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Dates: Received: 06 June, 2016; Accepted: 27 June, 2016; Published: 29 June, 2016

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www.peertechz.com

ISSN: 2455-5282

Keywords: Solid-pseudopapillary tumour; Pancreas; CCK; CCK-2/gastrin-R; North African woman

Case Report

CCK-2/Gastrin-R Immunodistribution in a Solid Pseudopapillary Pancreatic Tumor: A Case Report of a 28-Years-Old North African Woman

Abstract

The presence of a large bulky pancreatic tumour in a young female should raise suspicions of the diagnosis of solid-pseudopapillary tumour of the pancreas.

Solid pseudopapillary neoplasms of the pancreas are uncommon, accounting for only 1-2% of all pancreatic neoplasms. These tumors are being detected at an increased rate, probably due to the increased awareness and the liberal use of imaging.

We report a case of a 28-year-old North African woman with no prior medical or surgical history diagnosed with solid pseudopapillary pancreatic tumor. Our immunohistochemical study demonstrated that the tumor cells were positive for CCK-2/gastrin receptors and that were highly expressed within the cytoplasmic area of the cells. Hence we attempted to raise a hypothesis and to establish a link between some female hormones which represents powerful regulators of the expression of CCK and their possible impact on the development of solid pseudopapillary pancreatic tumours in young women.

Introduction

Solid Pseudopapillary Tumor (SPT) of the pancreas is a very rare entity with a reported incidence of 0.13% to 2.7% of all pancreatic tumors [1], this tumor was once described in many other terms, such as Frantz's tumor, solid and cystic tumor, papillary cystic neoplasm, and solid and papillary epithelial neoplasm [2].

It is almost exclusively seen in females and occurs in the second or third decades of life [3], suggesting that this tumor is associated with some female hormones and their receptors such as estrogen, progesterone and opioids [4,5]. Several lines of evidence support the role of G protein-coupled receptor cholecystokinin 2 and gastrin (CCK-2R/gastrin-R) in pancreatic cancer development [6,7].

In order to study immunohistochemical features of G protein coupled CCK2/gastrin receptors in this kind of rare tumors, we herein present a case of solid pseudopapillary pancreatic tumor associated with a positive CCK-2/gastrin-R reactivity.

Case Report

A 28-year-old North African woman with no prior medical or surgical history presented with complaints of epigastric and right upper quadrant (RUQ) pain and decreased appetite during one month. Her pulse rate was 72 min⁻¹ and her blood pressure was 110/60 mmHg. There was no precipitating or aggravating factor and no evidence of jaundice. On physical examination her abdomen was soft, non-tender and non-distended; there were no palpable masses and bowel sounds were audible. Other physical examinations

were unremarkable. Laboratory data including hematology, blood chemistry including amylase and lipase, as well as tumor markers were within the reference limits (CEA = 0.692 ng/ml, CA 125 = 12.27 U/ml, and CA 19-9 = 22.59 U/ml).

Ultrasound imaging (Figure 1) showed a solid heterogeneous mass at the level of left quadrant measuring 124 mm.

CT scan of the abdomen (Figure 2) revealed a voluminous hypoattenuating mass in the tail and the body of the pancreas, measuring 127mm x 87mm with multiple intratumoral vessels.

After a surgical biopsy was performed; histological examination demonstrated a solid pattern with non infiltrant pseudopapillary cores; the tumor was found to be confined to the pancreas (Figure 3). Our immunohistochemical analysis revealed that the tumor cells



Figure 1: Ultrasound imaging showing a solid heterogeneous mass measuring 124 mm.

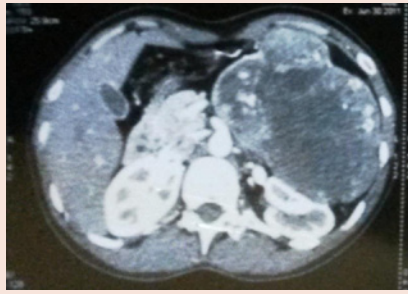


Figure 2: CT scan of the abdomen showing a voluminous necrotic mass in the tail and the body of the pancreas measuring 127mm x 87mm.

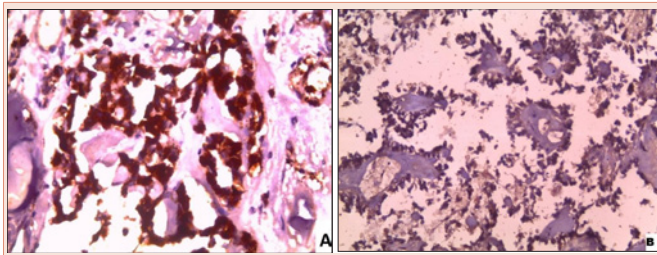


Figure 3: Histological examination demonstrating a solid pattern with non infiltrant pseudopapillary cores; and the immunohistochemical analysis is revealing that the tumor cells are positive for CCK-B receptors which were highly expressed within the cytoplasmic area of the cells; **a** (magnification x400) **b**(magnification x200).

were positive for CCK-2/gastrin receptors that were highly expressed within the cytoplasmic area of the cells. (Figure 3). The next strategy for patient treatment was chemotherapy.

