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Thymic Carcinoma with Overexpression of Mutated *KIT* and the Response to Imatinib

TO THE EDITOR: In April 2002, a 54-year-old man presented with thoracic pain and respiratory distress; a mediastinal mass, 7.7 by 6 cm, was found on positron-emission tomographic and computed tomographic scanning. Further examination showed elevated liver-enzyme levels and multiple liver metastases. Liver biopsy revealed metastatic, poorly differentiated epidermoid carcinoma of the thymus,[1] with strong KIT expression (Fig. 1). The patient started taking imatinib at a dose recommended for the treatment of gastrointestinal stromal tumors (400 mg per day).[2] Within one week, his pain and respiratory distress disappeared. His liver metastases shrank within four months, and his liver-enzyme levels normalized, while the mediastinal tumor showed stable disease.

Partial sequencing of the *KIT* gene revealed an activating mutation caused by an in-frame deletion in exon 11, resulting in the loss of valine at position 560 (V560del), which has previously been described in gastrointestinal stromal tumors.[3] Western blotting showed that the phosphorylation status of KIT and of typical downstream targets in the KIT signaling cascade (e.g., Akt [or protein kinase B], STAT3 [signal transducer and activator of transcription 3], MAPKs [mitogen-activated kinases], and BAD

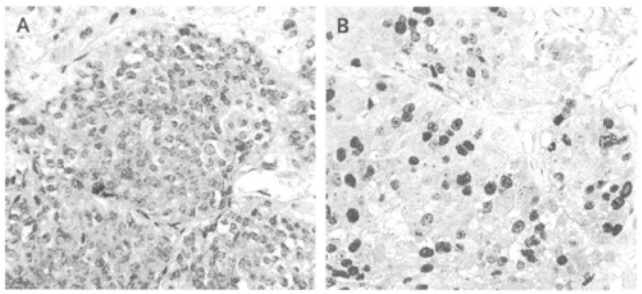

Figure 1. Metastatic Thymic Carcinoma in a Patient with an Activating *KIT* Mutation, before Treatment with Imatinib (Panel A, Hematoxylin and Eosin, ×400; Panel B, Immunohistochemical Ki-67 Staining, ×400).

[Bcl-2 antagonist of cell death]) strikingly resembled the findings in imatinib-responsive gastrointestinal stromal tumors.[4]

After six months of imatinib therapy, the tumor in the mediastinum and liver progressed, and bone metastases developed. A mediastinal biopsy showed a tumor resembling the liver metastasis seen at the first presentation in terms of KIT overexpression and the presence of the V560del KIT mutation. However, there was less tumor-cell proliferation and apoptotic tumor cells were more numerous than before imatinib treatment. Imatinib was discontinued, and the patient received radiochemotherapy with autologous hematopoietic stem-cell rescue, which resulted in partial remission. The patient died 20 months after the first presentation, with progressive tumor growth in the mediastinum, liver, and bones.

A response to imatinib has been observed in 93 percent of patients with gastrointestinal stromal tumors who have an activating mutation in exon 11 of *KIT*.[5] To our knowledge, the current case is the first case of a carcinoma with such an activating *KIT* mutation. However, our preliminary studies suggest that *KIT* mutations are rare in thymic carcinomas. Since the efficacy of imatinib in the treatment of gastrointestinal stromal tumors and various tumors without activating *KIT* mutations has been disappointing, the current case suggests that screening for activating *KIT* mutations may identify KIT-expressing carcinomas that could benefit from imatinib.

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