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, 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). Within one week, his pain and respiratory distress disappeared. His liver metastases shrunk 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. 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...
(Bcl-2 antagonist of cell death) strikingly resembled the findings in imatinib-responsive gastrointestinal stromal tumors.

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.

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.

Philipp Ströbel, M.D.
Martina Hartmann, M.D.
University Institute of Pathology
D-97080 Würzburg, Germany
Andreas Jakob, M.D.
Offenburg Hospital
D-77054 Offenburg, Germany
Kristina Mikesch, M.D.
Ingo Brink, M.D.
University of Freiburg
D-79106 Freiburg, Germany
Stefan Dirnhofer, M.D.
University Institute of Pathology
CH-4403 Basel, Switzerland
Alexander Marx, M.D.
University Institute of Pathology
D-97080 Würzburg, Germany
alex.marx@mail.uni-wuerzburg.de


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