ROLE OF ENDOSCOPIC ULTRASONOGRAPHY IN THE DIAGNOSIS OF BIOPSY NEGATIVE UPPER GASTROINTESTINAL SUBMUCOSAL TUMOURS

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LIST OF ABBREVIATIONS

- ***BUN:*** Blood urea nitrogen.
- ***CBC:*** Complete blood count.
- ***CD:*** Cluster differentiation.
- ***Cm***: Centimeter.
- ***CMV:*** Cytomegalovirus.
- ***CT scans:*** Computed axial tomography.
- ***EMR:*** Endoscopic mucosal resection.
- ***ERCP:*** Endoscopic retro-cholangio-pancreatography.
- ***EUS:*** Endosonography.
- ***Fig.:*** Figure.
- ***FNA:*** Fine-needle aspiration.
- ***GANT:*** Gastrointestinal autonomic nerve tumours
- ***GISTs:*** Gastrointestinal stromal tumors.
- ***GIT:*** Gastrointestinal tract.
- ***H.P.F:*** High power field.
- ***IDUS:*** Intraductal ultrasound.
- ***KIT:*** Tyrosine kinase proteins.
- ***MHz***: Megahertz.
- ***MP:*** Miniprobes.
- ***MRI:*** Magnetic resonance imaging.
- ***N:*** Number.
- ***NCI-SEER:*** National Cancer Institute's Surveillance, Epidemiology and End Results (NCI-SEER) program.
- ***PDGFR alpha:*** Platelet-derived growth factor receptor alpha.
- ***SMA:*** Smooth muscle actin**.**
- ***SMTs:*** Submucosal tumors.
- ***US:*** Ultrasound.

Introduction

Gastrointestinal submucosal tumours (SMTs) include a heterogeneous group of mesenchymal tumours, e.g. GISTs, lipoma, liposarcomas, fibroma, fibrosarcoma and non-Hodgkin lymphoma of the gastrointestinal tract predominance ***(Miettinen; et al 1998).*** GISTs are the most common submucosal tumor of the GIT, with an incidence of 4 per million of the population per year. 10-30% of GISTs show malignant behavior. Distant metastases tend to appear late in the course of the disease in most cases with the common sites are the liver and peritoneum. Lymph node involvement is rare, occurring in only 0-8% of cases ***(Al-Nafussi; et al 2001).***

Gastrointestinal SMTs are either discovered coincidentally in patients undergoing routine upper gastrointestinal endoscopy or may be the cause of symptoms such as bleeding, dysphagia, abdominal pain, rarely obstruction or an acute abdomen due to tumor rupture ***(Miettinen; et al 1998).***

Endoscopically, they are seen as a bulge into the lumen, usually covered by normal looking mucosa, and their exact nature may be difficult to diagnose accurately from endoscopy alone ***(Kojima; et al 2002)*** and since the lesion is under the mucosa, endoscopic biopsies usually do not demonstrate any abnormality or reveal non-specifically inflamed superficial mucosa in few cases. Usually the CT doesn't add any additional information about these lesions ***(Sakai 2001).***

The development of EUS since the early 1980s added greatly to the quality of imaging of the gastrointestinal wall as well as organs in close proximity to the GIT ***(Mallery; et al 2000)*** by using high frequency sound waves which is unmatched by any other imaging methods ***(Caletti; et al 2004).***

Thus, EUS can clearly demonstrate the distinct 5 layers of the intestinal wall (mucosa, muscularis mucosa, submucosal, muscularis propria and serosa), as well as abnormalities of these layers and can visualize structures adjacent to the intestinal wall. As such, it can distinguish intramural lesions from extrinsic compression reliably, can tell solid from cystic or vascular lesions, and can often accurately diagnose the nature of SMTs on the basis of their wall layers of origin, margins and echo-characteristics ***(Rosch; et al 2002).***

EUS is probably the investigation of choice for local staging of several gastrointestinal tumors and evaluation of submucosal masses as it can provides unique diagnostic information that is only obtained by laparotomy or resection ***(Boyce; et al 2001).***

