Complete Response after Imatinib Mesylate Administration in a Patient with Chemoresistant Stage IV Seminoma

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Abstract. *The case of a young man with stage IV chemoresistant pure seminoma overexpressing KIT, who achieved complete remission (CR) after the administration of imatinib mesylate (400 mg once daily), along with a third-line chemotherapy regimen, consisting of paclitaxel (150 mg/m^2), oxaliplatin (100 mg/m^2) and gemcitabine (800 mg/m^2) every 2 weeks with granulocyte colony-stimulating factor (G-CSF) support is reported. The patient had received first- and second-line regimens consisting of ifosfamide, bleomycin, etoposide cisplatin (5 cycles, every 3 weeks) and methotrexate, vinblastine, actinomycin D, cyclophosphamide, cisplatin (3 cycles, every 3 weeks) respectively, without having normalized β-human chorionic gonadotrophin (β-HCG) levels. Following treatment with imatinib plus third-line chemotherapy (paclitaxel, oxaliplatin, gemcitabine), the levels of β-HCG were reduced to within the normal limits during the first month of treatment. Therefore, the patient underwent surgical resection of the residual disease from the retroperitoneum and liver, which proved to be only necrotic tissue. The patient is under close follow-up, with no evidence of disease, 36 months after the completion of chemotherapy and 32 months post surgery.*

Case Report

A 24-year-old man, with a previous history of cryptorchism, sought medical attention in May 2004, for lumbar pain and galactorrhea lasting for more than two months. Clinical evaluation, which included testicular ultrasonography, computed tomography (CT) scans of chest and abdomen and tumor marker measurement, revealed a small infrasonic mass within the left testicle, a retroperitoneal mass (10×10 cm), multiple lung and liver metastatic deposits and an elevated β-human chorionic gonadotrophin (β-HCG) (3,300,000 IU/l). The patient underwent an inguinal orchiectomy and the histology of the specimen revealed a small, well-defined pure seminomatous mass of 0.8 cm diameter. Due to very high levels of β-HCG, unusual for a pure seminoma, pathologists examined the whole specimen in detail, but no indication for a non-seminomatous component was detected. Several sites of intratubular germ cell neoplasia, carcinoma *in situ* (CIS) were recognized.

The patient was treated with five cycles of ifosfamide, bleomycin, etoposide, cisplatin (IBEP) every 3 weeks, but due to an incomplete response and continuous high levels of β-HCG (plateau at 113 IU/l), the chemotherapy regimen was switched to methotrexate, vinblastine, actinomycin D, cyclophosphamide and cisplatin every 3 weeks. After 3 cycles, the β-HCG levels ranged from 27.5 IU/l to 35 IU/l. As up to 80% of tumor cells (Figure 1) gave intense positive cytoplasmic and membranous staining for KIT (a gene encoding a tyrosine kinase transmembrane receptor), the patient received a third-line salvage regimen, consisting of paclitaxel (150 mg/m^2), oxaliplatin (100 mg/m^2) and gemcitabine (800 mg/m^2), every 2 weeks with granulocyte colony stimulating factor (G-CSF) support, along with imatinib mesylate (Gleevec®; Novartis Pharmaceuticals AG, Basel, Switzerland) 400 mg once daily. During the first month, the patient achieved a biological complete remission (CR) (β-HCG: 0) and partial response to the lung metastatic lesions. After 6 cycles of intensive chemotherapy along with imatinib, while the patient was in biological CR, the metastatic deposits from the lung had disappeared, but those in the liver were still imaged on CT scans (large cystic lesion in part IV of the left lobe and a second in the right lobe) as was that in the retroperitoneum (5 cm lymph node mass). One month after the completion of chemotherapy, the patient underwent a 2-^{18}fluoro-deoxy-D-glucose positron emission tomography

