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A VERY RARE TUMOR IN A RENAL TRANSPLANT DONOR CANDIDATE: PRIMARY MESENTERIC NEUROENDOCRINE TUMOR

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ABSTRACT

Neuroendocrine tumors arise from neuroendocrine system cells, and constitute a heterogeneous group of neoplasms. Usually these tumors cause no symptoms and are diagnosed during several screenings incidentally. In this case; a renal transplantation donor candidate, who had no complaints of any illnesses, was diagnosed with a rare primary mesenchymal neuroendocrine tumor based on the calcified mass found in the examinations. A computed abdominal tomography angiography was carried out in order to view the kidney arteries of the donor candidate. We determined a mass at the small curvature of the stomach, a large part of which had calcifications. The mass was found between the mesenteric fat planes and it caused a thrust in the small curvature of the stomach in cardioesophageal junction. The tumor was resected surgically. The pathological diagnosis was considered as a low-grade, secondary, degenerative neuroendocrine tumor. This case demonstrates the importance of rigorous screening of renal transplant donor candidates renal transplant donor candidates should be screened rigorously. In case report a very rare primary mesenteric neuroendocrine tumor, which was detected incidentally during the screenings, is presented in the light of existing literature.

INTRODUCTION

Living kidney donation has become a popular option worldwide due to the long waiting period for a kidney transplant, the increasing need for donated kidney and the higher kidney transplant survival rates. The evaluation of the living kidney donor candidate includes a comprehensive medical, surgical and psychosocial evaluation processes [1]. During the evaluation processes, the donor candidate can be diagnosed with various kidney diseases, diabetes mellitus, hypertension and other diseases that have not been complained of and previously detected [2].

In addition to the endocrine glands, the endocrine system consists of glandular tissues and cells, such as the endocrine cells present in the digestive and respiratory tracts, that have spread to the exocrine cells [3]. Tumors originating from this system are called as neuroendocrine tumors (NETs) [4]. Neuroendocrine tumors are rarely encountered and they grow slowly. Some types of neuroendocrine tumors such as carcinoid tumors, pancreatic neuroendocrine tumors, medullary thyroid cancers, pheochromocytomas are characterized by growing slowly and, frequently vasoactive substances and hormone release [5-7]. These tumors are mostly found in women and in the 5th and 6th decades of life. Having an incidence rate of 2/100.000, they comprise approximately 0.5% of all malignities [8]. In this article, the primary mesenchymal

neuroendocrine tumor, which was detected incidentally during the evaluation of the kidney donor candidate in our transplantation unit, is presented along with the literature review.

CASE HISTORY

A 37-year-old father applied to our renal transplantation unit as a kidney donor candidate for his daughter who had been undergoing dialysis treatment due to renal failure. The donor candidate was complaint-free. He did not have any chronic illnesses previously known and the physical examination was normal. Laboratory test results showed no abnormalities in hematologic, biochemical, serological, immunological and hormonal parameters (Table 1). The data with regard to the lung graph (PA) and thorax tomography were within normal limits. A computed abdominal tomography angiography was carried out in order to view the kidney arteries of the donor candidate. The following findings have been detected: Hepatomegaly, hepatosteatosis, small curvature of the stomach -intravenous contrast agent (IVCA)-a mass was found at the small curvature of the stomach between the mesenteric fat planes with an axial size of 32x29 mm. This mass caused a thrust in the small curvature of the stomach in cardioesophageal junction. Also, a large part of it was calcified and it included a soft tissue component. In addition, a mass lesion with minimal contrast was detected and a few hypodense nonspecific lymph nodes with oval configuration, the largest of which was with a short axis of 9.5 mm, was seen between the intestinal loops and mesentric fat planes (Figure 1).

The donor candidate was removed from list and an evaluation of the patient with a pre-diagnosis of a mass in abdomen was carried out. Tumor markers were found to be within normal limits. Abdominal ultrasonography showed that there was no metastasis in the liver. For mass resection and citologic diagnosis purposes, a surgical resection was carried out. A hard, mobile mass measuring approximately 4 cm was detected in the small stomach curvature diaphragm junction.

