International Journal of New Technology and Research (IJNTR)
ISSN:2454-4116, Volume-2, Issue-4, April 2016 Pages 110-114

Clinical and Molecular Anatomy of Gastrointestinal Stromal Tumors (GIST)

Giorgio Maria Paolo Graziano, Giovanni Castelli, Prof Anthony Graziano

***Abstract*—Introduction Gastrointestinal stromal tumors GISTs are rare and fall into the category of non-epithelial tumors of the gastrointestinal tract , involving the stomach at a higher percentage (70 %). The purpose of this study , through a retrospective analysis of the observed cases , is to obtain data on the incidence , survival curve identification of prognostic and predictive parameters .The goal is to collect data concerning the natural history of GIST , 65% of patients were female, 35% male , mean age 64 years. Metastatic disease was assessed by cd171. In this study, n 11 (65 %) cases were L1 (cd171) positive for smooth muscle tumors . Of which 8 with headquarters in the stomach, ileum en 3 . Investigations have been performed immunohistochemistry with CD117 , CD99 , ema . all enrolled patients tested positive for CD117 .Discussion Thread What are the prognostic factors of GiST is still a matter of debate, but the consensus conference (NIH) in 2001 defined BETHESTHA n 2 parameters which are: the size and mitotic index of 50 HP for the lesions found were reported as accidental the size ranged < 10mm to > 50mm . . . The study carried out shows that the markers are the key to the histological diagnosis of GIST malignancies in GIST have introduced anti-angiogenic therapy with administration of sunitinib at a dose of 50mg/die for 4 weeks every 6 . For the purpose of inhibiting tumor growth with a time of disease-free interval longer. It is evident that in the histological diagnosis of GIST are inserted reporting the results of molecular biology with immunohistochemical markers , in combination with mitotic index , and tumor size in order to define a complete risks MTS**

***Index Terms*—Intestinal Tumors Histology GIST.**

I. Introduction

Gastrointestinal stromal tumors GISTs are rare, it is estimated that 1.5 / 100,000 cases with an average age 50-60 years. [1,2] Fall into the category of non-epithelial tumors of the gastrointestinal tract , involving the stomach at a higher percentage (70 %) and to a lesser extent the esophagus to the small intestine, colon , with a further minority who are interested in the omentum and mesentery retro peritoneum (GiST extra gastrointestinal) .[3,4] Based on the characters and ultra structural immunohistochemistry if they identify a form smooth muscle , neural shape , and a mixed form an undifferentiated form (Uncommitted) . Then confirm that the differentiation from interstitial cells of Cajal, the latter CD117 receptor tyrosine kinase type III with oncogenic potential capable of activating phosphorylation that stimulates uncontrolled cell proliferation , activation of the KIT gene present in 80% of GIST ,[5,6] has introduced a new therapeutic approach for these tumors . The purpose of this study , through a retrospective analysis of the observed cases , is to obtain data on the incidence , survival curve identification of prognostic and predictive parameters .

II. Materials and Methods

For the study were examined retrospectively patients referred from 1996-2004 at La II clinical surgery and specialist in the Department of Surgery II Policlinico Catania and from 2005 to 2014, including by consulting the database referred to the same period the Institute of Anatomy Pathology of AUO Policlinico Catania. The goal is to collect data from the copies of medical records of patients with transposition of all the information necessary for the examination of the following parameters: the TNM staging, location, size, Surgical treatment and chemotherapy, the recovery of the disease, survival, pathological anatomy, with tumor markers In biological tumor characteristics were evaluated all the information related only to malignancy or borderline, and were included mesenchymal neoplasm morphology consistent with the diagnosis of GIST, with reference to the natural history of GIST, and the incidence of prognostic parameters and predictive. The recruited patients were 20 cases referred n n 9 to living today and described in Table 1 (a),(b),(c) &(d).

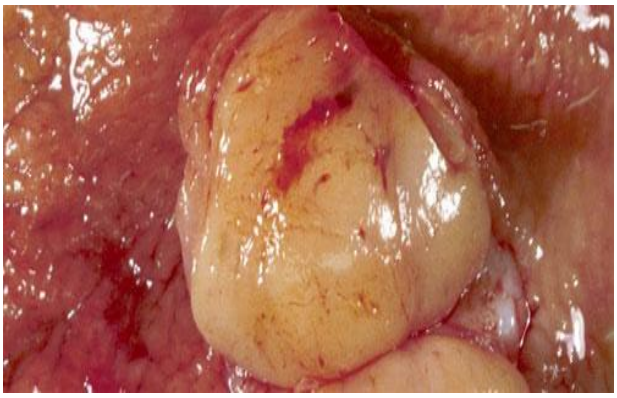

Fig 1: Nodule Immobilized to the Wall of the Yellow Stomach.