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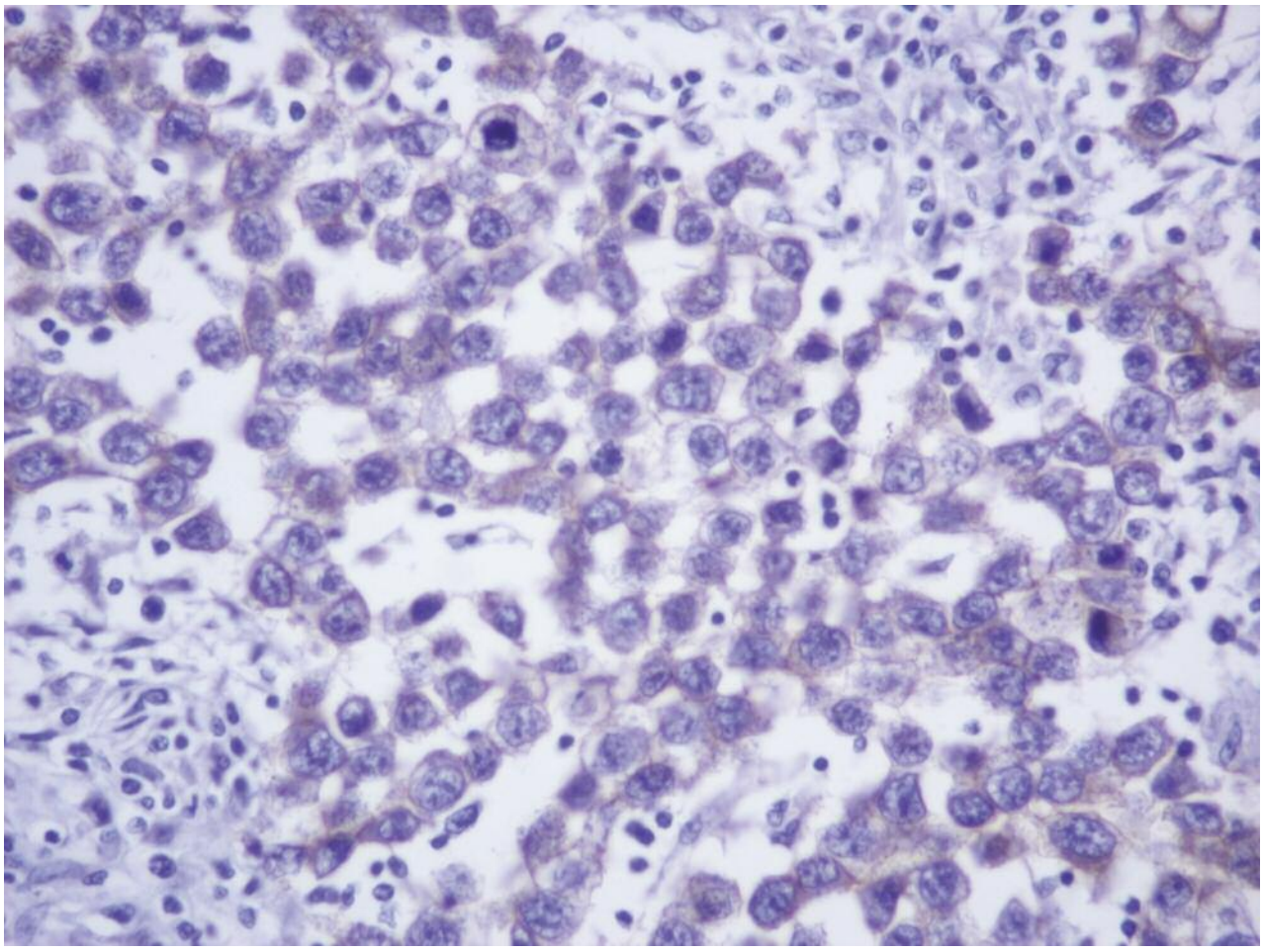

Figure 1. *KIT immunohistochemical staining of the patient's seminoma (×400).*

(FDG-PET CT scan) which revealed metabolic activity compatible with a viable tumor (standard uptake value=2.5) in the periphery of the retroperitoneal mass and the liver cystic lesion (Figure 2). All this time, β-HCG had remained within the normal limits and the patient continued to receive only imatinib mesylate. Therefore, he was subjected to post-salvage surgical resection of the residual disease (left hepatectomy and retroperitoneal lymphadenectomy). Histopathological findings revealed only necrotic tissue in both specimens. The patient is now under close follow-up and maintains a disease-free status 32 months post surgery.

