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Prikaz slučaja/
Case Report

SYNCHRONOUS ENDOCRINE MICROADENOMATOSIS WITH WELL DIFFERENTIATED NEUROENDOCRINE TUMOR OF PANCREAS

ENDOKRINA MIKROADENOMATOZA SA NEUROENDOKRINIM TUMOROM PANKREASA

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Ključne reči
pankreas, mikroadenomatoza, NET

Abstract
Introduction: Endocrine microadenomatosis is defined as the presence of multiple, usually innumerable, microadenomas. Endocrine microadenoma is a neuroendocrine neoplasm measuring less than 5mm in size. **Case report:** This article showed pathohistological case report of pancreatic endocrine microadenomatosis in addition to synchronous well differentiated neuroendocrine tumor of the pancreas in 49-year-old female patient. Histological appearance of tumor was typical and was positive to neuroendocrine immunohistochemical antibodies. **Conclusion:** Pancreatic endocrine microadenomatosis in addition to synchronous well differentiated neuroendocrine tumor of the pancreas is rare, so this case is presented.

INTRODUCTION

Endocrine microadenomatosis is defined as the presence of multiple, usually innumerable, microadenomas (1). Endocrine microadenoma is a neuroendocine neoplasm mesuring less than 5mm in size. Microadenomatosis of neuroendocrine cell is considered as a hallmark of MEN1 or VHL and occasionally can occur in individuals without an apparent genetic syndrome (1). Rarely, it is accompanied with synchronous pancreatic adenomas (1).

This case report presents pancreatic endocrine microadenomatosis in addition to synchronous well differentiated neuroendocrine tumor of the pancreas.

CASE REPORT

For pathohistological analysis it was received irregular resection of the body and tail of the pancreas of a 49-year-old female. The surgery was indicated because of the clinical and objective signs that were referring to insulinoma localized in cauda pancreas.

Macroscopically, the material corresponded to the lobular, glandular tissue, gray pink color, whose dimensions were 7x3x0.9 cm. On serial cutting of the material it was found demarcated, pale pink colored node that measured 0.3x0.7x0.1cm.

After fixation in formaldehyde, described node with surrounding tissue of pancreas was taken in eight paraffin blocks for pathohistological analysis, which were processed by a standard histological technique, stained with hematoxylin and eosin (Figure 1a). Histologically, described node revealed as encapsulated tumor with surrounding fat tissue, in diameter about 1cm. Tumor cells were uniform and oval with small amount of cytoplasm without mitotic activity. Nuclei of the cells were oval with granular chromatin – type „salt-and-pepper" chromatin (Figure 1b). Tumor cells were arranged in trabecular growth pattern between which there was a well-vascularized hyaline stroma. Necrosis in the tumor was not found.

In addition to the described node it was also found several small nodes in pancreas with absence of capsule to surrounding tissue and in diameter up to 5mm, which were the same histologic characteristics as the encapsulated tumor (Figure 1c).

Immunohistochemically, both cells from the tumor and from the small nodes showed positivity for Synaptophysin, Chromogranin and negativity for p53. Ki67 showed reactivity in tumor node (proliferative activity was less than 2%) and negativity in all small nodes (Figure 1d, 1e, 1f).

Based on the pathohistological appearance and immunohistochemical characteristics of lesions the pathological diagnose was pancreatic endocrine microadenomatosis with additional synchronous well differentiated pancreatic neuroendocrine tumor (G1).

DISCUSSION

Neuroendocrine tumors are arising from diffuse neuroendocrine system (DNES). Into the pancreas this type of tumor develops from Langerhans islet cell and it is the second commonest neoplasm of pancreas, representing about 5% of all pancreatic tumors [1, 3].

