Case Report

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New Diagnosis Diabetes and Deep Venous Thrombosis with Glucagonoma Cases; Case Report

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ABSTRACT

Glucagonomas; is a rare neuroendocrine tumor originating from alpha cells of the pancreas. Glucagonoma syndrome is a paraneoplastic entity known as diarrhea, weight loss, stomatitis, thrombosis, diabetes, and necrotizing migratory erythema. It is difficult to come to mind in the differential diagnosis with the very rarely seen and little known reason. We also wanted to present a patient with bilateral deep vein thrombosis and a new diagnosis of diabetes that we were difficult to diagnose.

Keywords: Deep ven thrombosis, new diagnosis diabetes, glukagonoma, diarrhea

Introduction

Neuroendocrine tumors (NETs) are the tumors originating from the neuroendocrine system in any part of the body. NETs are rare tumors that are mostly benign but may also be aggressive. Today, NETs are divided into two groups as pancreatic NETs and other NETs (1). 60-90% of NETs occur in the gastrointestinal tract and pancreatic system. They are rarely seen in other organs (lung, adrenal gland, thymus, bladder, ovary, testis) (2). Pancreatic NETs, 90-95% of which are insulinoma and gastrinoma, constitute 7% of all NETs. Glucagonoma constitutes only 4% of pNETs (3). 80% of glucagonomas are malignant. It is often sporadic and is associated with genetic factors in 20% of cases (MEN1). Glucagonomas may present with migratory necrotic skin rash (dermatitis), diabetes, depression, diarrhea (4D syndrome), glossitis, stomatitis, angular cheilitis and severe weight loss (4). We present the case because it is a rare entity.

Case Report

Our case was a 72-year-old male patient. The patient was brought to the emergency unit with fatigue, loss of appetite, diarrhea, swelling and redness on the legs. He was admitted to our hospital because his serum glucose level was 553 mg/dL. Lower extremity Doppler ultrasonography (USG) showed bilateral acute deep vein thrombosis (DVT). It was thought that it might be associated with malignancy, especially the pancreas, due to DVT and diabetes newly diagnozed at advanced age. Ca19-9 (655 U/mL) was found to be high in the examinations. Other test results are given in Table 1. Abdominal USG revealed a 81*64 mm mass between the superior of the left kidney and the spleen. Gastroscopy and colonoscopy were unremarkable. In the abdominal computed tomography, there were homogeneously contrasting soft tissue appearances in the spleen lodge and anterior pararenal area, the largest of which was measured as 90x67 mm. A nodular soft tissue density of 13x10 mm was observed in the neighborhood of the superior of the pancreatic corpus. Abdominal magnetic resonance imaging revealed solid mass lesions measuring 80x65 mm in the spleen hilus and 46x40 mm in the medial neighborhood and showing different intensities with the splenic parenchyma (Figure 1, 2). The patient was aspirated with two 22 G from the paraaortic area with the help of endoscopic US, and smear and cell block were prepared. The liver was aspirated from a 50