Discussion

Germ cell tumors are generally highly sensitive to chemotherapy. Even in metastatic disease, 70-80% of patients achieve long-term survival with cisplatin-based chemotherapy. More specifically, pure seminoma histology is recognized as particularly chemotherapy sensitive and is associated with a higher chance of cure. However, a minority of patients with advanced pure seminoma do not achieve a CR with initial chemotherapy or may relapse after a CR and require salvage therapy. Although new chemotherapeutic agents such as paclitaxel, gemcitabine and oxaliplatin have been identified as active for salvage therapy, offering partial remissions of short duration, therapeutic options are still very limited (1-3). Identifying new treatment strategies for patients with cisplatin-refractory disease remains a priority.

The recent development of tyrosine kinase inhibitors (TKIs), addressing the stem cell factor receptor KIT, has offered new therapeutic options for patients with tumors overexpressing any of these tyrosine kinases. KIT encodes a transmembrane protein, with intrinsic tyrosine kinase activity, which functions as the receptor for stem cell factor (SCF). It is expressed in a variety of cell types, including mast cells, hematopoietic progenitor cells, melanocytes, gastrointestinal pacemaker cells and germ cells. The KIT–SCF interaction is essential for regulation of

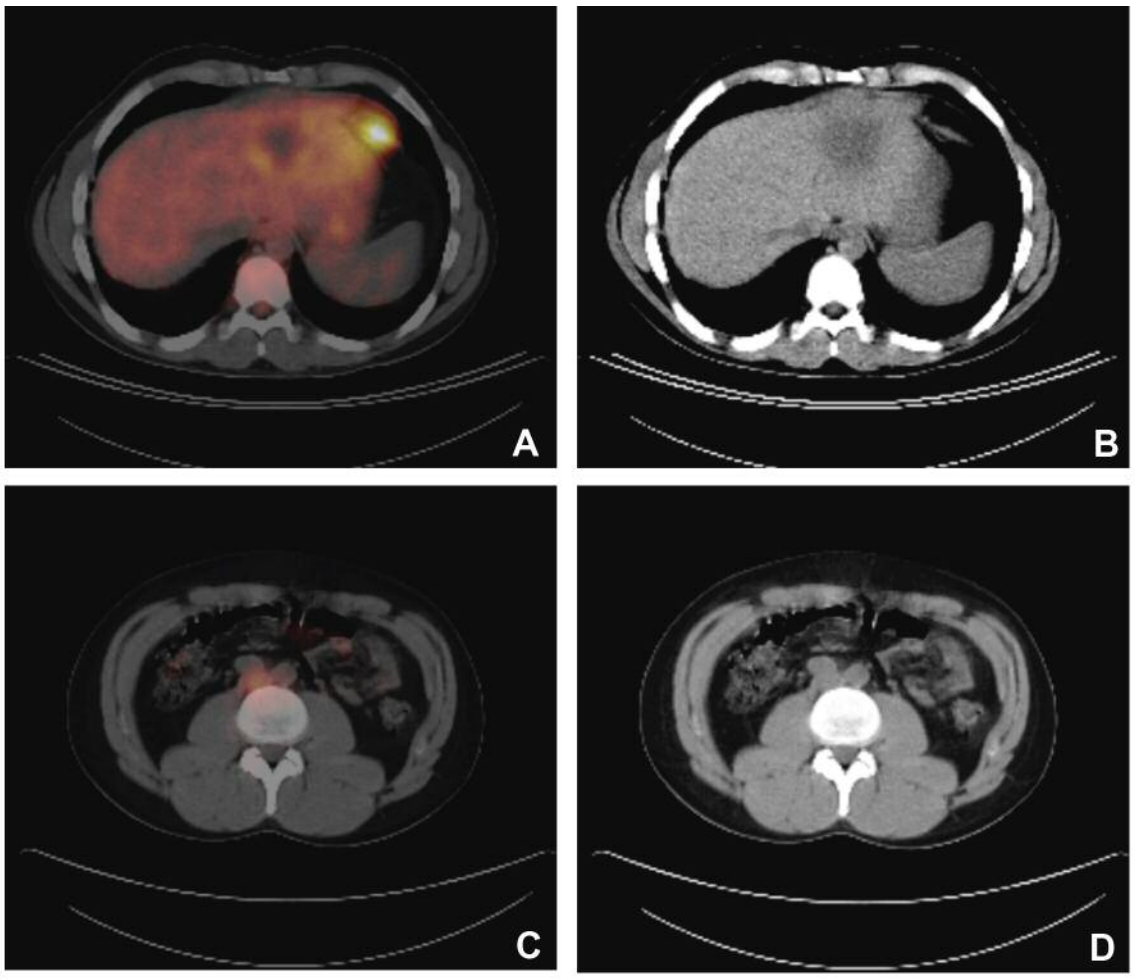

Figure 2. *FDG-PET and CT scan before post-salvage resection. A, B: Liver lesion imaged in FDG-PET and CT scan. C, D: Retroperitoneal lymph node block in FDG-PET and CT scan. Although both lesions were compatible with viable tumor (SUV=2.5), histopathology after resection revealed necrotic tissue. Metabolic activity was attributed to inflammation.*

proliferation and survival, particularly for germ cells as it regulates oogenesis, folliculogenesis and spermatogenesis (4). Up-regulation of KIT signaling has been associated with oncogenic transformation in cells expressing the molecule and this fact makes KIT a logical target for drug inhibition.

