Expression of thyroid transcription factor 1 in primary brain tumours

J Zamecnik, M Chanova, R Kodet

**Background:** Thyroid transcription factor 1 (TTF-1) is expressed in a proportion of carcinomas derived from follicular thyroid cells and respiratory epithelium. Immunohistochemical detection of this protein was shown previously to be a helpful aid in tumour diagnosis, specifically in deciding whether a tumour is primary to the lung/thyroid gland or metastatic. Recently, TTF-1 expression was also observed in certain areas of postnatal brain.

**Aim/Method:** To investigate the expression of TTF-1 protein in a spectrum of 73 primary brain tumours including astrocytomas, glioblastomas, ependymomas, oligodendrogliomas, medulloblastomas, and gangliogliomas of different sites.

**Results:** All the tumours were negative for TTF-1 except for two ependymomas of the third ventricle.

**Conclusions:** The expression of TTF-1 in brain tumours appears to be site specific rather than associated with tumour dedifferentiation. The presented expression of TTF-1 protein in certain primary brain tumours should be taken into consideration when interpreting the immunohistochemical staining of brain tumours of uncertain primary site.

**DISCUSSION**

In this pilot study, we investigated 73 PBTs from different sites in both children and adults (table 1). The patients’ medical records were reviewed so that relevant analyses of survival and of a possible prognostic impact of TTF-1 detection could be performed.

Resected tumours were fixed in 10% formalin and embedded in paraffin wax. Tissue sections were dewaxed and rehydrated. Heat induced epitope retrieval was performed in sodium citrate buffer solution (pH 6.0), which was warmed to 96°C in a water bath for 40 minutes. Mouse monoclonal antibody against TTF-1 (clone 8G7G3/1; Neomarkers, Freemont, California, USA) was used at a dilution of 1/100; the incubation was performed overnight at 4°C. The antigen–antibody complexes were visualised by a biotin–streptavidin detection system (ChemMate detection kit; DakoCytomation, Ely, Cambridgeshire, UK) with 3,3’-diaminobenzidine (Fluka Chemie GmbH, Buchs, Switzerland) as chromogen. All sections were counterstained with Harris’ haematoxylin. Nuclear staining only was considered as a positive result. Tissues of non-neoplastic thyroid gland and lung and of a pulmonary adenocarcinoma with known TTF-1 positivity served as positive controls.

To confirm the nature of the tumours, each was subjected to immunoperoxidase staining using primary monoclonal antibodies (DakoCytomation) against glial fibrillary acidic protein (GFAP; clone 6F2; diluted 1/1000), synaptophysin (clone SY38; diluted 1/20), and cytokeratin (clone AE1/AE3; diluted 1/200).

**RESULTS**

All PBTs were negative for TTF-1 except from two ependymomas in which strong nuclear staining was seen in most of the tumour cells. In these ependymal tumours, the cell processes of the perivascular pseudorosettes were stained by anti-GFAP antibody, but immunohistochemistry for cytokeratin and synaptophysin was negative. Both of these ependymomas were localised in the third cerebral ventricle, were incompletely resected, and the children were treated by chemotherapy and radiotherapy. One of these ependymomas (in a 5 year old boy) was classified as grade III (fig 1). It recurred 14 months after surgery and the patient died as a result of tumour progression four months later. The other patient had grade II ependymoma (a 12 year old girl); the patient is well 72 months after tumour removal.

**Abbreviations:** GFAP, glial fibrillary acidic protein; PBT, primary brain tumour; TTF-1, thyroid transcription factor 1
Most primary brain tumours are thyroid transcription factor 1 (TTF-1) negative

However, TTF-1 protein might be expressed in certain brain tumours, especially those in the third ventricle region

These facts should be taken into consideration when interpreting the immunohistochemical staining of brain tumours of uncertain origin

Most PBTs can be distinguished from metastatic tumours by histology. However, epithelioid features of PBTs, including papillary pattern of growth of brain tumours (particularly of ependymomas), can cause diagnostic problems. In such cases, the interpretation of TTF-1 protein expression in brain tumour cells could be misleading, especially in small biopsy specimens.

In conclusion, most PBTs are TTF-1 negative; however, TTF-1 protein might be expressed in certain brain tumours, especially those in the third ventricle region. This should be taken into consideration when interpreting the immunohistochemical staining of brain tumours of uncertain origin.

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