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Table 1. Patient results

	13.03.2018	31.03.2018	02.04.2018	23.04.2018	Referans değer	
Glucose	183	500	183	159	70-105	mg/dL
BUN	22	29	84	24.3	8.4-25.7	mg/dL
Creatinine	0.96	1.46	3	1.07	0.72-1.25	mg/dL
Uric acid	3.3		11.2	3.3	3.5-7.2	mg/dL
T. Protein	5.3		4.9	5.5	6.2-8.1	gr/dL
Albumin	3.0		2.2	2.7	3.4-4.8	g/dL
AST	29	48	39	11	5-34	U/L
ALT	61	49	50	11	0-55	U/L
ALP	110	157	129		40-150	U/L
GGT	36	34	49		12-64	U/L
LDH	219	498	382	192	125-220	U/L
CK	34		189	15	30-200	U/L
T. BİL	0.50	0.79	0.38	0.42	0.3-1.2	mg/dL
D. BİL	0.17	0.16	0.28	0.20	0-0.5	mg/dL
Amylase	90		30		20-160	U/L
Lipase	9		14		8-78	U/L
Calcium	8.2		7.8	6.8	8.4-10.2	mg/dL
Magnesium	2.27			1.37	1.6-2.6	mg/dL
Phosphorus. inorg	2.0			2.1	2.3-4.7	mg/dL
Na	136	134	142	138	135-145	mmol/L
K	4.48	5.17	4.43	3.01	3.5-5.1	mmol/L
Cl	107		112	107	98-107	mmol/L
Folic acid	5.4		5.0		3.1-20.5	ng/mL
B12	503				157-883	pg/mL
Ferritin	620		3397		21.81-274.66	ng/mL
CK-MB			4.3		0-7.2	ng/mL
Troponın I			30		0.40	pg/mL
D-Dimer			4449		0-300	ng/mL
PTH	63		247		15-68.3	pg/mL
CRP	7.2	21	25	5.37	<0.5	mg/dL
Procalcitonin	0.6		335	2.94	<0.5	ng/mL
ESR	15		71		<20	mm/h
Hb	9.8	9.65		8.55	14.1-17.5	g/dL
Hct	10	30.3		25.7	40-52	%
MCV	87	87		85	80-97	fL
WBC	7500	14900		7540	4.6-10.2	10*3/mL
PLT	158.000	222.000		158.000	142-424	10*3/mL
Glukagon				>500	<209	pg/
TSH	0.26				0.35-4.94	mIU/mL
CEA	3.52				0-5	ng/mL
Ca19-9	655.54				0-37	U/mL
C-peptide	2.82				0.78-5.19	ng/mL

AST: Aspartate transaminase, ALP: Alkali phosphatase, ALT: Alanine transaminase, GGT: Gamma-glutamyl transpeptidase, LDH: Lactate dehydrogenase, CK: Creatine kinase, T. BİL: Total bilirubin, D. BİL: Direkt bilirubin, Na: Sodium, K: Potassium, Cl: Chlorine, CK-MB, Creatine kinase myocardial isoenzyme, PTH: Parathyroid hormone, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean erythrocyte volume, WBC: White blood cell, PLT: Platelets, TSH: Thyroid-stimulating hormone, CEA: Carcinoembryonic antigen, BUN: Blood urea nitrogen

mm cyst and carcinoembryonic antigen (CEA), amylase and cytology were sent for evaluation. In the cyst fluid, amylase value was found as 15 and CEA as 0.9 ng/mL. After the treatment of the patient was arranged and glycemic regulation was achieved, he was discharged for outpatient follow-up of biopsy results. However, the patient was admitted to the emergency service again and hospitalized in the clinic after twelve days because of deterioration in his general condition and swelling of his feet. The patient's previous biopsy result was evaluated as 'fine-chromotine neuroendocrine cell groups'. At this time, diarrhea and rashes on the lower extremities developed (Figure 3) and the patient was thought to have glucagonoma. Serum glucagon was >500 pg/mL (N<209 pg/mL). Surgery was recommended to the patient, but the patient and his relatives did not accept this recommendation. By the department of oncology, lanreotide was initiated to be administered every 28 days. Within days, the need for insulin decreased. The patient is still being followed up in the outpatient clinics of general internal diseases and oncology with lanreotide, glargine insulin and coumadin treatment.

