SMALL INTESTINAL NEUROENDOCRINAL TUMORS

Essay

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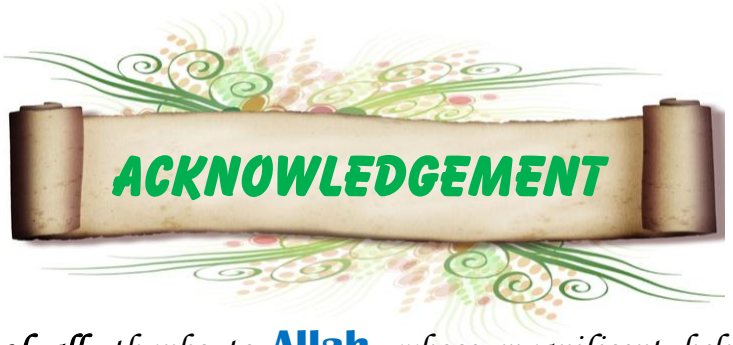

First of all, *thanks to* **Allah** *whose magnificent help was the main factor in completing this work.*

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Abstract

Background: In 1907, the German physician Obendorfer described several cases of multiple small tumors in the ileum. This was by many contemporaries believed to be the first sighting of small intestinal neuroendocrine tumors. Neuroendocrine tumors of the small intestine, arise from serotonin-producing, intraepithelial cells in the small intestine referred to as enterochromafin cells**.** SI-NETs are the most common small bowel tumors in the western world.

Aim of the Work: This essay aims to review unknown or unclear aspects of small intestinal neuroendocrinal tumor disease, in connection with prognosis, treatment and follow-up.

Methodology: The rising incidence of SI-NET might be explained by a combination of improved diagnostic techniques, improved reporting to different registries, and possibly also a true rise in SI-NET incidence. Another imaginable explanation for the increase in clinical incidence might be a greater tendency for metastatic spread during the latter decades in previously dormant SI-NET.

Conclusion: Surgery is the preferred option for patients with resectable disease, but palliation with tumor debulking, chemotherapy, and targeted radionuclide therapy is often needed because of the high frequency of metastases.Surgical removal of the primary tumour is the mainstay treatment. The patients will have either localized surgically curable disease or metastatic incurable disease. The goal is to obtain tissue for diagnosis, document the extent of disease, remove tumour for potential cure, palliate symptoms and to prolong survival. The success depends on the site, size and presence of metastases.

Keywords: Small Intestinal, Neuroendocrinal Tumors

Contents

List of Abbreviations

Abbrev.	Meaning
5-HTP	: 5-Hydroxytryptophan
CECT	: Contrast- enhanced Computed Tomography
CEUS	: Contrast- enhanced Ultrasound
CgA	: Chromogranin A
CGH	: Comparative genome hybridization
CNN- LOH	: Copy number neutral loss of heterozygosity
DOTATOC	DOTA - d - Phe(1) - Tyr(3) - octreotide
EC-Cell	: Enterochromaffin cell
E-NETS	: European Neuroendocrine Tumor Society
FDG	: Fluorodeoxy- glucose
GCCs	: Goblet cell carcinoids
GEP-NET	: Gastroenteropancreatic neuroendocrine tumor
GI-NET	: Gastrointestinal neuroendocrine tumor
HPF	: High power field
LAR	: Long acting release
L-DOPA	: L-Dihydroxyphenylalanine
LINE	: Long interspersed nucleotide elements
LOH	: Loss of heterozygosity

