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Peer Review File

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Reviewer A

Congratulations to the authors on reporting a rare lung neoplasm with metastatic thymoma. Both are rare and interesting conditions. I will organize my comments under following sub-headings:

1. Writing/editing:

Comment: - avoid using acronyms in abstract

Reply: **line 35-37 of Manuscript rewied corrected.**

Comment: - manuscript needs English editing. For example, in line 26, which needs to spelled correctly, in keywords thymic carcinoma needs to be spelled correctly.

Reply: line 13 -14 the term Thymic carcinoma was added in the keywords.

Comment: - correction in line 57 'paratrcheal' or 'pretracheal'

Reply: corrected line 119 Surveillance CT chest performed 1 year later showed some lymph node enlargements.

- in line 67 fibrous septa is written twice

Reply: corrected

- correct line 71-72 to something like "surveillance CT chest performed 1 year later showed enlarged retro-naval and pre-tracheal lymph nodes.

Reply: corrected line 119 Surveillance CT chest performed 1 year later showed some lymph node enlargements.

- expand acronym TPS in line 75

Reply: line 122 (Tumor proportion score > 10%)

- in addition to this there are multiple other English writing mistakes that would require editing. for example lines 54-55.

Reply: corrected.

2. Clinical Case

- does patient have any relevant past medical history?

Reply: line 93: No other medical past history was recorded

- In line 47 please write X-ray of the Chest or chest radiograph and use correct acronym of RLL which would be right lower lobe.

Reply: line 93-96. The chest radiograph showed a nodule with irregular borders in right lower lobe (RLL) which was confirmed with a chest computed tomography (CT) which led to suppose in the first instance a pulmonary malignant process.

- Please also explain the though process in taking care of this patient to interest readers. for example, was there a CT Chest done after chest x-ray and before PET scan? What differentials

were considered after the initial Chest CT. please explain clearly.

Reply: line 93-96. The chest radiograph showed a nodule with irregular borders in right lower lobe (RLL) which was confirmed with a chest computed tomography (CT) which led to suppose in the first instance a pulmonary malignant process.

- Acronyms PET and CT should be expanded when they first appear in the text. example in lines 48 and 51.

Reply: line 93-96, The chest radiograph showed a nodule with irregular borders in right lower lobe (RLL) which was confirmed with a chest computed tomography (CT) which led to suppose in the first instance a pulmonary malignant process. The positron emission tomography (FDG-PET) scan of the whole body

- Also explicitly explaining CT of the chest and PET scan of whole body or skull to thigh area would be appropriate

Reply: line 93-96, The chest radiograph showed a nodule with irregular borders in right lower lobe (RLL) which was confirmed with a chest computed tomography (CT) which led to suppose in the first instance a pulmonary malignant process. The positron emission tomography (FDG-PET) scan of the whole body

- Before VATS, was CT-guided transthoracic biopsy considered for the RLL nodule? please explain.

Reply: line 100-101 Due to the central location of the lesion, it was not technically possible to perform a transthoracic biopsy

- In line 77-78, describe the type of lesion like blastic vs lytic when describing osseous involvement.

Reply: line 124-126 A new chest CT scan showed a lytic L3 involvement at the level of the left supra acetabular area and suspicion of involvement of the right greater trochanter.

- Describe treatment plan after diagnosis metastatic thymic carcinoma and follow up course if any.

Reply: line 128 The patient begins treatment with radiotherapy

3. Discussion:

- Change heading 'comments' to 'discussion' in line 82

Reply: line 129 Discussion, corrected

- discussion sectioned needs to structure in an appropriate format

Reply: corrected

- since you are highlighting both CPMT and metastatic thymic carcinoma, please discuss about both if possible

Reply: line 130-140. The CMPT is a rare entity, the diagnosis is histological and the presence of basal cells is required for the diagnosis. An association between CMPT and epithelial tumors of the thymus has not been described. In the case presented, it seems a finding of two independent lesions. The published cases, like the patient presented, have been in older adults with the exception of a TMNC in a 19-year-old adolescent (5), therefore, it should be considered as a differential diagnosis in a wider age range.

