Stabilization of Disease after Targeted Therapy in a Thymic Carcinoma with KIT Mutation Detected by Clinical Next-Generation Sequencing

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ABSTRACT

Precision medicine uses individually determined genomic information to guide treatment in cancer and other diseases. We have implemented a clinical genomics assay that uses targeted next-generation sequencing of 25 cancer-related genes to guide the use of targeted therapies in diverse malignancies. We report the case of a 55-year-old woman with a poorly differentiated squamous cell carcinoma of thymic origin, with disease progression after standard treatment. Targeted tumor sequencing revealed the presence of a KIT codon 579 deletion (p.D579del). This specific mutation has not previously been associated with thymic tumors, but has been reported in gastrointestinal stromal tumors and has been associated with response to imatinib. Imatinib therapy was instituted for and resulted in stabilization of disease. This case illustrates the potential of clinical next-generation sequencing to open unexpected avenues for treatment and thereby improve patient outcomes.

INTRODUCTION

Although standard therapies exist for many malignancies, there is increasing interest in using individually determined genetic information to guide cancer therapy. This is especially true in treatment-refractory cases for which standard options have failed. Clinical next-generation sequencing (NGS) makes it possible to use genetic variants present in the tumor to guide the selection of targeted therapies. Although data from prospective clinical trials may guide use of a given therapy in patients with certain defined genetic lesions (for example, EML4-ALK rearrangement is used to triage lung cancer patients for crizotinib therapy), in other instances mutations that are novel or atypical for a given tumor may suggest the use of a therapy that would not otherwise have been considered (e.g., a tyrosine kinase inhibitor [TKI] for a mucosal melanoma).2

We present a case of a poorly differentiated thymic carcinoma in which clinical NGS revealed a therapeutic target. Therapy directed against the target mutation resulted in stabilization of previously progressive disease.

MATERIALS AND METHODS

Targeted NGS

For this case, Genomics and Pathology Services at Washington University (GPS@WUSTL) performed targeted NGS of 25 cancer-related genes (all exons of BRAF, CHIC2, CSF1R, CTNNB1, DNM3A, EGFR, FLT3, IDH1, IDH2, JAK2, KIT, Kras, MAP2K1, MAPK1, MET, NPM1, NRAS, PDGFRα, PIK3CA, PTEN, PTPN11, RET, RUNX1, TP53, and WT1) using DNA extracted from formalin-fixed, paraffin-embedded tumor tissue. The assay used Agilent SureSelect capture followed by Illumina HiSeq 2000 sequencing. GPS@WUSTL is accredited by the College of American Pathologists and certified under the Clinical Laboratory Improvement Amendments.

Regulatory Compliance

The institutional review board at Washington University determined that the present report does not constitute human research. The patient consented to the publication of this case report.

CASE REPORT

The patient was a 55-year-old woman with a poorly differentiated thymic carcinoma, metastatic to the liver (Fig. 1). Computed tomography (CT) scan showed a 2.3 × 2.0 cm anterior mediastinal mass, two liver lesions measuring 4.3 and 1.6 cm, and two indeterminate nodules in the right lung, 5 and 6 mm in diameter. Fluorodeoxyglucose positron emission tomography showed increased tracer uptake in the mediastinal and liver lesions. A CT-guided core biopsy and fine-needle aspiration were performed on the largest liver lesion and showed a poorly differentiated squamous cell carcinoma, presumed to be of thymic origin.
Clinical targeted NGS was used to guide therapy in this treatment-refractory malignancy. Sequencing identified an in-frame deletion of three nucleotides in the juxtamembrane domain (exon 11) of the KIT receptor. KIT encodes a receptor tyrosine kinase, which is often mutated in gastrointestinal stromal tumors (GISTs) and represents a target for therapeutic inhibition by various semiselective TKIs.
including imatinib and sunitinib.\textsuperscript{9} Thymic carcinomas, too, have occasionally been found to harbor \textit{KIT} mutations;\textsuperscript{10} In one series of seven cases, two had \textit{KIT} mutations;\textsuperscript{6} another report estimated the prevalence of \textit{KIT} mutation in thymic carcinoma at 9%.\textsuperscript{4} The mutations are diverse and a sequencing-based approach is necessary to comprehensively identify them (Table 1).

Moreover, \textit{KIT} mutations predict the effectiveness of TKI therapy in both GIST and thymic carcinoma. In GIST, mutations in the juxtamembrane domain, including p.D579del specifically, are known to confer sensitivity to imatinib.\textsuperscript{11,12} In one series, patients with GIST harboring \textit{KIT} exon 11 mutations showed a partial response to imatinib in 83.5% of cases, whereas no patient with wild-type \textit{KIT} showed a response.\textsuperscript{13} In thymic carcinoma, several different \textit{KIT} mutations have been associated with sensitivity to TKIs (Table 1). Most notably, a three-codon in-frame deletion, p.P577–D579del, similar to the one identified in our patient, was discovered in one patient using research (nonclinical) testing and was associated with response to sorafenib.\textsuperscript{14}

Although a majority of thymic carcinomas express \textit{KIT},\textsuperscript{15} immunoreactivity alone does not seem to correlate with imatinib susceptibility.\textsuperscript{16,17} A phase 2 trial of imatinib in unselected thymic carcinomas also failed to show a benefit.\textsuperscript{26} These observations underline the importance of mutation testing in patient selection.

\begin{figure}
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\caption{Molecular evidence for a single-codon \textit{KIT} deletion. A, In-frame deletion of three nucleotides in exon 11 of \textit{KIT} as visualized in the Integrative Genomics Viewer.\textsuperscript{24} B, Electropherogram from confirmatory Sanger sequencing, showing reference trace (top) and patient sample (bottom). C, Ribbon diagram of juxtamembrane and tyrosine kinase domains of \textit{KIT} receptor, residues 565–933. The deleted residue (Asp579) and a bound imatinib molecule (STI-571) are shown as stick figures. Drawn from PDB entry 1T46\textsuperscript{3} using the SwissPDB Viewer.\textsuperscript{25}}
\end{figure}
Kit p.D579del has occasionally been identified as a germline change in patients with an inherited predisposition to GIST. Because nontumor tissue was not sequenced for the present patient, it is not possible to fully exclude the possibility that this was a germline variant, but the patient did not have a personal or family history of GIST.

In conclusion, we report here a case of treatment-refractory thymic carcinoma in which targeted tumor NGS provided guidance for salvage therapy. The tumor was found to harbor Kit p.D579del, a mutation that has previously been associated with susceptibility to TKIs. Treatment with imatinib resulted in stabilization of the patient’s disease. Patients such as this one show that clinical NGS has the potential to guide therapy in clinical oncology.

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REFERENCES