Primary gastrointestinal stromal tumor of the liver with lung metastases successfully treated with STI-571 (imatinib mesylate)

Annarosaria De Chiara ¹, Vincenzo De Rosa ², Secondo Lastoria ³, Renato Franco ¹, Gerardo Botti ¹, Vincenzo Rosario Iaffaioli ⁴, and Gaetano Apice ⁴

¹ U.O.C. Pathology, ² U.O.C. Radiology, ³ U.O.C. Nuclear Medicine, ⁴ U.O.C. Medical Oncology B, Istituto dei Tumori di Napoli “G. Pascale”, Italy

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1. ABSTRACT

We report a case of a primary malignant GIST of the liver metastatic to the lung in a 37 years-old man. The liver tumor showed histological feature of a GIST and expressed vimentin, and diffusely exhibited CD117. One year after the resection of the liver mass, the patient developed multiple small lung metastases which completely disappeared with STI-571 (imatinib mesylate – Gleevec) therapy. C.T. or PET did not show any mass in the abdomen. These findings suggest that the liver mass was a primary rather than a metastatic tumour. They also support the hypothesis that GIST could originate from undifferentiated mesenchymal cells capable to differentiate toward a pacemaker cell phenotype, which are present in sites other than the G.I. tract.

2. INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are a group of mesenchymal tumors characterized by the expression of KIT protein (CD117) (1). The understanding of biological role of activating KIT mutations in the majority of the cases of GIST led to the development of a target-based therapy using the receptor tyrosine kinase inhibitor STI-571 (imatinib mesylate) (2). GISTs are typically found in the gastrointestinal tract (3-8), but they are also been described in extragastrointestinal sites such as abdominal cavity and retroperitoneum (9), and biliary tract (10). Recently, a case of a malignant primary GIST of the liver has been reported (11).

Here we report a case of a primary malignant GIST of the liver metastatic to the lung in a 37 years-old
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3. MATERIALS AND METHODS

In February 2002 a 37 years-old man presented a huge mass in the fifth segment of the liver (Figure 1). No other suspected masses were detected by total body computed tomography (CT). He underwent to surgery in the School of Medicine closest to his job area. The surgical specimen was 18x16x10 cm. and weighted 1700 gr. The histological report describes the tumour as a neoplastic proliferation of spindle cells with storiform areas (Figure 2). The nuclei showed only mild pleomorphism. There was necrosis and high mitotic index (20/50 HPF). The neoplastic cells were immunoreactive for vimentin but negative for keratin, smooth muscle actin, S100, CD31, FVIII and CD34. The tumor was interpreted as primary high-grade sarcoma possibly a MFH at that institution. The slides were then sent aboard in consultation and the diagnosis was again “high grade sarcoma” possibly fibrosarcoma. Based on these diagnoses, five courses of chemotherapy with epirubicin and ifosfamide were recommended.

Soon after, in May 2002, the patient came to our institution before starting the proposed chemotherapy. The slides were reviewed by some of us (ADC, GB, RF). The immunohistochemical findings were basically similar to the other reports but we tested the neoplastic cells also for CD117 which resulted in a diffuse strong staining (Figure 3). Based on this result, a diagnosis of GIST was made. Because no abnormal masses by a second total body C.T., small bowel contrast radiology, endoscopy, endoscopic ultrasound neither pathologic uptake of 18F-FDG by positron emission tomography (PET) were found in the gastrointestinal region, the tumor was interpreted by us as “GIST of the liver, possibly primary”. Therefore, we choose do not treat the patient but to closely monitor him.

In April 2003, a total body C.T. showed multiple lung metastases (Figure 4A) also positive to PET (Figure 4B), but not other masses including liver and abdomen were still found. Shortly after the patient was started on oral therapy with 400 mg/daily of STI-571 (imatinib mesylate – Gleevec®), the pulmonary lesions completely disappeared (Figure 5A and B). The patient is free of disease at the last control (May 2005) while he is still taking the aforementioned therapy.