Pathological analysis revealed that the excisional material was microscopically 4x3.5x3 cm with a well limited capsule. In its segments, there was a cream white colour mass with a calcified center. It was surrounded randomly by 5 lymph nodes with a diameter of 0,3-0,5 cm in mature fat tissue (Figure 1). In the microscopic analysis it was identified that all of the 5 lymph nodes were reactive. In the mass analysis, it was detected that there was total calcification in some areas and there was calcification intertwined with areas formed by tumoural cells which had a trabecular pattern at low magnification and a sporadical insular growth pattern. The high magnification showed that tumoral cells consisted of a round-oval spindle shaped nuclei with narrow cytoplasm and rough granular chromatin, whose nucleoli were unspecified (Figure 1). Mitosis was rare. There were two examples of mitosis at maximum 10 high magnification areas. No atypical mitosis was recognized. The pathological diagnosis revealed a low-grade, secondary, degenerative neuroendocrine tumor. Considering the primary gastrointestinal neuroendocrine tumor, paraganglioma and gangliocytic paraganglioma, immunohistochemical staining was performed for the differential diagnosis. Immunohistochemistry and histochemistry findings are as follows: Pancytoceratine: Positive, Synaptophysin: Positive Vimentin: Positive, CD 56: focal Positive, CD117: Negative, Kromogranin A: Negative, S100: Negative, SMA: Negative, CD34: Negative, Ki67 prolipheration index 2% and PAS: Positive. In the light of these results, the patient was diagnosed with neuroendocrine tumor of primary mesenteric origin (Figure 2).

Endoscopy and colonoscopy were performed in order to explore the effect of the gastrointestinal system of tumor and to find out primary focus. Pangastritis symptoms were detected in the upper gastrointestinal system endoscopy examination. Colonoscopy results were normal. The echocardiographic examination carried out to check the risk of cardiac failure gave normal results. It was revealed that there were no hormones, neuropeptides or biogenic amines associated with the tumor (Table 2). As a result, the patient was diagnosed with a neuroendocrine tumor of primary mesenteric origin and he was transferred to the medical oncology service.

Table 1. The hematological and biochemical parameters of the patient

Parameters	Results (Normal Range)
Hemoglobin (g/dl)	16.4 (14-18)
Hematocrit (%)	45.5 (36-48)
White blood cell (/µL)	8000 (4000-11000)
Mean corpuscular volume (fl)	82.7 (80-96)
Platelets (/µL)	222000 (140-440000)
Coagulation time (second)	12.7 (9.5-14)
C-Reactive protein (mg/dl)	7 (0-8)
Sedimentation (mm/hour)	6 (8-15)
Urea (mg/dl)	35 (10-45)
Creatinine (mg/dl)	0.9 (0.5-1.2)
Fasting blood glucose (mg/dl)	98 (70-110)

Sodium (mmol/L)	142 (136-145)
Potassium (mmol/L)	4.5 (3.5-5.1)
Calcium (mg/dl)	8.8 (8.4-10.2)
Phosphorus (mg/dl)	3.5 (2.7-4.5)
Cloride (mmol/L)	107 (98-109)
Total bilirubin (mg/dl)	0.5 (0.2-1)
Aspartate transaminase (U/L)	23 (10-40)
Alanine transaminase (U/L)	19 (10-35)
Gamma glutamyl transferase (U/L)	25 (0-50)
Lactate dehydrogenase (U/L)	200 (124-243)
Serum albumin (g/dl)	4.2 (3.5-5.5)

