EDITORIAL

Endoscopic Ultrasound-guided Fine Needle Aspiration Biopsy for the Molecular Diagnosis of Gastrointestinal Stromal Tumors: Shifting Treatment Options

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Gastrointestinal stromal tumors (GISTs) have been well characterized as mesenchymal neoplasms with distinctive clinical, pathological and molecular characteristics, but also with a favorable response to targeted therapy [1]. Although the tumors histologically resemble smooth muscle cell tumors and neuronal cells, they have an uncertain malignant potential, originating most probably in the interstitial cells of Cajal [2]. The majority of these tumors over-express CD117 (KIT), as well as activating mutations in c-kit or platelet-derived growth factor receptor alpha (GFRα) genes [3]. The protein product of the c-kit proto-oncogene is the cell-surface transmembrane receptor KIT (~95%), which has a cytokine named stem-cell factor (SCF) as a ligand. The intracytoplasmatic portion of KIT functions as a tyrosine kinase. KIT activation occurs in the majority of GISTs and consequently determines an uncontrolled cell proliferation and resistance to apoptosis. Targeted therapy was successfully employed in these tumors, where imatinib mesylate was demonstrated to be a promising treatment for advanced GISTs, by inhibition of both KIT and PDGFRα signal-transduction pathways [4].

Approximately 60% of GISTs occur in the stomach, 25% in the small intestine, and 10% in the colon and rectum [5]. The rest of the tumors are located in other areas of the GI tract, as well as in rare locations: gall bladder, appendix, omentum, or mesentery. The symptoms are representative for the site of origin, but the tumors are also detected by computer tomography or endoscopy evaluation for other causes. Endoscopy is initially used to examine submucosal tumors, although endoscopic mucosal biopsies are usually non-diagnostic. Submucosal tumors are further examined by endoscopic ultrasound (EUS), which shows a hypoechoic tumor and clearly delineates the layer of origin (muscularis propria), thus allowing a presumptive diagnosis of GIST [6]. Several papers have attempted to assess the utility of EUS for the differential diagnosis of GISTs, although the appearance of benign and malignant lesions overlap, leading to an overall accuracy of only 80%. Moreover, due to the indeterminate malignant potential, diagnosis cannot rely on imaging alone and pathological proof is still needed.

In the past issue of *Journal of Gastrointestinal and Liver Diseases*, Chatzipantelis et al [7] described their results of EUS-guided FNA in 17 patients with gastric GIST. A cytopathologist attended all procedures in order to assess specimen adequacy, and this allowed a 100% diagnostic yield with confirmation of the presence of c-kit and CD34 in all cases. Immediate on-site diagnosis was available in 14 patients (82.35%) based on cytological analysis of smears alone. Furthermore, in the remaining three cases the diagnosis was established by cell-blocks. Immunohistochemistry was performed in all cases in the cell blocks, with the tumor cells showing positive CD 117, CD34 and vimentin, but negative smooth muscle actin, S100 and desmin.

Pathology is always considered a gold standard for a definitive preoperative diagnosis, beyond the usual capabilities of imaging methods. However, it is not easy to obtain tissue for pathological diagnosis of a GIST before resection, because these tumors are difficult to penetrate, with fibrosis that frequently prevents achievement of sufficient material by aspiration. The obtained material is often not enough to allow a correct assessment of the malignant potential of GISTs according to the National Institute of Health consensus conference [8]. This consensus conference recognized that size and mitotic count should be used to stage the risk of malignancy. The first method employed for diagnosis was indeed EUS-guided fine needle aspiration (FNA) biopsy with analysis of smears, cell-blocks or core specimens (microhistology). Although the diagnosis can be established on the smears or cell blocks (including immunohistochemistry for CD 117, CD34, SMA, S100, etc.), mitoses cannot be properly evaluated. Other authors used a trucut biopsy (TCB) needle in order to obtain a larger core specimen for histology and immunohistochemistry. The results of the published studies were reviewed well in

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a landmark paper, clearly showing that the diagnosis yield is certainly not 100% [6]. The yield of sufficient tissue acquisition seems to be better with EUS-TCB (~ 90%) as compared with EUS-FNA (~70%), although direct head-to-head studies are largely missing and difficult to organize [9, 10].