MEN : Multiple endocrine neoplasia

miRNA : Micro RNA

MRI : Magnetic resonance imaging

MPS : Massively parallel sequencing

mTOR : Mammalian target of rapamycin

NEC : Neuroendocrine carcinoma

NEN : Neuroendocrine neoplasm

NET : Neuroendocrine tumor

OS : Overall survival

PDEC : Poorly differentiated endocrine carcinoma

PET : Positron emission tomography

P-NET : Pancreatic neuroendocrine tumor

RFA : Radiofrequency ablation

SCNA : Somatic copy number alteration

SEER : Surveillance, epidemiology and end results

SI-NET : Small intestinal neuroendocrine tumor

SNP : Single nucleotide polymorphism

SNV : Single nucleotide variant

SPECT : Single photon emission computed tomography

SRS : Somatostatin receptor scintigraphy

SSA : Somatostatin analogues

SSTR : Somatostatin receptors

SYP : Synaptophysin

TACE : Chemoembolization

TAE : Transcatheter arterial embolization

TNM : Tumor, node, metastases

TSG : Tumor suppressor gene

U-5-HIAA : Urine 5 - hydoxyindoleaceticacid

VMAT1 : Vesicular monoamine transporter 1

WDEC : Well differentiated endocrine carcinoma

WDET : Well differentiated endocrine tumors

WHO : World Health Organization

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Introduction

In 1907, the German physician Obendorfer described several cases of multiple small tumors in the ileum. This was by many contemporaries believed to be the first sighting of small intestinal neuroendocrine tumors. Neuroendocrine tumors of the small intestine, arise from serotonin-producing, intraepithelial cells in the small intestine referred to as enterochromafin cells **(Kloppel et al., 2007).**

As Obendorfer recognized these ilealtumors to be histopathologically different from adenocarcinomas,ten years earlier, in 1897, Kulchitsky had discovered the enterochromaffin cell (EC-cell), Masson recognized both the EC-cells and the carcinoid tumors to have endocrine features . Following this, Friedrich Feyrter´s and Anthony Pearse´s studies mounted the concept of a diffuse endocrine cell system. All the tumors originating from this system were named carcinoids and subsequently the ileal tumors firstly described were often called classical carcinoids. The carcinoids are distinguished by the ability to take up amine precursors in similarity with cells in the central nervous system **(Oberndorfer et al., 2007).**

This lead to the thought that carcinoids were embryologically derived from the neural crest and the common term neuroendocrine tumor (NET) was proposed, and although that they have later been shown to be of primarily endodermal origin, the term NET has prevailed. Thus, tumors originating from the neuroendocrine system in the gastrointestinal tract or pancreas are after the WHO classification 2010 called gastroenteropancreatic neuro-endocrine tumors (GEP-NETs) and the term carcinoid will probably become obsolete **(Klimstra et al., 2010).**

SI-NETs are the most common small bowel tumors in the western world **(Bilimoria et al., 2010)**.

Small intestinal carcinoids also occur with increased frequency in a few inherited syndromes. Specifically with the autosomal dominant disorder, Multiple Endocrine Neoplasia type 1 (MEN1), there is an increased occurrence of duodenal gastrinomas and with von Recklinghausen's disease (VRD) (neurofibromatosis 1) (NF-1) an increased occurrence of duodenal somatostatinomas, characteri-stically in the periampullary region **(Jensen et al., 2006).**

The most common symptoms that lead to the detection of the duodenal carcinoid that leads to increase in

the use of upper GIT endoscopy are vague abdominal pain (37%), UGI bleeding (21%), anemia (21%) and jaundice (18%) **(Hoffmann et al., 2005).**

CT scans, MRIs, sonography (ultrasound), and endoscopy (including endoscopic ultrasound) are common diagnostic tools. CT-scans using contrast medium can detect 95 % of tumors over 3 cm in size, but generally not tumors under 1 cm **(Tan et al , 2011).**

Surgery is a curative treatment for some neuroendocrine tumors. Even if the tumor has advanced and metastasized, making curative surgery infeasible, surgery often has a role in neuroendocrine cancers for palliation of symptoms and possibly improved survival **(Warner et al., 2005).**

Most gastrointestinal carcinoid tumors tend not to respond to chemotherapy agents, showing 10 to 20% response rates that are typically less than 6 months. Combining chemotherapy medications has not usually been of significant improvement showing 25 to 35% response rates that are typically less than 9 months. The exceptions are poorly differentiated (high-grade or anaplastic) metastatic disease, where cisplatin with etoposide may be used **(Benson et al., 2010).**