Peer Review File

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Reviewer A

Interesting case in a well written article

Reviewer B

Comment 1: Since an intraoperative rapid diagnosis was conducted, it is inferred that the fine-needle aspiration biopsy was insufficient for malignancy detection. Elaborating on the reasons for this could enhance the article's quality.

Reply 1: FNAB has a high diagnostic value in thyroid carcinomas. Indications for FNAB in thyroid nodules are as follows: the diameter of nodules preferably is larger than 10 mm, nodules are solid and hypoechoic with irregular margins, extra-thyroidal extensions, and vascular spots or microcalcifications in nodules. There are reports of patients with incidental thyroid carcinoma who did have an FNAB performed preoperatively, but those sampled only benign nodules. A multicenter study, published in 2013 by Smith et al, showed that incidental thyroid carcinoma rate reached 15.6% of the 1,523 patients operated for benign preoperative pathologies (excluding pathologies of undetermined significance and suspected for malignancy). Thus, the high incidence of incidental thyroid carcinoma may be due to problems with thyroid biopsy site selection. In addition, it has reported that FNAB is prone to misdiagnose or underdiagnose in primary squamous cell carcinoma of thyroid. The reason may be that squamous cells may firmly present in the tumor by promoting connective tissue hyperplasia and fibrosis, resulting in unsuccessful puncture, or sampling error caused by uneven distribution of squamous cells in the tissue and less acupuncture tissue. No tumor cell components were detected by FNAB in this patient, and the presence of malignant tumor tissue components was confirmed by postoperative pathology. Therefore, the above studies suggest that FNAB has a false negative in the diagnosis of incidental thyroid carcinoma, especially in squamous cell carcinoma with other malignant tumors. FNAB alone is not enough to diagnose rare coexisting tumors, and should be combined with intraoperative rapid diagnosis.

Changes in the text: We have modified our text as advised (see Page 5, line 83-87).

Comment 2: The diagnosis of papillary thyroid carcinoma with squamous cell differentiation, taking into account the squamous cell component, should hinge on the presence of SCC. Is the diagnosis of SCC based on nuclear atypia, mitotic figures, or tumor necrosis?

Reply 2: The diagnosis of SCC depends on pathology and immunohistochemistry. Immunohistochemistry has been introduced in this article. The SCC is distinguished histologically by differentiation of the tumor cells, sometimes to a considerable degree, with well marked intercellular bridges and horny pearl. In this case, postoperative pathology suggested squamous cell differentiation. Microscope observation (as Figure 2A,B): papillary carcinoma and squamous carcinoma with invasive growth. Papillary carcinoma cells were glandular tubular and papillary with large nuclei and hairy glass-like. While squamous carcinoma cells were irregularly distributed in strips and clusters with long spindle-shaped, or irregular polygonal cells, large and deeply stained nuclei, eosinophilic cytoplasm, obvious nuclear atypia, and easy to see nuclear mitotic figure as well as intracellular keratinisation and inter-cellular bridges. Therefore, based on the pathologic histomorphology observed under the microscope, the diagnosis of SCC can be based on nuclear atypia, mitotic figures.

Changes in the text: We have modified our text as advised and described in this section(see Page 6, line 96-101).

Comment 3: The case presentation should include details about the presence of an STI component.

Reply 3: We have supplemented an STI component in the original text and drawn the time axis diagram.

Changes in the text: We have modified our text as advised (see Page 7, line 121-124 and Page 16, line 298-299).

Comment 4: The authors discuss immunostaining results for carcinoma cells. However, did the immunostaining results for papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, squamous cell carcinoma, and their respective components remain consistent? While differences

are mentioned in the Discussion section (e.g., TTF-1 negativity), they should also be highlighted in the case presentation section.

Reply 4: The immunostaining results for papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, squamous cell carcinoma are remain consistent. We have already highlighted in the case presentation section.

Changes in the text: We have modified our text as advised and described in the case presentation section (see Page 6, line 104-108).