Giorgio Maria Paolo Graziano, Department of Sciences Medical Surgery and advanced technologies, University of Catania Medical School, Italy
Giovanni Castelli .MD, Department of Sciences Medical Surgery and advanced technologies, University of Catania Medical School, Italy
Prof Anthony Graziano , Department of Sciences Medical Surgery and advanced Technologies University of Catania Medical School, Italy Adress via S Sofia 86 Catania cap 95125

Fig 2: Nodular Lesions MTS

Table 1(a): List of diseases

Human Organ	Cases	Sex	Follow up(5anni)	Dimension	Venue
Stomach	**14**	4 male 10 female	2 exitus 5 exitus	2 – 5 cm 0,5 – 14 cm	Antrum-body-bottom Antrum-body
Ileum	**4**	2 male 2 female	2 exitus 1 exitus	15-16 cm 2-5 cm	Retroperitoneum Small Intestine
Colon	**2**	1 male 1 female	1 exitus 1 exitus	7 cm 2 cm	Multifocal rectum

Table 1(b): Risk Class

Class Of Risk	N°	Sex	Cell Morphology
Low	4	Male	Fusilly
Low	8	Female	Mixed
Intermediate	2	Female	Fusilly(70%),Epithelioid(23%),Mixed(46%)
High	6	70%Female, 30%Male	Fusilly(70%),Epithelioid(23%),Mixed(46%)

Table 1(C): Comorbidities

Class Of Risk	N°	Sex	Cell Morphology
Low	4	Male	Fusilly
Low	8	Female	Mixed
Intermediate	2	Female	Fusilly(70%), Epithelioid(23%),Mixed(46%)
High	6	70%Female, 30%Male	Fusilly(70%), Epithelioid(23%),Mixed(46%)

Table 1(d): Surgical Treatments

Associated Surgical Treatments	Gallbladder, Uterus, Thyroid, Breast
Surgical treatments (70% cases)	Total gastrectomy + lymphadenectomy
(20% cases)	ileal resection, resection of colorectal cancer
(10% cases)	retroperitoneal lesion excision

65% of patients were women 35% Male, mean age 64 years. Metastatic disease was evaluated by cd171 glycoprotein family of immunoglobulin, highly expressed in GIST, Whose cell adhesion and the presence in serum and tumor has an unfavorable prognostic significance. instrumental diagnosis (Fig 2) has played a major role in 'specification of a seat, and the TMN. For neoplasm of such small dimensions .The key role have also been implemented in the immunohistochemistry., Associated scintigraphic examination.

III. Results

In this study n 11 (65%) cases were (cd171) positive for smooth muscle tumors. Of which 8 with headquarters in the stomach, and No. 3 seat in the ileum. . Immunohistochemical studies were performed with CD117, CD99, EMA. the other immunohistochemical markers were assessed nonspecific listed in Table 2.

Table2:

CD34 positive in 15 (80 %) of cases
SMA (muscle specific actin) positive in 5 cases (30 %)
S-100 protein positive in 1 case (5 %)
Desmin positive in 2 cases (10 %) .

With the help of diagnostic tests (CT and MRI) it was obtained a TNM staging fair and confirmed the intervention, in addition to 'finding the tumor site, in neoplasm small. The surgical treatment performed in patients enrolled group was a total gastrectomy + lymphadenectomy in 70% (14 cases), ileal resection and segmental colon resection in 20% (n 4 cases), a removal of the lesion retroperitoneal nel10% (.n 2 cases). The TNM staging in 55% of cases testifying to an advanced disease with MTS. In staging procedures that dealt with rectal GIST, MRI has provided better preoperative staging information. Chest CT and routine laboratory testing complement the patient's staging framework asymptomatic. The evaluation of FDG uptake using FDG-PET (positron emission tomography), or FDG-PET-CT / MRI, is useful especially when it is of particular interest in the early detection of tumor response to targeted molecular therapy. Pathologic examination The finding of a nodular lesion was <8 cm adherent to the stomach wall (Fig 1) yellow with histological appearance of a lesion in the prevalence of spindle cells with rare istociti, and hyaline thickening of the vessel wall, always put a differential diagnosis with GIST. all patients enrolled in this study resulted positive to CD117. The poor response to chemotherapy expression of multidrug resistance in GIST have introduced in the treatment strategies neoadjuvant antiangiogenic therapy with the administration of Sunitinib at 50mg / day dose for 4 weeks every 6.mesi, in order to inhibit tumor growth. The antitumor activity resulted in a reduction in tumor size in most patients but some patients showed only variations in the density or the tumor on CT, these changes detected the radiation display were regarded as positive tumor response Once the maximum obtained tumor response, generally after 6-12 months.

