

Glucagon-producing mucinous tubular and spindle cell variant of renal cell carcinoma with paraneoplastic diabetes: Case report and review of literature

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ABSTRACT

Renal cell carcinoma (RCC) is known as the internist tumor because of the myriad paraneoplastic manifestations associated with it. One of the rarely described paraneoplastic manifestations associated with this malignancy is hyperglycemia. Only 11 cases in the English and Japanese literature have been reported. We report the occurrence of paraneoplastic hyperglycemia with a rare variant: mucinous tubular and spindle cell variant of RCC. To the best of our knowledge, the association of paraneoplastic hyperglycemia with this variant has not been reported earlier.

INTRODUCTION

Renal cell carcinoma (RCC) has been called the “internist tumor” because of paraneoplastic manifestations associated with it. These manifestations have been reported in around 20% of cases of RCC.^[1] Hyperglycemia associated with RCC has been rarely reported. To the best of our knowledge, paraneoplastic diabetes mellitus (DM) with mucinous tubular and spindle cell variant of RCC has not been reported.

CASE REPORT

A 63-year-old female, a known diabetic for 4 years, on metformin 500 mg twice a day with a hemoglobin A1C (HbA1c) of 7.0%, presented with hematuria and passage of clots in the urine. Examination revealed a 13 cm × 11 cm left abdominal mass which was confirmed on contrast-enhanced computed tomography (CT) to be of renal origin [Figure 1a]. The patient underwent open radical nephrectomy. Grossly, the tumor was seen to replace the whole of the left kidney. On cut

section, it appeared to be homogenous gray to white with shiny mucoid areas [Figure 1b]. Postoperative convalescence of the patient was good, and the patient maintained normal glycemic control without any hypoglycemic agents during the hospital stay. Histopathology of the specimen revealed mucinous spindle and tubular (MTS) cell variant of RCC (pT2bN0M0) [Figure 1c-e]. On subsequent follow-up for 2 years, she was found to be normoglycemic with HbA1c ranging from 5.5% to 5.7% and had no recurrence on follow-up imaging with contrast-enhanced CT. This prompted further evaluation of the tumor specimen. The tissue blocks were subjected to available immunohistochemical (IHC) markers: adrenocorticotrophic hormone (ACTH), glucagon, insulin, and growth hormone (GH). Staining was positive for glucagon [Figure 1f].

DISCUSSION

MTS variant has been recognized as a rare distinct variant of RCC in 2004 by the World Health Organization.^[2] It is characterized by a mixture of cuboidal cells in tubules and

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sheets of spindle cells and variable amounts of mucinous stroma. Pathologically, the tumor is considered a low-grade carcinoma with an indolent clinical course.^[3] The tumor affects patients in the age range of 13–82 years with a female predominance (4:1).

In our case, the patient became normoglycemic following radical nephrectomy and remained so during follow-up. The staining of the tumor tissue for glucagon on IHC further substantiates the causal relationship of the renal mass with this paraneoplastic hyperglycemia.

As this association was not assumed preoperatively, we do not have the serum glucagon levels in this patient. Staining for other markers such as ACTH, GH, and insulin was negative. PubMed/MEDLINE search did not reveal any study, in which glucagon staining of normal renal parenchyma or RCC tissue was done. Probably, there was no rationale or indication for performing this test in nondiabetic individuals with renal tumor.

MEDLINE/PubMed search revealed 11 cases of either new-onset diabetes (6/11) or worsening of preexisting diabetes (5/11) in patients with RCC. The patient details and tumor characteristics are shown in Table 1. The mean age of the patients was 61 years (range 35–71 years). Ten out of 11 cases were above the age of 50 years. This age group overlaps the common presenting age of Type II DM. Synchronous metastasis was noted in one patient, and one patient developed metastasis on follow-up associated with the reappearance of diabetes. Seven out of the 11 reported cases achieved

normoglycemia postoperatively without oral or injectable hypoglycemic agents. In two patients, there was a reduction in the insulin requirement and two others maintained normal sugar profiles on oral agents. Paraneoplastic hyperglycemia was reported with a variety of histologic subtypes of RCC: clear cell ($n = 3$), alveolar variety of clear cell ($n = 2$), granule cell ($n = 1$), papillary ($n = 1$), and not specified ($n = 4$). To the best of our knowledge, our case is the first reported association of hyperglycemia with MTS variant.

