Parafibromin as a Tool of Screening in Parathyroid Neoplasms

Parathyroid carcinoma is the rare malignant form of primary hyperparathyroidism frequently associated with mortal outcome due to uncontrolled hypercalcemia. The diagnosis of benign and malignant parathyroid tumor depends strictly on certain morphological features or histologically documented metastasis. The diagnosis of parathyroid carcinoma thus requires either vascular or perineural invasion, invasive growth into adjacent tissues and/or metastases. The morphological features do not accurately predict the risk of malignancy and the tumor may already be incurable at the time of diagnosis. Therefore, the diagnosis of parathyroid carcinoma is often made in retrospect after surgery or sometimes after relapse.

A category of parathyroid neoplasms of uncertain malignant potential also known as atypical adenoma shows few morphological features suggestive of malignancy but lacks definite criteria of malignancy further adding to the complexity of parathyroid tumors. Sandelin et al. showed that half of the cases that were diagnosed as benign on histology showed recurrence or metastasis later. According to Marsh et al., approximately 50% of biologically malignant parathyroid tumors are diagnosed as benign by histological criteria, whereas around only 15% of histologically diagnosed parathyroid carcinomas actually behave biologically in an aggressive manner and rest behave as biologically benign. These tumors may represent either histologically benign tumor mimicking as malignant or malignant tumor being cured by surgical excision. Still there are some parathyroid tumors which are large sized but benign on histology. These tumors have different molecular characteristics that are more similar to malignant tumors.

The expression of immunohistochemical (IHC) markers has variable sensitivity and specificity in predicting malignancy due to difference in diagnostic criteria and different cut offs used in published studies. The markers studied include molecules involved in cell cycle proliferation and regulation such as parafibromin, APC, galectin-3, PGP9.5, Ki67, Rb, p53, p27, cyclin D1, FHIT and so on. Some of these markers like parafibromin, APC, PGP9.5 and galectin-3 have shown relatively high but variable sensitivity and specificity.

The HRPT2 gene was first known to cause sporadic parathyroid carcinoma in 2003. The protein product of this gene, parafibromin, is ubiquitously expressed and functions as tumor suppressor protein. Parafibromin is a nuclear protein that functions as transcription regulator. Its overexpression inhibits cell growth and causes cell cycle arrest at G1 phase partly due to cyclin D1 regulation as shown by Lin et al. in 2008. Somatic HRPT2 mutation occurs in 66% to 100% of parathyroid carcinomas, resulting in absent expression of parafibromin in atypical adenomas and carcinomas. The sensitivity and specificity of parafibromin has been reported to be 96% and 99% respectively in the diagnosis of parathyroid carcinoma by Tan et al. Absence of parafibromin in adenomas related to HPT-JT syndrome suggests HRPT2 mutation. Gill et al. showed 76% sensitivity of parafibromin in carcinoma considering complete loss. Howell et al. showed 67% sensitivity and 100% specificity for complete loss of parafibromin in parathyroid carcinoma. Thus, absent parafibromin immunoreactivity suggests either parathyroid adenoma or carcinoma with underlying genetic alteration of HRPT2 gene. However, positive parafibromin immunoreactivity strongly suggests benign tumor. According to Brown et al., presence of parafibromin staining in histologically atypical adenoma confirms a diagnosis of benign adenoma whereas if it is absent, it suggests having some malignant potential. On the contrary in a histologically malignant tumor, presence of parafibromin indicates low grade malignant tumor and absence indicates malignant tumor with more aggressive course. We studied 170 cases of parathyroid lesions including adenoma, carcinoma and atypical adenoma and found a sensitivity of 70% and specificity of 85.9% for parafibromin (unpublished data).

Thus, the results of above studies show that sensitivity and specificity of parafibromin is variable. The other issue is that parafibromin is a nuclear stain and nuclear stains are sometimes technically difficult. Therefore, instead of relying on parafibromin as single marker which is expressed in adenomas and negative in carcinomas, it should be combined with panel of markers including a cytoplasmic marker as well as positive markers for carcinoma to improve the sensitivity and specificity of differentiation between adenomas and carcinomas. Parafibromin may be accompanied by PGP 9.5, galectin and APC. The use of panel of IHC markers is important especially in cases of large adenomas (>1-2 gm), adenomas with atypical morphological features and clinically suspected carcinomas. In cases of adenomas even if parafibromin is absent, a close follow-up with serial serum calcium levels should be done. Atypical adenomas and suspected carcinomas with positive parafibromin support benign nature of the lesion and these patients may be relieved off from the worry of carcinoma.

Thus in my opinion, parafibromin along with the above panel of antibodies should be used routinely as a screening tool in all parathyroid neoplasms. It will be complimentary to histological features in differentiating benign and malignant parathyroid neoplasms and will help to segregate cases that need aggressive follow-up.
References


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