- start discussion with epidemiology describing CPMT and metastatic thymic carcinoma briefly then their clinical or presenting features. (see ref 1)

Reply: line 130-140. The CMPT is a rare entity, the diagnosis is histological and the presence of basal cells is required for the diagnosis. Kamata et al have described the clinicopathological characteristics in ten cases: half had a history of smoking, all the lesions were small and peripheral, solid or partially solid, of irregular contour, and the average size was 1 cm. All, except one patient, were asymptomatic, and the irregular appearance of the nodular contour suggested the possibility of adenocarcinoma in all cases (1,5).

- then talk about diagnosis, role of imaging (how does CPMT appear on CT, differential diagnosis) and especially MRI in thymoma

Reply: line 141-157 Onishi et al, in a retrospective study on 16 patients whose median age was 70 years, described the tomographic characteristics of TMNC. In most cases the lower lobes were affected, they were peripheral, solid nodules, close to the visceral pleura and with an average size of 9.1 mm. The same author compared the mucin content with the tomographic pattern and the expression of fluorodeoxyglucose (FDG) in the PET. Most of the nodules with a pure or subsolid ground glass (GGO) pattern contained a high percentage of mucin, unlike the solid nodules (10) and it can be inferred that those CMPTs with a high mucinous component may present as subsolid lesions, while when the cellular component is predominant, they are expressed as solid tumors. It was not possible to establish any relationship between the level of FDG uptake and mucin content: of the 14 patients with low uptake, with SUV values of 0.51 to 1.35, 12 had a high mucin content, and the remaining two had a higher component mobile. The only case with moderate uptake and SUV value of 3.67 presented <30% mucin. The authors concluded that it is not possible to establish a clear relationship between the amount of mucin and the expression of FDG. As early stage adenocarcinomas, CMPT have radiologic silimarities, it is important that radiologists bear in mind this possible differential diagnosis (11).

- Then talk about histopathological diagnosis and considerations. may talk about immuno-histochemical staining and genetic studies as well.

Reply: line 158-192 The diagnosis of TMNC is morphological with the finding of a papillary proliferation in the lung parenchyma with mucinous, ciliated and basal cells and accumulation of intraalveolar mucin unrelated to the bronchiolar lumen. The proportion of cellular components is variable with the exception of the basal cells that are required to make the diagnosis. These can be highlighted with immunohistochemistry (expression of cytokeratins 5/6 and p63 / p40), but they are not necessary to make the diagnosis. Classic and non-classical TMNC terminology was proposed to describe these histological variants. Recently, the morphology, immunohistochemistry and genetic analysis of a series of 25 cases were reviewed and the concept of Bronchiolar Adenomas was proposed, including the classic TNMC with or without papillae, considering them of the proximal bronchiolar type. Another subgroup, with almost no mucin or cilia, would be of the distal bronchiolar type. However, there are intermediate patterns, which leads to interpreting the group of bronchial adenomas as a morphological spectrum from the proximal to the distal type with occasional overlaps. It is important for the pathologist to be familiar with this entity to provide an accurate diagnosis given its clinical importance. Intraoperative frozen sections might be challenging not only because it is a rare lesion, but also because ciliated cells are difficult to identify in frozen sections and in cytology smears. In our case, the intraoperative FNA showed mucin-producing cells in the smear that, based on the location of the lesion, were diagnosed as neoplastic cells. Still in permanent slides, because of the focal stromal destruction and complex architecture, these lesions may be confused with adenocarcinomas. However there two key features to consider in the diagnosis of CMPTs: the basal cell layer and the cilia, both of which were found in our patient's specimen together with the papillary architecture (9). The importance in the differential diagnosis lies in the fact that none of the published CMPT had recurrences or metastases with a benign clinical behavior. But given their histological characteristics that sometimes present fibrosis that distorts the architecture, focal proliferation along alveolar septa, absence of capsule (although always circumscribed) and micropapillae, it seems more appropriate to consider them as tumors with low malignant potential (10).

An alert is a recently reported case with invasion by isolated less differentiated cells in a fibrosis focus that was interpreted as a possible malignancy from the basal cells (11).