IV. Discussion

What are the prognostic factors of GIST is still subject to debate, but the consensus conference (NIH) of BETHESTHA back in 2002 has defined the first two parameters are: the size of the tumor and mitotic index per 50 HPF. In the cases observed, the incidence was higher in the stomach less frequently in the ileum. the identified lesions were reported as accidental, the size ranged <10mm to> 50mm.[7,8,9,10] They were nature Solid headquarters in the subserosal, intramural submucosal, and sometimes intraluminal pedunculated. histology of GISTs spindle cell made it difficult to diagnose with smooth muscle neoplasm .while the response becomes easier for GIST in epithelioid cells round .The Gist in mixed form with hyaline or fibrillar structures occurred more frequently in the ileum. For the differential diagnosis of the immunohistochemical markers were evaluated are listed in Table 2. The study carried out shows that the markers are the key to the histologic diagnosis of GIST. Related stromal tumors then as part of syndrome / or lesions associated with other diseases has seen in this casista the detection of a single case (5%) of Carney triad with multiple formations in the stomach, and mediastinal neoplasm, and later with evaluation and genetic confirmation . This therapeutic approach adopted seems to have a predictive role on survival and assessment of efficacy was obtained with a KIT extracellular fragment used as a prognostic marker during treatment, with results that need confirm.[11,12,13,14] In relation to surgical treatment When detected small esophageal-gastric or duodenal nodules <2 cm size, can be difficult to perform endoscopic biopsy and laparoscopy / laparotomy excision may be the only way to make a histological diagnosis. In a small GISTs histologically established, surgical treatment is the excision, unless it is awaiting a major morbidity. A follow-up strategy can be an option to be shared with the patient in the case of small lesions and in specific clinical settings (clinics University, centers of excellence). the choice of monitoring is based on the logic low-risk GIST,[15.16.17] where it can be shared with the patient the decision to examine over time the injury. In such cases it is necessary to have a first short term control (for example at 3 months), and then, in case of no evidence of growth, you can choose a control program for the less frequent follow-up, and associate a scintigraphic evaluation functional, reserving excision for patients whose tumor increases in size or becomes symptomatic. [18,19,20,21]. Alternatively, for rectal nodules (or rectovaginal) after typing and ultrasound evaluation, surgical resection is indicated in our experience regardless of the size of the tumor, because the risk that a GIST metastasizes in this location is higher and the implications premises for surgery are the most critical. Then in the presence of nodules ≥ 2 cm of l 'surgical therapeutic orientation dimension is mandatory because, question also of GIST, with a higher risk. As well as in the presence of an abdominal nodule not easily assessable. especially if the cancer involves surgery of multiple visceral resection. Finally, in the presence of obvious metastatic disease, the biopsy of metastatic focus is sufficient and therefore there is not a laparotomy for diagnostic purposes. [22,23,24,25] The sample of the tumor was fixed in 4% buffered formalin (Bouin fixation should not be used , as it hampers the molecular analysis). By histopathologic analysis, the diagnosis of GIST was based on cell morphology and immunohistochemistry (CD117 and / or DOG1) [7, 8] .. Mitotic count has prognostic value and should be expressed as the number of mitosis on a surface total of 5mm [26,27], which is conceptually equivalent to 50 high power fields. Mutational analysis for known mutations involving KIT and PDGFRA genes confirms the diagnosis of GIST, though this is uncertain (especially in patients with GIST suspects CD117 / DOG1-negative). Mutational analysis has a predictive value of the sensitivity molecular targeted therapy and prognostic value. It may be useful to the centralization mutational analysis in a laboratory, and a second opinion from an experienced pathologist in all cases in which the original diagnosis is made outside of a center of reference.[28.29,30,31]

V. Conclusions

It seems evident that the diagnosis with histological reporting of GIST are inserted the results concerning the molecular biology such as immunohistochemical markers, mitotic index in association with the size of the tumor in order to establish a comprehensive risk MTS. Surgical treatment is effective if complemented by complementary therapies

increasingly innovative. The clinical diagnosis is still defined in the occasional limits or syndrome or lesions associated with other diseases. the identification of more effective prognostic and predictive parameters has seen a greater understanding of the disease and the possibility of targeted therapies prepare. [32,33,34]In patients with unresectable locally advanced disease and in patients with metastasis, the antiangiogenic therapy is the standard treatment [35, 36.37]. As well as for metastatic patients that have been surgically removed all lesions, although surgery, is no longer referred to as the 'primary approach to metastatic GIST. The risk assessment based on mitotic count, tumor size and location of the tumor can be helpful in choosing the method of operation of the follow-up routine.

COMMENT

The goal is to collect data for the implementation of all the information on the biological characteristics of the tumor with the help of diagnostic tests (CT and MRI) was obtained a fair and TNM staging, the 'identification of the tumor site, in neoplasms small size. The surgical treatment in the group of patients enrolled gave better information on preoperative staging. The poor response to chemotherapy expression of multidrug resistance in GIST introduced in curative strategy neoadjuvant anti-angiogenic therapy. Whose activity resulted in a reduction of the tumor mass in most patients. The work shows originality and innovation, as well as developing a greater understanding in small tumors.

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