EUS can also accurately delineate the depth of penetration, thus allowing safe endoscopic removal of these lesions ***(Villmann 2000).*** In addition, it is the only technique able to demonstrate complete disappearance of the intramural infiltration and reappearance of the normal five-layer wall architecture ***(Fujishima; et al 2001).*** EUS has progressed from being a purely imaging modality to one that can provide a tissue diagnosis by guided- FNA ***(Bhutani 2000).***

Investigations of GISTs by immunohistochemistry reveal phenotype variability that includes myoid, neural, and indeterminate characteristics which show expression of CD117 and other various antigens, such as nestin (90-100% positivity), CD34 (70% positivity), CD44, vimentin, desmin, muscle-specific actin, smooth-muscle actin, S-100 protein & neurofilament.

CD117 (c-kit protein) plays an important role in the latest specific diagnostic criteria for GISTs, as although it is not tumor-specific, it is expressed in all GISTs but not in true smooth muscle tumors and neural tumors ***(Kikuchi; et al 2006).***

CD34 is another important diagnostic marker. It is detected in approximately 70% of GISTs, and its presence may indicate a higher probability for a malignant phenotype. CD44 is variably expressed by GISTs, but its expression has been demonstrated to correlate with a better prognosis ***(Tzeni; et al 2005).***

Aim of the work

The aim of the work is to evaluate the role of EUS in the assessment of patients referred with suspected submucosal tumours in the oesophagus, stomach or duodenum with negative endoscopic biopsies, depending on:

1) The echocharacteristics of the lesion.

2) Endosonography guided fine needle aspiration cytology or biopsy from suspicious lesions.

CHAPTER 1

GASTROINTESTINAL SUBMUCOSAL TUMOURS

Background:

Gastrointestinal submucosal tumors (SMTs) are a heterogeneous group of stromal or mesenchymal tumors that arise from the embryologic mesoderm and thus, they may have very diverse origins and as such usually occurs within the wall of the GIT. They often protrude into the lumen of the hollow viscus, where they can be seen on endoscopic or radiographic studies. Such an appearance is referred to as a ‘‘SMT’’ which is really a misnomer because lesions in this category do not necessarily arise or confine themselves to the submucosa. Any growth underneath the mucosa of the GIT whose etiology cannot readily be determined by luminal diagnostic endoscopy or barium radiography is called a SMT. Experienced endoscopists often make an educated guess about the etiology of an SMT on the basis of size, shape, firmness, color, and overall appearance of the “tumor” but are histologically limited due to normal biopsies of the overlying mucosa ***(Rösch,et al 1992).***

SMTs were originally divided into being of muscular or neural derivation. However, in the past decade it has become more obvious that the gastrointestinal stromal tumors group (GISTs), cannot be placed in any

of these groups. This conclusion has been drawn based on the electron microscopic and immunohistochemical features, since GISTs in about 95% of cases stain positively for the protein CD117 ***(Day, et al 2003).*** This protein is not expressed by any of the other SMTs, except for heterotopic pancreatic tissue, which however does not pose a differential diagnosis, since it is easily differentiated from GISTs by light microscopy. However, as metastases from various sites may also present as SMTs, there is almost no limitation to the origin of SMTs ***(Day, et al 2003)***.

They are divided broadly into two groups. About 95% of stromal tumours of the stomach are classifiable as GISTs ***(Miettinen, et al 2005).*** And about 15% is comprised of a spectrum of tumors that might arise in any soft tissues in the body. These include lipomas, liposarcomas, leiomyomas, true leiomyosarcomas, desmoid tumors, schwannomas, fibroma, fibrosarcoma, non-Hodgkin lymphoma of the gastrointestinal tract predominance and peripheral nerve sheath tumors ***(Medeiros, et al 2004).***

Tumor type	***Examples***
Stromal tumor	GIST, smooth muscle tumor (true leiomyoma or leiomyosarcoma), glomus tumor
Lipocytic tumor	Lipoma, liposarcoma
Vascular tumor	Hemangioma, hemangiosarcoma, Kaposi's sarcoma
Neural tumor	Neuroma/neurofibroma
Miscellaneous tumors	Granular cell tumor, inflammatory fibroid polyp, fibrovascular polyp

Table 1
"Mesenchymal tumors of the GI tract"