

Peer Review File

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Reviewer A

Comment 1:

This is an interesting paper describing the abscopal effect which is attracting increasing interest as our understanding of immune mechanisms grows. Though description of the abscopal effect is the main point of the case report, with the occurrence of a solitary plasmacytoma of the thyroid slightly less so, you only cite two references of the abscopal effect (Mole 1953, Aboudeh 2016). I would suggest including Demarai & Formenti *Br J Radiol* 2020;93:20200042 and Lippert & Greenberg *J Clin Invest.* 2021;131(9):e148274 (or similar) and including a short statement in the Discussion about this. The latter paper does not really support your contention that the Hashimoto's thyroiditis in some way predisposed t the abscopal effect, more that the DNA damage from the irradiation was in some way the trigger.

Reply1:

We appreciate the Reviewer's comment on this point. In accordance with your comment, we added the following sentences to the 156-158th lines. And reference 7 (Demarai & Formenti *Br J Radiol* 2020;93:20200042), reference 8 (Lippert & Greenberg *J Clin Invest.* 2021;131(9):e148274) and reference 9 were added.

Changes in the text:

The abscopal effect is one of an antitumor immune response [7, 8, 9]. Recent studies suggest that immunotherapy and radiation in combination may enhance the abscopal effect [7, 8, 9]. (156-158th lines)

7. Demaria S and Forment SC. The abscopal effect 67 years later: from a side story to center stage. *Br J Radiol* 2020; 93: 2020042.
8. Lippert TP and Greenberg RA. The abscopal effect: a sense of DNA damage is in the air. *J Clin Invest* 2021; 131: e148274.
9. Liu Y, Dong Y, Kong L, et al. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. *J Hematol Oncol* 2018; 11: 104.

(220-225th lines)

Comment 2:

Your Ethical Statement (lines 193-202) is somehow duplicated in lines 116-123. Lines 193-195 have also been duplicated in lines 195-197.

Reply 2:

Thank you for your comment. The guidelines for authors require that the Ethical statements should be described in both the "Case Presentation" section and the "Ethical Statement" section on Footnote.

Comment 3:

SI units would be better for the biochemical results in lines 88-91.

Reply 3:

Thank you for your comment. In accordance with your comment, we added the following improved sentence to the 89-92nd lines.

Changes in the text:

Laboratory data were as follows: TSH, 3.15 mIU/L (normal 0.65–5.55 mIU/L); free T3, 5.07 pmol/L (normal 3.53–5.68 pmol/L); free T4, 0.10 pmol/L (normal 0.12–0.23 pmol/L); thyroglobulin (Tg), 58.94 pmol/L (normal 0.64-3.86 pmol/L); anti-Tg antibody titer, 1380 IU/mL (normal <28.0 IU/mL)

Comment 4:

The left upper arm bone is better called the humerus.

Reply 4:

Thank you for your comment. We added the improved term to the 46, 53, 77, 114, 242 and 252nd lines.

Change in the text:

CT showed osteolytic changes in the left humerus and right scapula, and a tumor in the right lobe of the thyroid gland. (46th line)

PET-CT showed the decreased accumulation of FDG in the left humerus and right scapula, and the amelioration of osteolytic changes on CT. (53rd line)

Computed tomography (CT) showed osteolytic changes at the end of the left humerus. (77th line)

PET-CT showed a reduction in the accumulation of FDG in the left humerus and right scapula. (114th line)

CT showed a mass of approximately 10 cm in diameter in the right lobe of the thyroid gland (a, white triangles), and osteolytic changes in the left humerus (b) and right scapula (c). The accumulation of FDG was observed in these bones (d, white arrows) (242 line)

CT showed the attenuation of osteolytic changes in the left humerus (a) and right scapula (b). PET-CT showed a decrease in the accumulation of FDG in these bones (c). (252nd line)

Comment 5:

The actual extent of the mass within the neck should be described (e.g. from supraclavicular fossa to larynx / mandible) and the neck dissection described by levels resected.