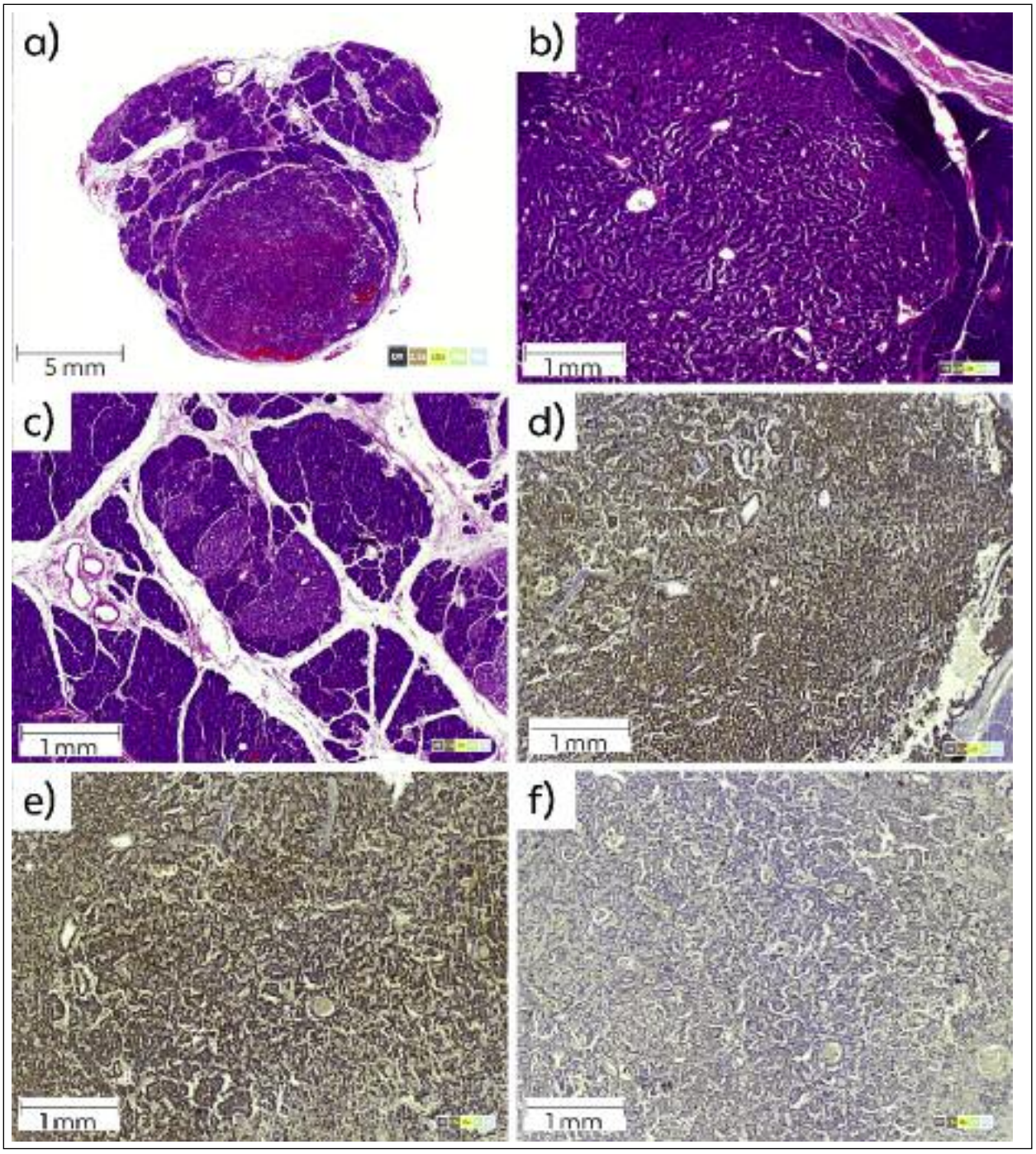

Figure 1: *a) Microphotography of endocrine microadenomatosis and neuroendocrine tumor of pancreas (HE, loupe); b) Microphotography of neuroendocrine tumor of pancreas (HE, 2.5x); c) Microphotography of endocrine microadenomatosis of pancreas (HE, 2.5x); d) Microphotography of tumor cells immunoreactivity for Synaptophysin (Synaptophysin, 2.5x); e) Microphotography of tumor cells immunoreactivity for Chromogranin (Chromogranin, 2.5x); f) Microphotography of tumor cells immunoreactivity for Ki 67 (Ki 67, 2.5x).*

Adult nesidioblastosis was first reported in 1980, a few cases have been reported in association with pancreatic tumors [2].

All neuroendocrine tumors, such as neuroendocrine tumors of the pancreas, World Health Organization (WHO) classified into three grade groups based on mitotic activity and Ki-67 index: grade 1 – low grade (G1) or well differentiated; grade 2 – intermediate grade (G2) or moderately differentiated and grade 3 – high grade (G3) or poor differentiated and according to aggressiveness of the neoplasms or rate of growth and spread (4-6). The pancreatic neuroendocrine tumor in this case had fewer than two mitotic figures per 10 HPF and a Ki67 index of <3% so it was diagnosed as low-grade (G1) pancreatic neuroendocrine neoplasm.

