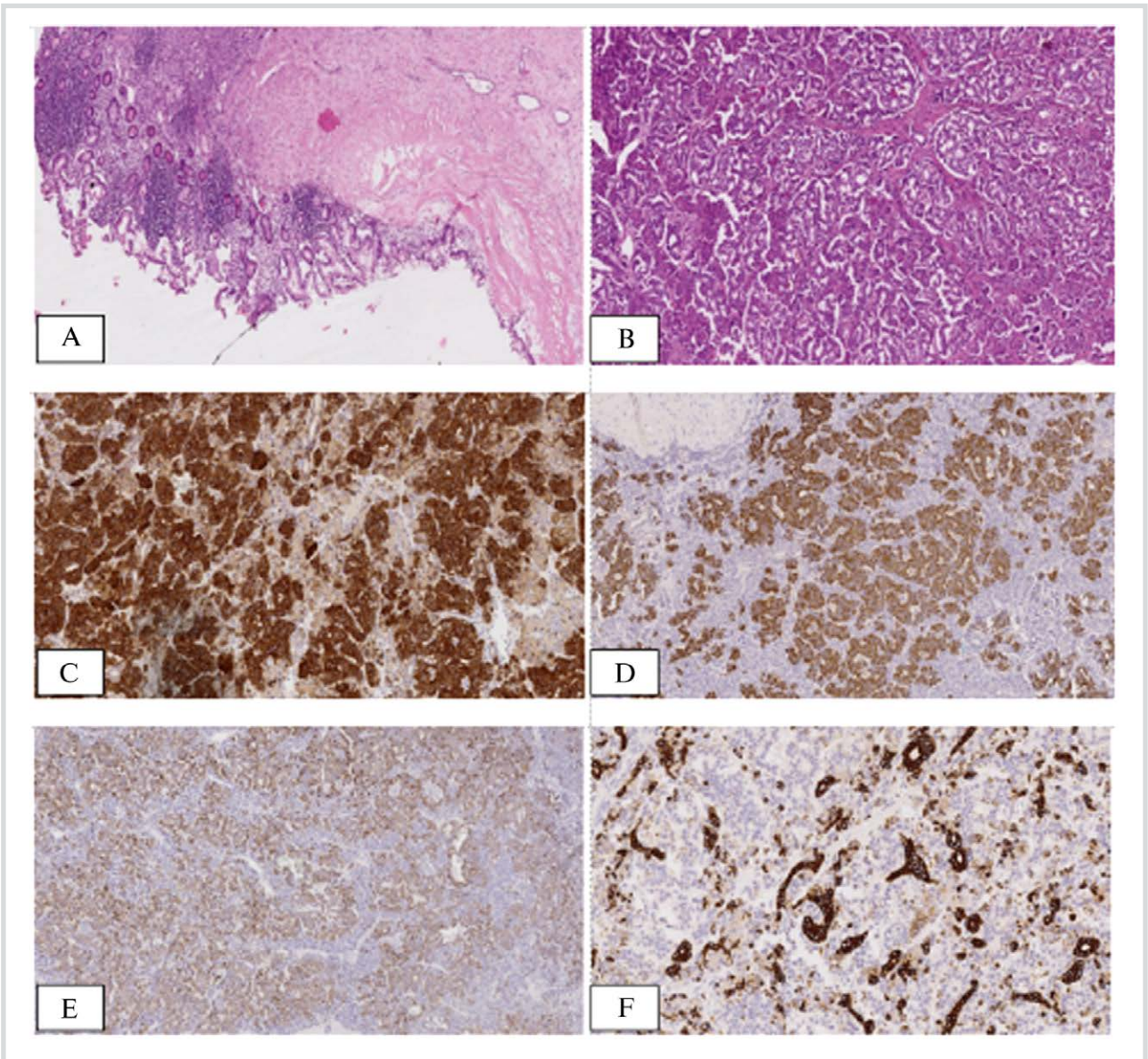

***Fig. 1*. The morphology and immunophenotype of mediastinal teratoma.**

A — tumor tissue contains various components, including the intestinal mucosa fragment (H—E × 50); B — immature pancreatic tissue with mixed areas having acinar and insular structure, multiple ductal structures are detected (H—E × 100); C — synaptophysin staining (× 100); D — chromogranin A staining (× 100), multiple ductal structures are detected in the insular tissue and in monomorphic areas; E — cell reaction with antibodies to insulin is positive in the insular component and trabecular areas, insular to acinar tissue ratio is about 1:1 (× 100); F — CK19 shows a large number of small and large tubular structures, including those involved in the ductulo-insular complexes (× 200).

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