Several compounds have been identified as having inhibitory activity against the tyrosine kinase activity of KIT. Interestingly, these compounds were originally developed to target other tyrosine kinases, such as the *bcr-abl* oncoprotein, and, apart from KIT, they also inhibit the platelet growth factor receptor (PDGFR). Imatinib mesylate (Gleevec®), which binds with high affinity to the inactive conformation of the kinase at its adenosine triphosphate-binding site, is the only such TKI approved for treatment of human disease and is particularly useful in the first-line treatment of Ph^+ chronic myeloid leukemia and in metastatic or unresectable KIT^+ malignant gastrointestinal tumor (GIST) as well.

Whether or not a malignancy can be treated effectively with a KIT TKI may depend largely on the extent to which the growth of the target tumor cells is influenced by KIT activity. Another critical issue is whether the drug will be active against mutant isoforms of KIT. Mutations affecting the enzymatic site of KIT (codon 816 mutations) confer resistance to imatinib by interfering with the binding of the drug whereas wild-type KIT and KIT with mutations at regulatory sites remain sensitive to imatinib (4, 5).

As expression of KIT tyrosine kinase is critical for normal germ cell development and is observed in the majority of seminomatous tumors, imatinib may rationally offer a chance of response to chemotherapy-resistant germ cell tumors overexpressing KIT. However, no studies or reports have been identified in the literature and therefore we were not ethically allowed to treat our patient with imatinib mesylate alone. In order to increase the chances of cure in our patient, we added

imatinib to third-line chemotherapy. Whether the chemotherapeutic regimen of paclitaxel, oxaliplatin, gemcitabine, or the imatinib mesylate administration, or the combination of both led to CR of this advanced stage seminoma patient remains unclear. Bearing in mind that these chemotherapeutic agents have been used as third-line regimen, where only few long-term disease-free status cases have been reported, we consider that this direct and rapid CR could most likely be attributed to imatinib mesylate administration. Even if chemoresistant advanced seminomas represent a selected and rare entity within germ cell tumors, a possible indication of cure has to be further evaluated.

In conclusion, we report a patient with chemoresistant seminoma who achieved a CR after the administration of third-line chemotherapy with imatinib.

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