A rare case of breast cancer showing distinct TTF-1 nuclear expression: small cell carcinoma or not?

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Conflict of interest
The authors declare no conflict of interest.

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Sir: We read with great interest the article entitled “TTF-1 expression in breast carcinoma: an unusual but real phenomenon”, as presented in *Histopathology*.[1] Ni and coauthors evaluated thyroid transcription factor-1 (TTF-1) expression in 1132 primary invasive breast carcinomas (IBCs) and 208 primary pulmonary carcinomas using tissue microarray sections. They detected moderate to strong TTF-1 nuclear expression in only one IBC (0.09%) and 149 pulmonary carcinomas (71.6%) by clone 8G7G3/1, and in no IBC (0%) and 147 (70.6%) pulmonary carcinomas by clone SPT24. The single IBC case with 8G7G3/1 positivity was histologically assessed as no special type, with histological grade 2, and showed estrogen receptor positivity, progesterone receptor positivity, and HER2 negativity. The authors concluded that both TTF-1 antibodies were useful in differentiating breast from pulmonary carcinomas.[1]

TTF-1, a 38-kDa homeodomain-containing nuclear protein encoded by the NKX2-1 gene, regulates the transcription of genes, particularly in the thyroid, lungs, and diencephalon, and immunostaining for TTF-1 is accordingly used in routine surgical pathology practice to facilitate identifying the origin sites of carcinomas. However, it has been demonstrated that TTF-1 is commonly detectable not only in pulmonary but also in extra-pulmonary small cell carcinomas.[2] In a study of the breast, Shin *et al.* described two of 10 cases (20%) with primary small cell carcinomas as showing moderate to strong, diffuse nuclear staining for TTF-1.[3] Similar TTF-1 immuno-reactivity in such cancers was subsequently reported by other investigators.[2, 4, 5] In addition, in an extremely rare mammary carcinoma with both small cell neuroendocrine and metaplastic features, which we very recently reported in this

journal,[6] only the former component was selectively TTF-1 (clone 8G7G3/1) positive (Figure 1).

Ni and co-workers described the IBC positive for TTF-1 (8G7G3/1) as being of no special type with histological grade 2 and luminal immuno-expressions.[1] However, the figure showing TTF-1 nuclear expression could prompt readers to consider the possibility of a small cell carcinoma. Unfortunately, immunohistochemical analyses of neuroendocrine markers, such as chromogranin A, synaptophysin and CD56 (NCAM), for this cancer were not included in their study. In our opinion, morphological review as well as further

immunohistochemical examination should be implemented for this specific case. Indeed, the results for neuroendocrine markers, whether positive or negative, would add to the interest of their investigation. In addition, we hope that if the authors accumulate additional cases of small cell mammary carcinoma, TTF-1 expression in these cancers including the differences between antibody clones 8G7G3/1 and SPT24 will be examined and comprehensively discussed.

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Figure 1. Immunohistochemical findings for TTF-1 in a small cell breast carcinoma with squamous differentiation. Note that TTF-1 expression is seen only in the nuclei of small carcinoma cells.