Table 2. Record of tests performed on the patient

Parameters	Results (Normal Range)
Insulin (mU/ml)	8 (3-7)
C-peptide (ng/ml)	3.2 (1.1 - 4)
Calcitonin (pg/ml)	3 (2-5)
Growth hormone (ng/ml)	0.71 (0.06-5)
Cortisol (ng/ml)	10.7 (6-19)
Adrenocorticotropic hormone(ACTH) (pg/ml)	40.2 (5-60)
Thyroid stimulating hormone (mIU/ml)	1.9 (0.27-4.20)
T_3 (Triiodothyronine) Free (pmol/L)	5.43 (3.10-6.80)
T_4 (thyroxine) Free (pmol/L)	14.42 (10.3-23.20)
Cancer Antigen 15-3 (U/ml)	20 (<25)
Cancer Antigen 125 (U/ml)	12 (<35)
Cancer antigen 19-9 (U/ml)	13.5 (<40)
Carcinoembryonic antigen (ng/ml)	2.1 (<4.3)
Alpha fetoprotein (ng/nl)	3.14 (<14)
Homovalinic asit in 24- hour urine(mg)	3.1 (2-6.9)
5-hydroxy indole acetic acid in 24- hour urine(mg)	4.6 (2-9)
Metanephrine in 24- hour urine(μg)	40.8 (74-297)
Normetanephrine in 24- hour urine(μg)	107 (105-354)
Vanilmandelic acid in 24- hour urine(mg)	1.6 (1.4-6.6)

Figure 1. The macroscopic and microscopic images of mass
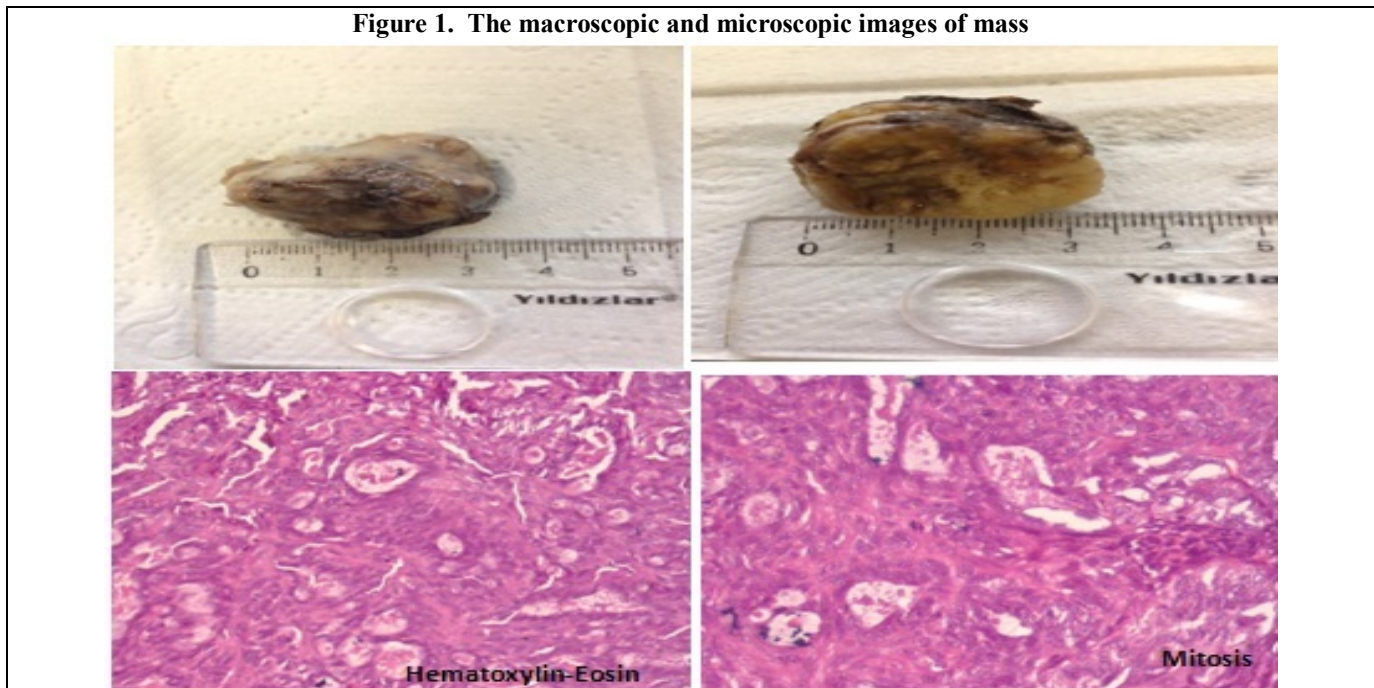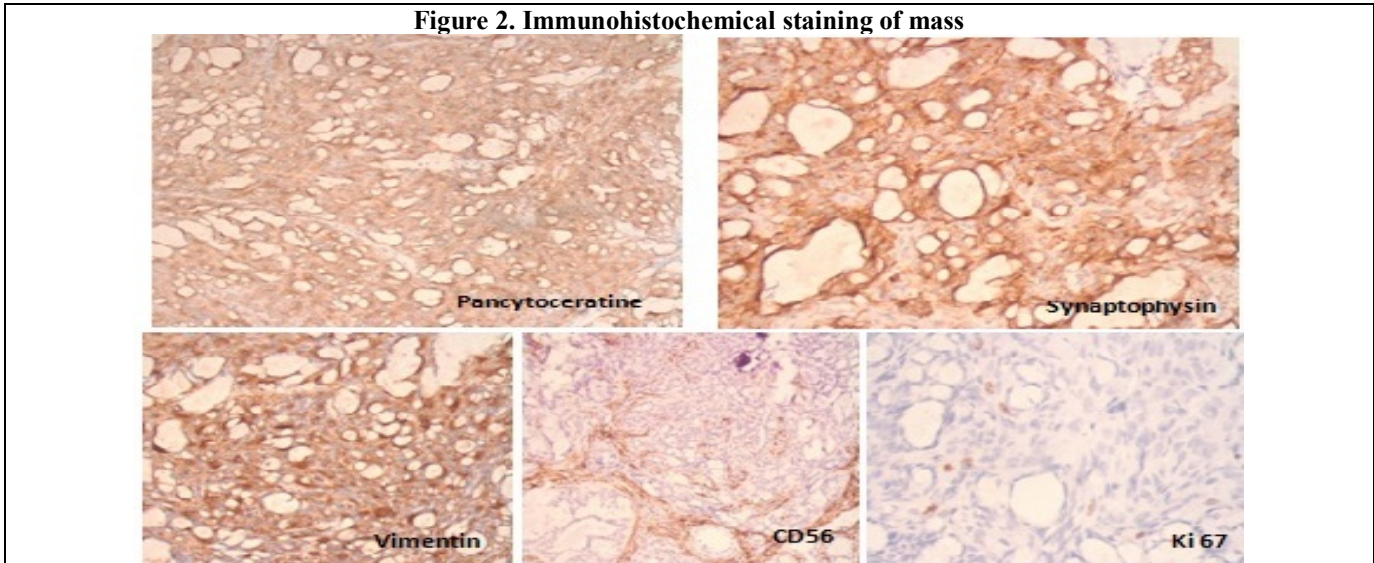
Figure 2. Immunohistochemical staining of mass