Paraneoplastic manifestations are related to the release of certain substances by the tumor. A variety of mechanisms have been proposed to explain the pathogenesis of tumor-related hyperglycemia as a paraneoplastic manifestation [Table 1 and Figure 2]. Palgon *et al.*^[4] hypothesized that diabetes in a case of renal carcinoma could occur due to the release of hormones that antagonize the effects of insulin or promote gluconeogenesis. Thus, tumor production of GH, glucagon, ACTH, and/or prolactin could be a possible mechanism.

Modulation of the immune system with the development of autoimmune responses has also been proposed as a plausible mechanism. Elias^[5] reported the development of insulinopenic diabetes in their patient due to elevated titers of antiglutamic acid decarboxylase antibodies (anti-GAD) and anti-islet cell antibodies. Production of biologically inactive but immunologically active insulin by the tumor might initiate the development of auto-islet cell antibodies culminating into the destruction of the pancreatic islet cells with consequent derangement in glycemic control.

The association between hyperglycemia and tumor production of interleukin (IL) 6 has been suggested.^[6,7] The normalization of glycemic control and IL6 levels postnephrectomy with worsening of both parameters concomitantly with the development of lung metastasis in a 59-year-old male with RCC pointed toward the possible

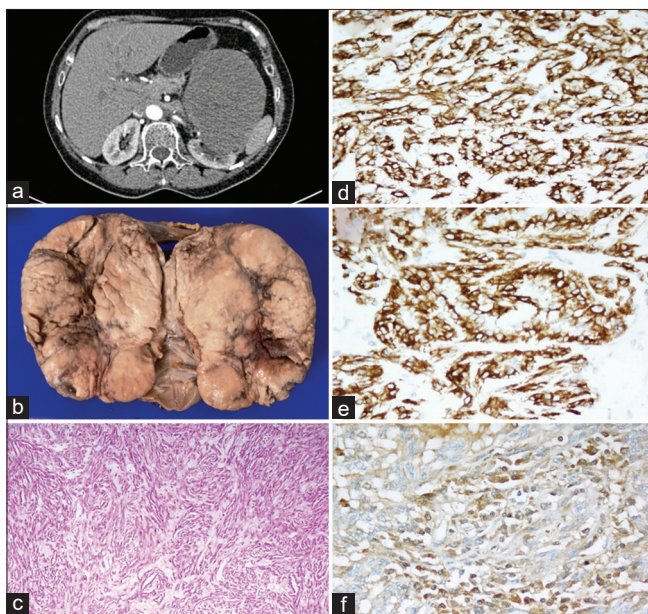


Figure 1: (a) Arterial phase axial section demonstrating relatively hypovascular homogenous solid tumor involving the left kidney, (b) On cut section, the tumor is homogenous and is completely replacing the renal parenchyma and is seen bulging out. Photomicrographs showing (c) Tumor composed of a mixture of tubular and spindle cells separated by a variable amount of mucinous stroma (H and E, ×200). Tumor cells are positive for CK7 (d), EMA (e) and glucagon (f)

