

Third and second generation assays as a marker for parathyroid carcinoma

Introduction: Parathyroid carcinoma (PCa) is a rare disease, comprising only 0.005% of all cancers. In the US National Cancer Database, only 286 cases have been described over 10 years. PCa accounts for less than 1% of sporadic primary hyperparathyroidism (PHP) and is associated with more severe clinical features than parathyroid adenomas. The severe hypercalcemia due to unchecked recurrent PTH hypersecretion is the main causes of morbidity and death in these patients. Differentiating Ca from parathyroid adenoma is challenging, particularly as the histopathology of parathyroid tumors can be equivocal. Indeed, the definitive diagnosis of PCa is largely made only when recurrence or metastasis occurs. As surgery remains the only curative treatment for PCa and as better outcomes are associated with complete resection of the tumor at the time of initial surgery, it is important to make a correct diagnosis at the time of first occurrence. Hence, a biological marker that could help to reliably distinguish PCa from parathyroid adenoma would be useful. It has recently been demonstrated that PCa over-secreted the amino form of parathyroid hormone (PTH), which is recognized by 3rd generation but not by 2nd generation (intact) PTH assays. In normal individuals, the 3rd generation/2nd generation PTH ratio should always be <1.

Material and methods: We studied the utility of the 3rd generation/2nd generation PTH ratio as a means of distinguishing PCa patients (n=24) from control groups with and without disorders of calcium secretion, including patients on renal hemodialysis (n=73), post-renal transplantation (60), elderly healthy (n=82) and PHP (n=30). Second (intact) and 3rd generation PTH were assayed with the PTH Duo kit from Scantibodies. The CV of these assays was <8%.

Results: The mean 3rd generation/2nd generation PTH ratio was 0.58±0.10 in the dialysis patients, 0.54±0.10 in the renal transplant group, 0.54±0.12 in the elderly healthy patients and 0.68±0.11 in the PHP group. All 245 of these patients presented a 3rd generation/2nd generation PTH ratio of <1. In contrast, we observed an inverted ratio >1 in 20 PCa patients, whereas only 4 PCa patients had a normal ratio of <1.

Conclusions: An inverted 3rd generation/2nd generation PTH ratio occurred in the majority of patients with advanced PCa and was absent in all 245 relevant controls. A 3rd generation/2nd generation PTH ratio >1 had a sensitivity of 83.3% and a specificity of 100% amongst PHP patients as a marker for PCa; among all published cases, the sensitivity was 75.8% and the specificity was 98.9%. Our results, based on a large cohort of PCa patients, shows that an inverted ratio may indeed have clinical utility as a tumor marker for PCa, as suggested in previous smaller series. Future investigations will be needed to assess if the dual determination of PTH with 2nd and 3rd generation PTH assays could be proposed in treated patients suspected of having PCa or as a pre-operative screening test to detect patients in whom an elevated suspicion for PCa exists. Alternatively, the 3rd generation/2nd generation PTH ratio could also be used as a new tool in the follow-up of the operated patients to identify those with persistent disease or later relapse.