In the study by Chatzipantelis et al, the high rate of tissue diagnosis (100%) might be indicative of a selection bias, since the study was performed retrospectively, based on a selection of patients from a cytology database. Most of the studies of EUS-FNA of GISTs reported lower values for the diagnosis yield obtained through aspiration. Moreover, when such EUS-guided techniques are employed, the yield of sufficient tissue acquisition seems to be dependent on the tumor diameter, being 71%, 86% and 100%, for tumors less than 2 cm, 2 - 4 cm, and larger than 4 cm in diameter, respectively [11].

Molecular analysis of c-kit mutations in EUS-FNA samples was proven to be feasible, especially in the context of the limitations in providing tissue diagnosis and assessing risk of malignancy in all cases of GISTs [12]. Likewise, mutations of PDGFRα were observed in a subset of GISTs lacking c-Kit mutations, based on the same elegant analysis of EUS-FNA cell blocks.

Recent studies indicated also that angiogenesis might play an important role in the progression of GIST. The presence of vascular signals during power Doppler EUS was proven to represent a sign of increased risk of malignancy [13], while metastatic GISTs are indeed hypervascular [14]. VEGF expression is correlated significantly with tumor size, tumor grade, liver metastasis, Ki-67 labeling index and microvascular density (MVD) [15]. Consequently, prognosis is significantly poorer in patients with tumors expressing VEGF than in patients with tumors lacking VEGF expression. Evaluation of MVD and VEGF could thus be extremely useful for predicting poor prognosis of GIST, but also to define a patient subset that might benefit from anti-angiogenic therapy.

Do we need preoperative evaluation of GISTs with EUS and EUS-guided procedures? This is certainly debatable, as a recent consensus for the management of GISTs included only contrast-enhanced computer tomography (CT), contrast-enhanced magnetic resonance imaging (MRI) and fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) as the initial techniques used for the evaluation [16]. Nevertheless, we would strongly encourage the use of EUS in order to exclude other subepithelial lesions: extrinsic compressions, cystic or vascular structures, lipomas and other solid tumors (carcinoid tumors, pancreatic rests, granular cell tumors, etc.). The use of EUS-guided procedures is even more controversial, being dependent on local expertise (EUS-FNA vs EUS-TCB), but also on the need of tissue confirmation before treatment. Both techniques can certainly be avoided if removal is directly recommended. Even so, EUS-guided procedures of tissue acquisition become essential in advanced cases, where a tissue diagnosis and evaluation of prognosis is needed before chemotherapy.

The options of treatment have evolved significantly after the introduction of EUS, which can accurately delineate the depth of penetration, thus allowing safe endoscopic removal for GISTs less than 2-3 cm. EUS is able to determine the precise layer of origin, to accurately measure the tumor and to appreciate its characteristics (margins, echogenicity, cystic spaces, calcifications, vascularization, etc.). Different techniques of endoscopic submucosal resection (ESMR) are currently used, being thoroughly reviewed in a recent paper [17]. The clinical decision for the management of GISTs should be tailored individually and currently includes open or laparoscopic surgical resection, endoscopic resection or even follow-up.

Molecular targeted therapy with imatinib mesylate changed the paradigm of non-response to chemo-radiotherapy for advanced GISTs, based on the dramatic responses observed in patients with unresectable and/or metastatic disease [5, 16]. Mechanisms of resistance are complex, but include primary mutations (before treatment) and secondary mutations (after imatinib treatment) of the c-kit gene, especially in exon 11. Nevertheless, mutation analysis is possible in EUS-FNA cell blocks and can thus assist in therapeutic decisions [18]. Based on the possible involvement of angiogenesis in GIST tumors, regimens targeting both KIT and VEGFR might be more useful than the regimens containing imatinib alone [19]. One such approach is based on sunitinib, a multitargeted inhibitor of VEGF receptor, PDGF receptor, as well as of c-kit. The anti-tumor activity may result from both inhibition of angiogenesis and direct antiproliferative effects on GISTs, with good results as second line treatment in GISTs [20].

To conclude, several recent advances have opened the era of combined mini-invasive treatment options for GISTs. EUS-guided and EUS-assisted procedures will certainly play an increasing role for the advanced molecular diagnosis and tailored neo-adjuvant or adjuvant treatment of GISTs, but will also enhance current treatment options in resectable tumors. Longitudinal follow-up of advanced cases is also possible by using EUS-guided tissue acquisition procedures, although the most accurate technique and the precise panel of markers used for immunostaining should be established in future prospective studies.

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