DISCUSSION

NETs originate from neuroendocrine cells, which are widely distributed throughout the body. They secrete various substances and hormones. These substanes result in diverse clinical presentations. NETs most commonly involve the lungs and gastrointestinal system. They have also been reported in other sites such as the ovaries, prostate, lymph nodes and cervix [9-12]. Gastrointestinal NETs usually involve the small bowel, rectum, appendix and pancreas. Primary mesenteric NETs are extremely rare and very few cases of primary mesenteric involvement have been reported worldwide [9,12,13]. We report the case of 37-year-old men who was examined as a renal transplantation donor candidate and was diagnosed with primary mesenchymal neuroendocrine tumor based on a calcified mass in abdomen.

The calcified mass found in the abdomen can be a gastrointestinal stromal tumor, a smooth muscle tumor and a tumor with vascular origin, paraganglioma, gangliocytic paraganglioma or a neuroendocrine tumor. Thus, primary source should be always investigated.

Ultrasonography, computed tomography, magnetic resonance imaging, endoscopy, endoscopic ultrasonography can be used in the diagnosis of the tumor. Furthermore, somatostatin receptor scintigraphy, positron emission tomography (PET-CT) and meta-iodobenzylguanidine (MIBG) scintigraphy can also be used in the diagnosis of the tumor. Despite all these imaging methods, in 13% of the neuroendocrine tumor cases the primary focus may not be detected. These tumors develop in less than 5% of the cancers of unknown primary focus [14-15]. To make the diagnosis of mesenteric NETs , one must rule out other primary sites by the use of CT, colonoscopy, small bowel series and scintigraphy [13]. The patient's endoscopy and colonoscopy findings were normal and no metastasis was observed.

