ABSTRACT

Objectives: This study aimed to review the prevalence of the BRAF V600E mutation in pediatric papillary thyroid carcinoma and its possible association with aggressive tumor behavior.

Study Design: This is a retrospective chart review using archived tumor tissue, which was then submitted for post-hoc BRAF V600E mutational analysis.

Methods: Patients between the ages of 0 and 18 years who underwent surgery for papillary thyroid carcinoma (PTC) from 1999-2012 were selected for a retrospective chart review to assess for aggressive disease characteristics. Microdissection was performed on archived tumor tissue, which was then analyzed for the BRAF V600E mutation by pyrosequencing.

Results: Tumor specimens were available for 19 of 27 patients who initially fit inclusion criteria. Age ranged from 2.8 to 18 years (median 13.7). Thirteen patients (68.4%) had metastases to the central neck, eight (42.1%) to the lateral neck, and five (26.3%) had pulmonary metastases. The BRAF V600E mutation was identified in seven patients (36.8%). Eleven patients had classic PTC, seven had a follicular variant of PTC, and one had an oncocytic variant. Seven (63.6%) of the samples with classical PTC were positive for the BRAF mutation. All samples with variant pathology showed wild type BRAF.

Conclusions: BRAF V600E mutations were more prevalent than previously thought in pediatric patients with PTC, but do not correlate with aggressive disease characteristics.

INTRODUCTION

Thyroid cancers comprise only 0.5-3% of all childhood malignancies and children often present at a more advanced disease stage than do adults.

Type RAF kinase (BRAF) is a serine-threonine kinase, and the T1799A/V600E mutation is thought to lead to malignant transformation2,9 by constitutively activating the protein.

The prevalence of BRAF mutations in adult papillary thyroid cancers (PTC) is estimated at 77.4% and is associated with aggressive disease behavior2,9,10.

The prevalence of the BRAF mutation in PTC was reported between 0-37% in five series published in the pediatric population, did not correlate with aggressive disease characteristics2,9,10.

We aim to determine the prevalence of this tumor marker in our pediatric population, and to determine its association with aggressive disease characteristics.

MATERIALS AND METHODS

Patients 0-18 were selected for a retrospective chart review if they underwent surgery for papillary thyroid carcinoma (PTC) at our institution between 1999 and 2012. Archived tumor specimens were microdissected10 to isolate tumor cells. DNA was extracted and amplified with polymerase chain reaction (PCR) and pyrosequencing11, which was performed to identify BRAF mutants (Figure 1).

Statistical tests included Fisher’s exact test for binary data, Pearson’s correlation coefficient was calculated for uniform binary data, and the t-test with two-sample equal variance for continuous data.

DISCUSSION

A recent meta-analysis including 14 studies and 2470 adult patients reported that the BRAF mutation was significantly associated with recurrence, lymphatic metastases, extrathyroidal extension, and advanced stage4.

Pediatric PTC is much more rare than PTC in adults and patients often present at a more advanced stage11.

In our study, the BRAF mutation was present in 7/19 patients (36.8%) overall, and in 7/11 patients (63.6%) with classical PTC. No patients with variant pathology showed the gene mutation.

Previous studies of pediatric patients with PTC demonstrated a BRAF mutation prevalence of 0 to 37%4,9,10. The prevalence of the BRAF gene mutation in our sample of patients with classical PTC (63.6%) is much higher than previously reported in the pediatric literature.

In our study, the BRAF mutation was not correlated with aggressive disease characteristics. This conclusion is in agreement with the existing pediatric literature4,9,10.

Patients 15 and older (P=0.09) and with smaller tumors (P=0.043) were more likely to show the BRAF mutation.

CONCLUSIONS

The BRAF V600E mutation may be more prevalent than previously thought in pediatric patients with PTC, but do not correlate with aggressive disease characteristics.