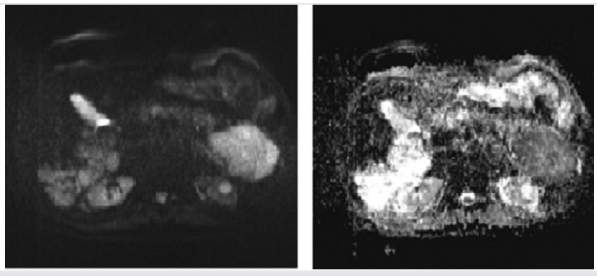

Figure 1. Abdominol MR image 1
MR: Magnetic resonance

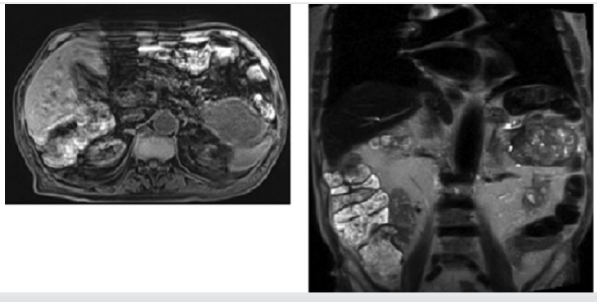

Figure 2. Abdominol MR image 2
MR: Magnetic resonance

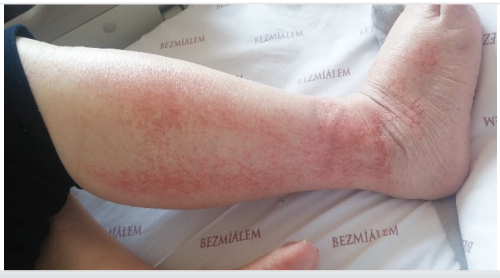

Figure 3. Lower extremity skin rash

Discussion

NET incidence is two per million and constitutes 0.5% of all cancers. It should be noted that NETs may coexist with other solid organ cancers. The gastrointestinal tract is the largest neuroendocrine system in the body, and NETs are often localized here. Gastroenteropancreatic NET (GEP-NET) cells are caused by diffuse endocrine system cells, which are phenotypically similar. These tumors are referred to as Neuroendocrine because they express proteins such as synaptophysin, neuron-specific enolase (NSE) and chromogranin A associated with neural cells. 65% of NETs occur in the gastrointestinal tract, 25% in the lungs, and the rest in other endocrine tissues. Clinical findings vary depending on the location of the NETs and the hormone that they secrete. Diagnosis is made by elevated blood glucagon level. The diagnosis is supported by the measurement of chromogranin-A (CgA) levels, 5-HIAA, CA19-9 and CEA levels. CgA has a sensitivity of 80% and specificity of 90% and has a better diagnostic value than 5-HIAA, NSE and pancreatic polypeptide. Plasma NSE identifies poorly differentiated NETs with 85% specificity and 70% sensitivity (5). Mitosis rate and ki-67 index are well below 2% in well-differentiated NETs and necrosis is not seen, whereas in poorly differentiated group, these rates increase above 10% and necrosis can be seen (6). Pancreatic NETs are also classified according to the hormones they secrete and they are called insulinoma, gastrinoma, glucagonoma, VIPoma. It can also be classified as local, regional and distant spread according to the extent of the disease. NETs may occur with metastases below 2 cm. Similarly, the rate of metastasis was 50% at the time of diagnosis (7). The metastasis rate is determined by the organ from which the tumor originated. Glucagonomas are located in the distal pancreas at a rate of 85%. In our case, the patient was examined considering GIS malignancy initially because there were weight loss, anemia, and DVT, and Ca19-9 was high (8). Abdominal imaging revealed a mass between the spleen and kidney; therefore, biopsy was performed under endoultrasonography. Meanwhile, basal-bolus insulin therapy for glycemic regulation and coumadin therapy for DVT were performed. After stabilization of the patient, he was discharged for outpatient follow-up. Then, the patient was brought back to the emergency unit due to deterioration of his general condition. Meanwhile, diarrhea and non-necrotic erythematous skin rash on the right leg were added to the complaints. In the immunohistochemical study of the previous biopsy, chromogranin (+), synaptophysin (+), pancytokeratin (+), LCA (-), ki 67 index was less than 1%. Results were evaluated to be consistent with neuroendocrine tumor (Grade I). Glucagon level sent to support the diagnosis was found to be significantly higher (9). Surgical intervention was planned but was not accepted. As a result of the consultation with oncology, lanreotide treatment was planned (10). After the treatment, his general condition recovered and glycemic regulation was achieved. The patient was discharged for follow-up in the outpatient clinics of oncology and general internal medicine.

We wanted to emphasize that glucagonoma should be considered in cases with newly diagnosed diabetes and DVT, erythematous

skin lesions, diarrhea and a mass in the abdomen and examinations for it should be performed.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Consept: T.K., C.K., Design: T.K., C.K., Data Collection or Processing: T.K., C.K., Analysis or Interpretation: T.K., C.K., Literature Search: T.K., C.K., Writing: T.K., C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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