

Peer Review File

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Reviewer A

The authors reported a very interesting clinical case of exophthalmos resulting from metastasis in the retro-orbital region. The description is clear and the literature review is well done.

Some details should be noted:

Comment 1: Did retro-orbital metastasis capture radioactive iodine? It would be interesting to insert a figure of the whole body scan performed on the development of ocular symptoms, as described.

Reply 1: Whole body scan was performed about 6 months before the onset of ocular symptoms and only neck and diffuse bilateral lung uptake were described. There was no ocular uptake.

Changes in the text: We added a new figure, Figure 1 (added at page 5, line 113 and page 23 line 453)

Comment 2: Figure 1 demonstrates the right retro-orbital metastasis, but the red circle does not seem to indicate the lesion, but the unaffected eye. It is necessary to review the figure.

It would be important to insert a figure of the radiological response of the metastasis after radiotherapy.

Reply 2: The red circle indicates the right eye, as described. I don't know if there was an upload error. The figure is now Figure 2.

Changes in the text: We added a new figure showing the radiological response of the metastasis after radiotherapy.

Comment 3: Serum thyroglobulin was elevated, as described, but the numerical mention would give greater clarity to the description, as well as the mention of the anti-thyroglobulin antibody dosage.

Reply 3: Thanks, we added the Thyroglobulin serum and anti-thyroglobulin antibody values.

Changes in the text: we have modified our text as advised at page 5, lines 108 and 111 and at page 6 line 147

Reviewer B

This is a case report of a patient with orbital metastasis from a particularly aggressive DTC. The manuscript is particularly interesting for its focus on the genomic study carried out, and it also includes a complete review of the literature. I have some comments for the authors:

Comment 1: Line 123: You should specify the thyroglobulin level.

Reply 1: Thyroglobulin value has been specified as suggested but at line 108, 111 and 146

Changes in the text: we added some data at page 5, lines 108 and 111 and at page 6 line 147

Comment 2: Line 124: What dose of 131I did the patient receive?

Reply 2: The dose has been added

Changes in the text: we have modified our text as advised at page 5 line 110

Comment 3: Lines 125-127: I think this is a bit confusing. The information about Tg and TgAb and neck ultrasound should appear before along with the data of the first follow-up after surgery (line 123). Here you should specify only where the post-treatment WBS showed uptake.

Reply 3: As requested, this sentence has been rephrased and ultrasound data moved subsequently.

Changes in the text: we have modified our text as advised at page 5 lines 111-115

Comment 4: It's not clear if the patient received a second 131I treatment. In case he received it, please specify the dose, and if the post-treatment WBS showed orbital uptake or in other sites.

Reply 4: A second treatment was not performed

Changes in the text: we have modified our text at page 5 line 117

Comment 5: Line 141: Please explain what the radiological and clinical response consisted of. Did the orbital metastasis decrease in size or did it disappear completely? Did the ocular symptoms improve? Did the patient have any ocular sequelae? Was there any change in thyroglobulin levels?

Reply 5: Thanks for your comment. The size of orbital metastasis decreased gradually from 18 mm to 4 mm. Ocular symptoms improved a few weeks after the end of the radiotherapy. The patient still shows mild eyelid ptosis. Thyroglobulin values initially increased probably due to cell lysis and subsequently dropped to values comparable to the previous ones.

Changes in the text: we added requested data at page 6 lines 128-130

Comment 6: In the abstract, you say that the metastases were radioiodine refractory, but in the case presentation section, it isn't explained how the refractoriness was diagnosed. Did the patient receive another dose of 131I after the diagnosis of bone metastases? Was a diagnostic WBS performed and metastasis showed no uptake?

Reply 6: Refractoriness was diagnosed for progression or structural disease over 6-12 months after 131I treatment.

Changes in the text: we added a sentence at page 2 lines 42-43 and at page 6 line 137

Comment 7: Lines 156 -157: Please specify that the gastrostomy was for enteral nutrition. Maybe you could rewrite the sentence as: “Percutaneous endoscopic gastrostomy was placed for enteral feeding, improving the nutritional status”, or something similar.

Reply 7: Thanks, the sentence has been rephrased.

Changes in the text: As requested, this sentence has been rephrased at page 6 lines 143-145

Comment 8: It’s curious that although the disease progressed during treatment with lenvatinib, after poor tolerance to cabozantinib it was decided to restart lenvatinib. Did the genomic study identify any mutation in any possible therapeutic target that allows considering the use of targeted drugs in case the disease progresses again?

Reply 8: Lenvatinib was restarted as few reported cases showed rechallenge after Refractoriness to this therapy and as no other specific therapy was currently available. Genetic analysis did not identify any mutations that could lead to a target therapy

Changes in the text: No changes.

Comment 9: Supplementary Table 1: I think you should include a footnote explaining what the mutations highlighted in bold mean (I guess they are the ones that have been described as higher risk). Genes such as BRAF or TERT don’t appear in the table. Were they included in the panel genetic test? Were no variants identified in those genes?

Reply 9: We included a footnote in Supplementary Table 1 explaining that alterations in bold are those which may have a role in tumor’s pathogenesis, as previously described in literature and as explained in the manuscript’s discussion. Alterations of *BRAF* and *TERT* were not retrieved in the analyzed samples, even though these genes were included in the NGS panel.

Changes in the text: We added a footnote in Supplementary Table 1. Furthermore, at page 7 line 152 we added that NGS panel included *BRAF* and *TERT* analyses.