Peer Review File

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Reviewer A

Comment 1: The manuscript describes a rare case of intrathyroidal thymic carcinoma. The report is interesting because of the rarity of the disease. However, in my opinion, there are now quite a few reports on this disease, although many of them are only case reports.

For example, the publication by Wei Ge et al summarized 2 cases of intrathyroidal thymic carcinoma. So the question is, what are the novel findings in the submitted case report that could add to the current knowledge of intrathyroidal thymic carcinoma? I myself cannot see any significant novel aspect.

Reply 1: We acknowledge the reviewers' concerns regarding innovation. While there are numerous case reports on ITTC, our study offers clinicians specific diagnostic insights by thoroughly detailing the challenges encountered in the diagnostic process and highlighting the significance of multidisciplinary collaboration. Furthermore, we have included the application of the latest immunohistochemical markers, such as CD5 and CD117, thereby underscoring their importance in diagnosis. This information not only enhances the clinical diagnostic experience of ITTC but also paves the way for future research directions.

Comment 2： I would like to make the following minor comments:

a) Line 92: the first word "Intrathymid" should be "Intrathyroidal".

b) Lines 101-102: ITTC is not associated with intrathyroidal thymoma. Although there may be such cases. However, this is not the typical presentation. Thymoma and thymic carcinoma are different.

c) Lines 156-157: In my opinion, instead of "in individual cases", better "in individual cells"?

d) Line 161: p16 is not a marker for thymic carcinoma. Or do you want to mention it for the differential diagnosis of metastases from head and neck cancer? This should be clarified for the reader.

e) It would be nice to add information on the patient's status after radiotherapy.

f) Line 169: The first word "IITC" contains a typo. One "I" needs to be deleted.

g) Line 227: The abbreviation "CK" should be explained. In addition, BCL-2 is not an

epithelial marker. It is an anti-apoptotic protein.

Reply 2:

a): Thank you for your kind advice. We have revised the article as advised. (see Page 4, line 90)

b): Thank you for your kind advice. We have revised the article as advised. (see Page 4, line 97-99)

c): Thank you for your kind advice. We have revised the article as advised. (see Page 6, line 153)

d): We appreciate the reviewers for highlighting this issue. In our study, the detection of p16 was not employed for the direct diagnosis of thymic cancer; rather, it was utilized as part of the differential diagnosis to exclude other potential malignancies. p16 (INK4a) is a cell cycle regulatory protein, and its expression is often abnormal in various malignant tumors, particularly in cancers associated with cell cycle dysregulation. Although p16 is not a specific marker for thymic cancer, it can be beneficial in certain cases to aid in diagnosis, especially when used in conjunction with other markers, such as CD5 and CD117, to differentiate between various types of malignancies.

In our case, the p16 test result was negative, which further supported the diagnosis of ITTC and helped us rule out other potential malignancies, such as poorly differentiated carcinoma or squamous cell carcinoma. We have elaborated on the interpretation of the p16 test results in the text and clearly outlined its role in differential diagnosis (see Page 6, line 158-160).

e): The patient lived in Japan for an extended period. After the diagnosis was confirmed, the patient returned to Japan for treatment. We attempted to contact the patient multiple times; however, due to the change in region, the patient's contact information was updated, resulting in a loss of communication. Consequently, we were unable to complete the follow-up. Despite this setback, we will continue our efforts to reach out to the patient to obtain the latest information regarding their treatment and prognosis.

f): Thank you for your kind advice. We have revised the article as advised. (see Page 6, line 167)

g): Thank you for your kind advice. We have revised the article as advised. (see Page 8, line 225)

Reviewer B

In this manuscript the Authors describe a case of intrathyroidal thymic carcinoma (ITTC) discussing the histological and immunohistochemical differential diagnosis and ultrasound characteristics. This tumor has been reported only in a limited number of previous reports, and from this point-of-view the manuscript could be of interest. However, in its present form it has significant flaws, and is not suitable for publication due to the following issues which should be addressed in depth by the Authors:

Comment 1: ITTC is described as a low-grade tumor. This seems to be in contrast with the nodal involvement described

Reply 1: We acknowledge the reviewers' questions. Although ITTC is generally classified as a low-grade malignant tumor, it still has the potential for lymph node metastasis. The literature indicates that the rate of lymph node metastasis in ITTC is approximately 35% to 45%. Therefore, while the biological behavior of ITTC is relatively indolent, the occurrence of lymph node metastasis is not contradictory; rather, it is an integral aspect of its clinical characteristics.

Comment 2: Surgical treatment is the treatment of choice of these tumors. In this patient thyroidectomy with lymphoadenectomy was not considered as a therapeutic option. This point should be discussed

Reply 2: In the final paragraph of the discussion section, we outlined the selection of treatment methods. Surgery is the preferred approach; however, in cases of locally advanced ITTC deemed unsuitable for therapeutic surgery, radiotherapy alone or in combination with chemotherapy may be considered as alternative treatments. Based on the physician's recommendations and the patient's preferences, the patient opted for radiotherapy alone as the initial treatment.

Comment 3: No information concerning follow-up is provided.

Reply 2: The patient lived in Japan for an extended period. After the diagnosis was confirmed, the patient returned to Japan for treatment. We attempted to contact the patient multiple times; however, due to the change in region, the patient's contact information was updated, resulting in a loss of communication. Consequently, we were unable to complete the follow-up. Despite this setback, we will continue our efforts to reach out to the patient to obtain the latest information regarding their treatment and prognosis.

Comment 4: The diagnostic approach was limited to ultrasound. CT and PET scan are indicated in the staging of the tumor.

Reply 4: We appreciate the reviewer's concerns about diagnostic methods.

Ultrasonography is vital for initial thyroid tumor screening, particularly for assessing size, location, and adjacent tissue relationships. However, computed tomography (CT) and positron emission tomography (PET) scans are essential for comprehensive tumor staging, evaluating boundaries, surrounding structures, and distant metastasis. We added that to the discussion section. (see page 9, line 241-251).

The ultrasound revealed a hypoechoic solid mass with indistinct boundaries, consistent with thyroid malignancy. Pathological analysis confirmed intrathyroidal thymic carcinoma (ITTC), supported by positive CD5 and CD117 expression in immunohistochemical staining.

We agree that future cases should integrate multiple imaging modalities for a comprehensive assessment of tumor stage and extent. We have emphasized the importance of computed tomography (CT) and positron emission tomography (PET) in the discussion section.

We appreciate the reviewer's insightful comments. Future research will focus on applying various imaging techniques to enhance diagnostic accuracy and thoroughness.

Changes in the text:

The biological behavior of ITTC is typically characterized as indolent, with a generally favorable prognosis for the majority of cases [12]. Research indicates that the 5-year and 10-year survival rates for ITTC are 90% and 82%, respectively [16]. However, due to the rarity of ITTC, there is a significant paucity of research both domestically and internationally, which has resulted in a lack of clear guidelines for its diagnosis and treatment [14]. While ultrasonography is a vital initial tool for thyroid tumor screening, its capacity for full tumor staging is limited. The diagnostic approach for ITTC should include advanced imaging techniques like computed tomography (CT) and positron emission tomography-computed tomography (PET-CT). These methods are essential for comprehensive staging, evaluating tumor boundaries, assessing surrounding structures, and detecting distant metastases. Their integration enhances diagnostic accuracy and improves treatment planning and patient prognosis. At present, the clinical management of ITTC is primarily informed by clinical experience rather than empirical evidence. Surgical intervention is considered the preferred treatment modality for ITTC [19].