Reply 5:

In accordance with your comment, the following sentences were added to the 82-84th and 101-102nd lines

Change in the text:

CT showed a mass of approximately 10 cm in diameter in the right lobe of the thyroid gland, which was present from supraclavicular fossa to mandible. (82-84th line)

He underwent total thyroid resection and cervical lymph node dissection from around the trachea to the outside of the right sternocleidomastoid muscle. (101-102nd line)

Comment 6:

Radiotherapy is best described as 40Gy given in n fractions over N days by a particular technique (i.e. IMRT or 3D conformal).

Reply 6:

Thank you for your comment. We added the following sentence to the 111-113rd lines.

Change in the text:

Four weeks after the surgery, three-dimensional conformal radiotherapy (40 Gy/ 20Fr) was performed on the neck because of the possibility of microscopic lesions remaining in the trachea.

Comment 7:

"After" (lines 109,110, figure 3) needs qualifying (i.e. how many weeks later)

Reply 7:

In accordance with your comment, the following sentences were added to the 111-113rd and 251st lines

Change in the text:

Four weeks after the surgery, three-dimensional conformal radiotherapy (40 Gy/ 20Fr) was performed on the neck because of the possibility of microscopic lesions remaining in the trachea. (111-113rd line)

CT and PET-CT of three weeks after the radiation therapy to the neck (251st line)

Comment 8:

"Immunogenic" (line 157). As our understanding of immune mechanisms and cancer increases, it is becoming clear that most, if not all, all cancers interact with host tissues on an immunological level, though the extent may vary. Lines 155-157 might be better replaced with some comment on immune mechanisms and the abscopal effect (as above).

Reply 8:

We appreciate the Reviewer's comment on this point. In accordance with your comment, the following sentences (156-158th lines) and reference 7-9 were added.

Change in the text:

The abscopal effect is one of an antitumor immune response [7, 8, 9]. Recent studies suggest that immunotherapy and radiation in combination may enhance the abscopal effect [7, 8, 9].

Reviewer B

Comment 1:

Aoyama and colleagues reported a case of solitary extramedullary plasmacytoma of the thyroid. The manuscript was well written and provided adequate information on the case. My only concern is the last paragraph of the "Case presentation" section which is redundant with the Ethical statements. This paragraph should be removed or

rewritten.

Reply 1:

Thank you for your comment.

The guidelines for authors require that the Ethical statements should be described in both the “Case Presentation” section and the “Ethical Statement” section on Footnote.

Reviewer C

Comment 1:

The paper entitled "Abscopal effect in a patient with solitary extramedullary plasmacytoma of the thyroid: case report" describes an interesting and unusual case of thyroid plasmacytoma in which bone metastases disappeared after thyroidectomy and cervical radiotherapy. Given the paucity of reports in the English literature (less than 100 cases), and controversy regarding the optimal management of this rare disease, this case report has a novel attribution in the field.

The paper is well written and interesting to read, however, I see the following point need to be clarify before publishing:

-Why was no immunohistochemical analysis from a biopsy specimen performed prior to surgery? Cytological examination is not generally helpful in the cases of rare thyroid tumors, but immunohistochemistry of biopsy specimen can facilitate the diagnosis and prevent surgery that is not always necessary.

Reply 1:

Thank you for your comment. We did not expect the patient to have plasmacytoma of the thyroid before surgery. In addition, based on the results of CNB, follicular tumor was strongly suspected, and immunostaining was not performed. However, as you pointed out, immunohistochemistry of biopsy specimen could facilitate the diagnosis as plasmacytoma. We appreciate the Reviewer’s comment on this point. And the following explanation was added to the 142-143rd lines.

Changes in the text 1:

If the immunohistochemical analysis of CNB specimen was performed, it might be possible to diagnose as SEP without surgery.