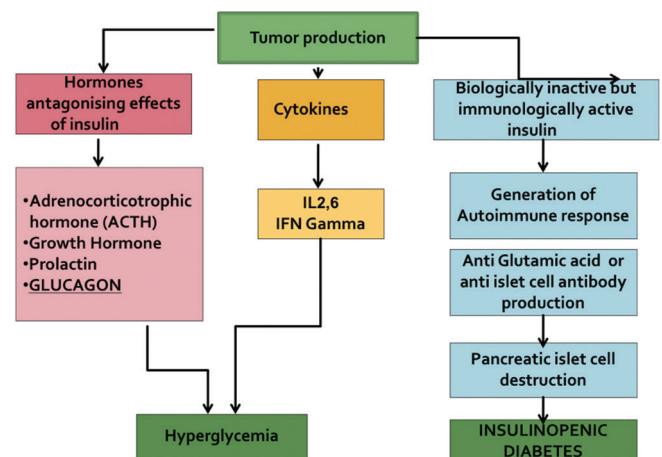


Figure 2: Flow chart summarizing plausible pathogenesis of paraneoplastic diabetes

Table 1: Depicting cases of new-onset diabetes or worsening of preexisting diabetes in patients with renal cell carcinoma, demographics, pre- and post-nephrectomy glycemic controls, histopathological findings, and plausible mechanisms proposed

Year	Author	Age	Sex	Presentation	Diabetes treatment		Histology	Metastasis	Etiology
					Pre-nephrectomy	Post-nephrectomy			
1981	Pavelić and Popović ^[9]	59	Female	New onset	NA	Cured	Not specified	Synchronous (liver, lung, bone)	Increased serum and tissue glucagon levels
1986	Palgon <i>et al.</i> ^[4]	67	Female	New onset with hyperglycemic coma	Insulin	Cured	Clear cell	No	Not found
1993	Jobe <i>et al.</i> ^[10]	66	Male	New onset, DKA	NA	Cured	Clear cell	No	Not found
1996	Matsumura <i>et al.</i> ^[11]	71	Male	Worsening of preexisting diabetes	Insulin	Cured	Alveolar type clear cell	No	Not found
1999	Callewaert <i>et al.</i> ^[12]	35	Male	Worsening of preexisting diabetes	Insulin	Improved: Reduced insulin dose	Papillary		Not found
2002	Macaulay <i>et al.</i> ^[13]	69	Male	Worsening of preexisting diabetes	OHA (gliclazide and metformin) and insulin	Improved: OHA (gliclazide only)	Clear cell	No	Not found
2003	Kazuhisa <i>et al.</i> ^[6]	59	Male	Worsening of preexisting diabetes	Insulin	Cured (restarted again with metastasis)	Granule cell carcinoma right, left mixed	Metachronous: lung	Raised serum IL-6, Tissue: IL-6 staining positive
2004	Yumura <i>et al.</i> ^[7]	61	Female	Worsening of preexisting diabetes	Insulin	Cured	Alveolar clear cell	No	Not found
		64	Female	New onset, DKA	Insulin	Cured	Not specified	No	Tissue IL6 staining +
2005	Elias ^[5]	52	Female	New onset, DKA	Insulin	Improved: Reduced insulin dose	Not specified	No	Anti-GAD and anti-islet cell antibody
2016	Harada and Hara ^[8]	68	Female	New onset	Insulin	Improved: OHA	Not specified	No	Not found

DKA: Diabetic ketoacidosis, NA: Not available, OHA: Oral hypoglycemic agents, IL: Interleukin, GAD: Glutamic acid decarboxylase

causal association. Thus, in patients who experience improvement of glycemic control or resolution of diabetes posttreatment, regular sugar monitoring may be used as a marker to predict tumor recurrence. Other paraneoplastic manifestations of RCC such as anemia, deranged liver enzymes, and fever have also been found to be due to the production of IL6 by the tumor. It has been suggested that RCC should be kept as a differential diagnosis in patients presenting with these paraneoplastic manifestations and hyperglycemia.^[8]

CONCLUSION

The return of glycemic control after tumor removal and the staining of the tumor tissue for glucagon indicate the causal relationship of the renal mass with this paraneoplastic manifestation. There have been 11 cases of either *de novo* diabetes or worsening of preexisting diabetes in patients with renal carcinoma. To the best of our knowledge, this is the first case of mucinous tubular and spindle cell variant of RCC causing paraneoplastic DM.

Informed consent

Written and informed consent has been taken from the patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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