The presence of driver mutations in BRAF, EGFR, and KRAS genes suggest that these lesions are neoplasms and not metaplastic, as could be interpreted morphologically. The most frequently found is p.V600E in exon 15 of BRAF. The alteration in EGFR (deletion in exon 19 E746-T751 / S752V) is unusual in lung adenocarcinomas (12)

- Then talk about proposed treatment plans, discuss about recurrence rate and malignant potential if any? (see ref 2)

Reply: line 193-196. The treatment of CMPT is surgery. Lobectomy can be avoided due to the low degree of malignancy described in most of the reported cases. However, the

impossibility of ruling out malignancy in the intraoperative period makes it necessary to practice lobectomy, the treatment of choice for lung cancer

1: Shen L, Lin J, Ren Z, Wang B, Zhao K, Lu Y, Wang F, Zhan L. Ciliated muconodular papillary tumor of the lung: report of two cases and review of the literature. J Surg Case Rep. 2019 Aug 31;2019(8):rjz247. doi: 10.1093/jscr/rjz247. PMID: 31528329; PMCID: PMC6736349.

2: Ishikawa M, Sumitomo S, Imamura N, Nishida T, Mineura K, Ono K. Ciliated muconodular papillary tumor of the lung: report of five cases. J Surg Case Rep. 2016 Aug 25;2016(8):rjw144. doi: 10.1093/jscr/rjw144. PMID: 27562578; PMCID: PMC4999048.

Reviewer B

This paper is a case report of a combination of CMPT and thymoma, in particular, the first case report of CMPT in Latin America.

However, several minor concerns should be addressed.

Minor comment

Key words
Key words might be three words: thymoma, thymic carcinoma, Ciliated muconodular papillary tumor (CMPT).

Reply: line 13-14 the term Thymic carcinoma was added in the keywords

Introduction, 39th line
'This is the first case of CMPT in Latin America' might be better.
Reply: line 50, corrected. This is the first case of CMPT in Latin America

Clinical case, 48th line
'The FDG-PET/CT scan….' might be better.

Reply: line 94-96, The chest radiograph showed a nodule with irregular borders in right lower lobe (RLL) which was confirmed with a chest computed tomography (CT) which led to suppose in the first instance a pulmonary malignant process. The positron emission tomography (FDG-PET) scan of the whole body

63th line

(Fig. 3)

Reply: line 111. corrected

Discussion

This case of CMPT described as moderate FDG uptake in PET/CT, however there is no discussion about this point. It might be better to discuss this point. The author might refer to the paper: Annals of Nuclear Medicine. 2020; 34: 448–452.

Reply: line 141-157 Onishi et al, in a retrospective study on 16 patients whose median age was 70 years, described the tomographic characteristics of TMNC. In most cases the lower lobes were affected, they were peripheral, solid nodules, close to the visceral pleura and with an average size of 9.1 mm. The same author compared the mucin content with the tomographic pattern and the expression of fluorodeoxyglucose (FDG) in the PET. Most of the nodules with a pure or subsolid ground glass (GGO) pattern contained a high percentage of mucin, unlike the solid nodules (10) and it can be inferred that those CMPTs with a high mucinous component may present as subsolid lesions, while when the cellular component is predominant, they are expressed as solid tumors. It was not possible to establish any relationship between the level of FDG uptake and mucin content: of the 14 patients with low uptake, with SUV values of 0.51 to 1.35, 12 had a high mucin content, and the remaining two had a higher component mobile. The only case with moderate uptake and SUV value of 3.67 presented <30% mucin. The authors concluded that it is not possible to establish a clear relationship between the amount of mucin and the expression of FDG. As early stage adenocarcinomas, CMPT have radiologic silimarities, it is important that radiologists bear in mind this possible differential diagnosis (11).

Figure

Fig.1 ‘Thoracic FDG-PET/CT’ might be better.

Reply: corrected, line 292.

Fig.2 ‘CT shows a nodule with pleural indentation in right lower lobe’ might be better.

Reply: corrected, line 294.