Galectin-3 Immunodetection May Improve Cytological Diagnosis of Occult Papillary Thyroid Carcinoma

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Abstract. Galectin-3 has been found recently to be neo-expressed in thyroid cancers compared to benign lesions and it could therefore be considered a marker of malignancy. We report the case of a 36-year-old woman with a history of occasional dysphagia and dysphonia first observed in November 2000. Thyroid ultrasound scan revealed two subcentimetric nodules in the right lobe. The larger one underwent ultrasound-guided fine-needle aspiration cytology (FNAC). Due to the nature of the lesion, only a few cells could be collected. Their morphological aspect was suspicious but not conclusive for malignancy, therefore we marked the cells using a monoclonal antibody anti-galectin-3. The cytological suspicions were supported by galectin-3-expressing cells, so the patient was referred to surgery. The final histological diagnosis was conclusive for multifocal occult thyroid papillary carcinomas. We conclude that the galectin-3 immunocytochemical assay should be part of the diagnostic protocol supporting conventional cytology to characterize scanty and/or suspicious cellular smears.

Thyroid occult papillary carcinoma (OPC) is a malignant tumor less than one centimeter in diameter, which usually remains clinically silent (1-3). In some cases, this lesion may be associated with lymph node metastases and disseminated disease (1-4).

Ultrasound-guided FNAC is the best method for investigating the nature of small thyroid lesions. However, it can be extremely difficult to accurately sample very small, mixed nodules and, as a consequence, the number of aspirated cells may be very small (3,5). When morphological changes indicating malignancy are not clearly evident in such hypocellular smears, the immunodetection of tumor-associated antigens, supporting the presence of transformed follicular cells, may be very useful.

Results

In two of the four smears there were very few cellular aggregates. A single follicular cells group, arranged in a mono-layered sheet, optically showed quite clear oval nuclei, with a thin cytoplasmic rim and inconspicuous nucleoli. There was a second cellular population, made up of four three-dimensional clusters comprising a few cells showing large hyperchromatic nuclei and vacuolated cytoplasm, similar to those present in a degenerative process. Both populations were considered suspicious for papillary carcinoma. A few, single, normal looking follicular cells were also present. No papillary fragment, psammoma...
bodies or pseudo-inclusion were detected. We analyzed the smears but no diagnostic agreement was reached.

Therefore we decided to perform an immunocytochemical staining using the rat-mAb to galectin-3. The immunocytochemical stain was performed on destained conventional smears as previously described (9). The suspicious cellular populations showed a marked specific cytoplasmatic positivity to galectin-3. The rare normal-looking follicular cells showed no reaction whereas macrophages expressing galectin-3 were considered an internal positive control (7).

The patient underwent surgery. Histological examination confirmed the presence of two subcentimetric papillary carcinomas within the right lobe. The larger nodule, 0.6 cm in diameter, showed cystic changes and was composed mainly of papillary structures. The smaller one was solid and presented both papillary and follicular features. The neoplastic cells showed pale, oval nuclei and some nuclear groves. On this basis, a diagnosis of multi-centric occult papillary carcinoma was made.

**Discussion**

At present, ultrasound-guided FNAC is the best way to assess the nature of a thyroid nodular pathology. Thanks to this diagnostic test, thyroid malignancies may be readily detected and patients harbouring benign nodules can avoid unnecessary surgery (1,5).

FNAC can be easily performed, being nontraumatic and well tolerated by the patients. Nevertheless, it is not without its drawbacks, showing false-negative diagnoses in 2.2% to 10% of the cases (1,5). False-negative results are relatively frequent, mainly in mixed/hemorrhagic nodules and in occult carcinomas smaller than 1 centimeter in diameter (1-3.5). The case described in this paper displayed both of these features. Although occult papillary carcinoma of the thyroid is known to be an indolent lesion with good prognosis, the disease may sometimes cause recurrent neck lateral lymph nodes or scattered metastasis (2-4). Early detection and surgical treatment are mandatory to improve survival, even in lesions of less than one centimeter in diameter.

In small tumors, FNAC has to be performed under ultrasound guidance and enough cells should be collected to allow cytological diagnosis. A collection is considered adequate if it comprises at least 6-10 well-preserved aggregates of epithelial cells (10,11). This is not always possible in small/hemorrhagic lesions. If the smears, as in our case, present only a few suspicious cells, a marker of malignancy is necessary to support the cytological diagnosis.

Several investigators (6-8) have reported recently that galectin-3, a glycoprotein having 31 K-Da molecular weight, is expressed selectively in malignant thyroid tumors and shows a strong immunostaining reaction in the majority of papillary carcinomas. Normal thyroid tissue, hyperplastic goiter and follicular adenomas do not show any detectable amounts of galectin-3 (6-8). Studies performed using paraffin-embedded tissue or fresh cytological sample demonstrated the value of the immunocytochemical assay for detecting galectin-3 expression in thyroid tissue (6-8).

We showed that galectin-3 expression can be detected in routinely stained FNAC smears, in particular in those cases in which there is no diagnostic agreement. This technique allows the protein to be specifically detected in suspicious cells, supporting the hypothesis of their malignant transformation.

The new high-resolution ultrasound techniques may improve the detection rate of very small thyroid nodules whose aspiration yields very few cells, thus underlining the need for new diagnostic markers.

We conclude that this easy, fast, accurate and cost-effective procedure, that may be applied to routinely-stained cytological samples, should be part of the diagnostic protocol in suboptimal smears.

**References**


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