Neuroendocrine tumors occur in sporadic forms in 90% of all cases. However, about 10% of them are associated with familial syndromes such as: multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), tuberous sclerosis complex (TSC) and glucagon cell adenomatosis (GCA) (3).

Histologically, PNETs are well demarcated, soft tumors, usually with surrounding capsule or invasion into pancreatic tissue. Tumor cells can be different in size, with granular cytoplasm and nuclei which are round to ovoid with „salt and pepper" chromatin [1, 5]. These characteristics are in accordance with the presented case.

Immunohistochemically any NET must be positive for neuroendocrine markers such as Synaptophysin and Chromogranin and other such in presented case [1].

Possible histological manifestations of disease of neuroendocrine cells in pancreas are microadenoma or microadenomatosis or hyperplasia of Langerhans islets [1].

Endocrine microadenoma is a neuroendocrine neoplasm measuring less than 5mm in size. Endocrine microadenomatosis of pancreas is defined as the presence of multiple, usually innumerable, microadenomas[1]. Beside on pancreatic morphometry in a clinical specimen, the diagnosis of pancreatic endocrine cell hyperplasia is often subjective [7]. Most would regard an islet size large than 250μm in diameter and an increase in islet number as evidence of pancreatic endocrine cell hyperplasia in contrast of Rindi et al. These autors define pancreatic endocrine cell hyperplasia as an expansion of the endocrine cell mass to more than 2% (in adults) or 10% (in infants) of the total pancreas mass (8).

Focal endocrine hyperplasia and microadenomas are not uncommon incidental pathological findings in the pancreas; if carefully screened, up to 10% of adults harbor these lesions at autopsy [9].

Pancreatic endocrine cell hyperplasia can be non-specific and involve most or all types of islet cells or specific and involve predominantly one cell type [7] but endocrine microadenomatosis is exclusively proliferation of β cells [1].

As a NET and microadenomas of pancreas, microadenomatosis usually occurs in association with familial syndromes, firstly MEN1 and VHL syndrome [10, 11]. Occasionally it can occur in individuals without an apparent genetic syndrome[1].

Endocrine hyperplasia, dysplasia and microadenoma, however, are not uncommon findings in the pancreas but still not known does these lesions are monoclonal or pancreatic endocrine cell hyperplasia represents precursor lesions for pancreatic neuroendocrine tumors [1, 7].

Clinically as only a select number of diagnosed adenomas eventually develop while with are numerous microadenomas. There have been no reports of similar precursor lesions for sporadic PNETs. It is possible that the additional mutations have to accrue to form larger and clinically significant pancreatic neuroendocrine tumors (PNETs). Although most of these lesions probably do not indicate clinical significance, they could represent precursor lesions giving rise to sporadic PNETs, since all clinical PNETs have to pass through a microadenoma stage during their growth. It is thus possible that PNETs develop from precursor (pre-malignant) lesions such as hyperplasia and microadenoma in familial PNET syndromes and at least partly in sporadic cases. The key question of what additional genetic changes are needed to transform a microadenoma to a clinical PNET remains unanswered [7, 8].

CONCLUSION

Pancreatic endocrine microadenomatosis with synchronous well differentiated neuroendocrine tumor of the pancreas is rare so we presented this case of 49-year-old female patient with clinical signs of insulinoma.

Sažetak:

Uvod: Endokrina mikroadenomatoza pankreasa predstavlja pojavu brojnih mikroadenoma porekla neuroendokrinih ćelija, koji su po definiciji prečnika do 5mm. **Prikaz slučaja:** U ovom članku je prikazan patohistološki slučaj mikroadenomatoze sa sinhronim dobro diferentovanim neuroendokrinim tumorom pankreasa kod pacijenta ženskog pola, starosti 49 godina. Histološka slika tumora i imunohistohemijski profil ćelija su bili tipični za navedene neuroendokrine lezije. **Zaključak:** Endokrina mikroadenomatoza pankreasa sa sinhronim dobro diferentovanim neuroendokrinim tumorom je niske incidence i otuda je odabrana za prikaz slučaja.

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