Discussion

Solid pseudopapillary tumors of the pancreas affect primarily young women, suggesting that hormonal factors contribute to the tumor growth [4,5,8]. In the current study, symptoms were reported at a woman of 28 years of age, an age at which female hormones and their receptors such as progesterone, estrogen are very active and might play a role in the development of solid pseudopapillary tumor of the pancreas [9,10].

Pancreatic cancer risk was elevated in women with early age at menarche, as noted previously [11,12], sex steroid receptors in normal and neoplastic pancreatic tissue have been found in animals and in humans [13,14]; the incidence of pancreatic cancer is lower in female than in male rodents [15], and estrogens and/or castration have an inhibitory effect on the early stages of pancreatic carcinogenesis [16].

Some epidemiological studies have assessed the role of hormone-related factors in the etiology of pancreatic cancer [11,12].

The exact cell of origin is still disputed [17], the strong female predilection [18,19] and the reported expression of progesterone receptors in some SPT cases [20], may suggest an association between female sex hormones and tumorigenesis, but a causal relationship has not been definitively proven. Yeh et al., have reported that the

progesterone receptor is uniquely expressed in solid pseudopapillary tumors while both estrogen and progesterone receptors are expressed in mucinous cystic neoplasm [21].

Zamboni et al. [22], attempted to give an explanation about pancreatic tumors that affect women by stating that pancreatic anlagen are very close to the genital ridge during embryogenesis. Primitive ovarian tissue may be incorporated into pancreatic tissue during the process of pancreatic fusion, after which dislocated ovarian tissue may start growing in response to female hormones during adolescence. Indeed, immune-profiles of pancreatic tumors which affect women are similar to those in certain ovarian tumors [22,23].

Our case showed that pancreatic tumor cells were positive to CCK-2R/gastrin-R according to our immunohistochemical study. Several studies has shown that CCK-2R/gastrin-R are present in pancreatic tumor cell lines and that exogenous administration of CCK to pancreatic cancer cells stimulates growth [24-26], however the role of CCK as an autocrine growth regulator in pancreatic cancer has not been examined.

In addition, it was reported in Elas-CCK2 transgenic mice, expressing functional human CCK-2R in pancreatic exocrine cells, an increased pancreatic growth, an acinar to ductal trans-differentiation, postulated to be a preneoplastic step in pancreatic carcinogenesis and the development of tumours [27,28].

We may explain the important rate of CCK-2R/gastrin-R in the solid pseudopapillary pancreatic tumor especially in young women by the interaction between cholecystokinin and female hormones; mainly estrogen and opioids.

Micevych et al., concluded that estrogen plays the role of a powerful regulator over the expression of CCK after the results of their studies showed that estrogen reduces CCK binding within 24 hr of treatment. The same research team have examined as well the estrogen modulation and its interactions in the hypothalamus and limbic system where opioids exert a dual regulation on the release and expression of CCK to modulate reproductive behavior and found that CCK-opioids reciprocal interactions modulated by estrogen state influence the response of mammals to stimuli altering reproduction, memory/learning and perception of pain in case one of those hormones is deregulated [29].

In summary, referring to our results and those of Micevych et al. [29], Zamboni et al. [22], Matters et al. [26] Yeh et al. [21], we may raise the following hypothesis: Solid pseudopapillary tumors of the pancreas affect mostly young women at an age when female hormones and their receptors are very active [9], however; unlike progesterone; estrogen was not found to be expressed in solid pseudopapillary pancreatic tumors [21,30,31], knowing that there are no doubt estrogen receptors and estrogen-binding protein are expressed in human healthy pancreas [32]. Estrogen represents as well a powerful regulator of the expression of CCK since it decreases cholecystokinin binding [29]. Thus if estrogen is down regulated; CCK binding would increase; and CCK-2/gastrin receptors would be overexpressed; and as Matters et al. reported this may lead cholecystokinin to play the role of a growth factor for human pancreatic cancer [26].

Conclusion

Solid pseudopapillary pancreatic tumors cells overexpress G protein coupled CCK-2/gastrin receptors that could be very interesting biomarkers for SPT diagnosis and target therapies.

Acknowledgments

The authors would like to thank the members of pathology department of Sidi bel Abbas hospital for their invaluable support, guidance, and educational insight.

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Citation: Sellam F, Harir N, Mrabent NM, Tou A, Belkralladi H, et al. (2016) CCK-2/Gastrin-R Immunodistribution in a Solid Pseudopapillary Pancreatic Tumor: A Case Report of a 28-Years-Old North African Woman. *Global J Med Clin Case Reports* 3(1): 015-017. DOI: 10.17352/2455-5282.000026