Author’s response to reviews

Title: Direct spread of Thyroid Follicular Carcinoma to the Parotid gland and the Internal Jugular Vein; a case report

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Author’s response to reviews: see over
Dear Sir/ Madam,

I am writing with regard to the submitted manuscript (Direct spread of Thyroid Follicular Carcinoma to the Parotid gland and the Internal Jugular Vein). I have submitted the revised manuscript and responded to the reviewers comments point by point. Should you wish to have any further information, I would be glad to supply it.

Many thanks

Yours truly,

Mr A Alzaraa

**Point by point response to the concerns raised by reviewers:**

**Reviewer 1**

1) “I am not sure there is anything new here other than major vascular invasion secondary to follicular carcinoma which was angioinvasive.”

This is true, but the emphasis of the article is that this angioinvasion resulted in a very unusual and unexpected site of metastasis. This is what is “new” about the article.
2) “I also suspect the parotid involvement was not due to hematogenous metastasis but due to retrograde tumor emboli in the jugular system.”

Reviewer 1 is probably correct in this suspicion. However, from a pathological and molecular perspective, whether a tumour spreads via retrograde emboli or haematogenously to distant sites is irrelevant. They are both regarded as haematogenous spread as opposed to other forms of tumour spread (local invasion, lymphatic spread, transcoelomic spread), and therefore in our discussion we have not made this distinction. For a tumour to spread haematogenously, it requires an identical sequence of genetic alterations that a tumour spreading via “retrograde emboli” requires. It requires the ability to breach vascular endothelium (intravasation), the ability to evade the host response, the ability to seed out in a foreign tissue (extravasation) and the ability to grow in the distant site (through angiogenesis etc). We do concede, however, that reviewer 1 has a fair point in that the actual physical mechanics of the vascular spread is slightly different in that one mechanism will probably have larger tumour emboli than the other.

3) “The patient did not have meaningful therapy so we do not learn much about managing angioinvasive thyroid cancer.”

Reviewer 1 is correct. We have not mentioned any specific therapy. Although, the patient was not fit for aggressive surgery, she was given two courses of radio iodine. An uptake scan performed approximately 14 months after her diagnosis (6 weeks after her last course of radio iodine) showed no further significant iodine uptake. At that time she was clinically well with no palpable residual or recurrent disease. She is still on routine follow up. This information has been included in the revised draft of the manuscript.

Reviewer 2

Many times, a tumor thrombus in the IJV from thyroid cancer is contiguous with the primary tumor or metastatic site of disease. In this case, was the IJV tumor thrombus contiguous with either the primary tumor or metastatic deposits?

The IJV tumor thrombus was contiguous with the primary tumor. This information has been added to the case presentation.
What palliative treatment was offered? Did she respond? Did she subsequently develop local disease progression of distant mets?

The patient was given two courses of radio iodine. An uptake scan performed approximately 14 months after her diagnosis (six weeks after her last course of radio iodine) showed no further significant iodine uptake. At that time she was clinically well with no palpable residual or recurrent disease. She is still on routine follow up. This information has been included in the revised draft of the manuscript.

**Reviewer 3**

My only recommendation would be to use more standardized language on page 4 with the sentence that begins "Two general types of metastases...." Thyroid cancer literature and official staging strategies generally use the terms "regional metastases" and "distant metastases" to succinctly describe matstatic disease. These terms have prognostic significance. Consider replacing the reference to "from the neighborhood" with the term regional metastases.

The suggested changes have been made.