4. DISCUSSION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract which harbour different clinical behavior. In the years many different parameters were proposed as being predictive of clinical behavior. At GIST Symposium held at National Institute of Health (NIH) on April 2001, an histological approach based mainly on mitotic count and tumor size for defining relative risk of malignant behavior was proposed (1) and now is widely in use. GISTs have many similarities with interstitial cells of Cajal, which prompted some authors to propose that these tumours originate from Cajal series (12). The occurrence of GISTs in anatomic sites other than G.I. tract makes this hypothesis

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Figure 1. CT shows a well demarcated mass in the fifth segment of the liver.

Figure 2. Hematoxylin&eosin section of the liver mass showing a spindle cell tumour with some whorling

Figure 3. The tumour is strongly positive to CD117.
likely. It is seems more likely that GISTs originate from stem cells that can differentiate toward a pacemaker cell phenotype. The present case supports the hypothesis that such undifferentiated still uncommitted cells are present in different anatomic sites, even though they are more frequent in G.I. tract [11].

Liver is the most frequent metastatic site from abdominal GISTs. In the present case, we were unable to identify any other abdominal mass using extensive radiological work-up in three-years follow-up. And on top of all, lung metastases developed one year after the liver mass resection. This clinical behaviour prompted us to define this tumour as “GIST primary in liver”. To the best of our knowledge, only another case was labelled as such. It showed histological features similar to our case and proved to be malignant because the patient developed a metastatic hepatic hilar lymphnode after sixteen months later. But she did not receive any chemotherapy. The present case is peculiar because the lung metastases completely disappeared after the patient was started on target-based therapy with Gleevec. It is important to underline that STI-571 is by far a targeted therapy effective only in GISTs and chronic myeloid leukemia (CML), because of relatively homogeneous pathogenetic mechanisms driven by a single dominant stimulus affecting the same receptor tyrosine kinase (aberrant signalling through BCR-ABL in CML and uncontrolled signalling through KIT in GIST). It has also been demonstrated that dermatofibrosarcoma protuberans (DFSP), driven by chromosomal rearrangement fusion collagen type Ialpha1(COL1A1) gene to PDGFR-B, was inhibited in vitro and in vivo experiments by STI571, predominantly through induction of tumoral apoptosis [14]. The dramatic clinical and histological response in selected cases shows that imatinib may provide a good alternative for the treatment of metastatic or unresectable DFSPs possibly improving the effectiveness of surgery [15].

Immunohistochemical staining for KIT (CD117) in soft tissue tumours has also been reported in several reports, but when extensively tested in a large number of different histotypes a very limited expression of KIT was identified, stressing that standardization and reproducibility of positive results is critically important for correct diagnosis and therapy [16]. At least in angiosarcoma, KIT expression seems to represent oncofetal expression (i.e., reversion of the tumor cell phenotype to that of fetal endothelial cells that may show KIT expression) and it is not at least commonly associated with the presence of activating c-kit mutations. This means that even though some sarcomas may show KIT immunostaining, often focal and weak, STI-571 will be ineffective because of the lack of the targeted activated KIT [18].

The strong and diffuse immunohistochemical staining for CD117, the clinical behaviour (i.e., lung metastases without any detected abdominal mass) and the impressive clinical response to target-therapy STI-571 found in the present case, all point out to the fact that primary GISTs in the liver do really exist, even though rare. Clinicians and expecially pathologists should be aware of

Figure 4. CT shows three small nodules in the lungs (A) which are also faintly positive to the PET (B).

Figure 5. After one month of STI571 treatment, the pulmonary nodules were not longer seen by both CT (A) and PET (B).
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this evenience to avoid incorrect diagnosis with usefulness chemotherapy while GISTs are now potentially curable disease.

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6. REFERENCES


Key Words: Malignant, GIST, Liver, Lung Metastases, Gleevec

Send correspondence to: Dr Anna De Chiara, U.O.C. di Anatomia Patologica, Istituto Nazionale dei Tumori "G. Pascale", Via M. Semmola, 80131 Napoli Italy, Tel: 011-39-081-590380, Fax: 011-39-081-5903718, E-mail: annadechiara@hotmail.com

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