Some types of neuroendocrine tumors, such as carcinoid tumors, pancreatic neuroendocrine tumors, medullary thyroid cancers and pheochromocytomas, grow slowly and often excrete hormones with vasoactive substances [5-7]. About 90% of carcinoid tumors occur in the gastrointestinal system and pancreas. These tumors are classified as foregut, midgut and hindgut depending on their embryologic basis. 46-64% of carcinoid tumors are located in the midgut and the majority of the midgut carcinoid tumors occur in the terminal ileum [16]. Although the carcinoid tumors of the primary mesenteric origin are rarely seen, their existence is controversial since most often it can develop in the intestines as primary origin [17]. Mesenteric carcinoid tumors are mostly metastatic. Indeed, midgut carcinoid tumors generally spread to the mesentery. Although this rate changes in each series, it is around 40-80% [18]. Other than the unspecified clinical presentations, such as stomach ache (57%), diarrhea, weight loss, fatigue and bowel obstructions, clinical presentations and syndromes can be revealed with regard to the excessive hormone excretion of the tumors [19]. In the computed tomography, calcification and fibrosis in different degrees are seen in the mesenteric carcinoid tumors (18). In our case, since there were no symptoms and the hormone examinations were within normal limits, it was assumed that there were no vasoactive substances from a hormone secreting neuroendocrine tumor.

Surgical resection of the tumor and pathological diagnosis are essential to identify the tumoral mass. Large tumors progress generally locally and/or cause distant metastasis [16]. Moreover, approximately half of the midgut carcinoid patients develop liver metastasis. Generally, for small tumors that are less than 2 cm in size and without lymph node metastasis, local segmental resection is sufficient [16,20]. For tumors that are larger than 2 cm and with regional mesenteric metastasis and lymph node, large intestinal and mesenteric lymph node dissection and larger excision are needed. In our case, the entire calcified mass and 5 lymph nodes, with a diameter

of 0.3-0.5 cm, which were in fat tissue, were dissected.

Besides the localization of tumoral masses and their morphological images, various specific immunohistochemical stainings are used in order to make a sound diagnosis. While synaptophysin, CD56 and kromogranin strains are the markers of neuroendocrine tumors, pancytoceratine and vimentin can be stained for neuroendocrine tumors along with other tumors. S100 (Leica Novocastra Polyclonal Antibody) staining indicate paraganglioma and gangliocytic paraganglioma; CD117, SMA and CD34 colourings indicate gastrointestinal stromal tumor, smooth muscle tumors and tumors of vascular origin, and calretinin, CK5/6 and Wilms tumor gen-1 staingss indicate the most mesothelioma [21-23].

The pathological examination of the material revealed that due to negative S100 staining, there were no paraganglioma and gangliositic paraganglioma. Also, negative CD117, SMA and CD34 stainings showed that there were no gastrointestinal stromal tumor, smooth muscle tumors and tumors of vascular origin. As for negative calretinin, CK5/6 and Wilms tümör gen-1 stainings, there was no mesothelioma. Based on the positive synaptophysin (Leica Novocastra Mouse Monoclonal Antibody Clone: 27G12) and strong diffus CD56 (Leica Novocastra Mouse Monoclonal Antibody Clone: 1B6) and focal positive, pancytoceratine and vimentin stainings, it was detected that the mass was neuroendocrine tumor. Although chromogranin A (biogenex Mouse Monoclonal Antibody Clone: LK2H10) is another neuroendocrine tumor marker, it was negative in our patient. The proliperation index was detected as 2% after the Ki67 (DakoMouse Monoclonal Antibody Clone: MIB-1) staining. The tests showed that there were no vasoactive substance and hormone releasing neuroendocrine tumor. However, based on the immunohistochemical stainings, neuroendocrine tumor of primary mesenteric origin was detected.

As a result, based on the calcified mass found in the examinations, the renal transplantation donor candidate, who had no complaints of any illnesses, was diagnosed with a very rare neuroendocrine tumor of primary mesenteric origin. This case report shows that a thorough examination of the renal transplantation donor and receiver candidates is crucial.

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