Author’s response to reviews

Title: Breast cancer metastases to the thyroid gland - An uncommon sentinel for diffuse metastatic disease: A case report and literature review.

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Version: 1 Date: 06 Aug 2017

Author’s response to reviews:

06.08.2017

Dear Professor Kidd,

Thank you for your constructive review of our manuscript a revised copy of which is attached. Below are the modifications and replies to the specific reviewer queries.

We thank you for considering this new version for your journal.

Yours sincerely,

Agata Plonczak
Reviewer #1:

1. Do you believe the case report is authentic?
   A. Yes entirely.

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.
   A. This is a report of patient management and no alteration of patient care has occurred. There are no ethical concerns

Comments:

3. Does the Introduction explain the relevance of the case to the medical literature?
   A. In the introduction we have sought to contextualise this report of an uncommon event.
   Authors provide relevant information support their manuscript, however, it is not clear why manuscript was written - whether to present rare metastasis of the breast cancer to the thyroid or authors experience in exploring the role of thyroidectomy in such a situation or both.

   The manuscript was written to share a rare clinical event and discuss the challenges in patient management in the context of the scarce existing literature.

   We have altered the last sentence of “background” now amended to address the comment: Here, we present a case of a patient with breast cancer metastases to the thyroid gland and discuss the role of thyroidectomy in the context of the current literature.

   However, developing recurrence of breast cancer with a diffuse metastatic disease to the bones and lungs and at the same time having metastases in the thyroid gland or in any other organ of the body could appear not surprising. If metastatic deposit would be found exceptionally in the thyroid gland that would be an extremely rare case. Therefore the question of uniqueness of this case report requires further clarification. If authors intended to present it as a unique case, because isolated thyroidectomy was performed in a patient with advanced recurrent breast cancer then it would be nice to mention the further outcome (at least short term). It would be worthwhile to consider it's (intervention) significance if metastases were only to the thyroid gland, however, in this case presentation there were the diffuse metastatic disease that is offsetting the role of thyroid gland metastasis and related intervention. It is difficult to make
inferences whether advanced recurrence of the breast cancer or thyroid secondary influenced the final outcome.

Outcome now added at the end of the case description: The patient was reviewed 14 months following the thyroidectomy. Overall, she remains clinically stable and is currently on treatment with Fulvestrant and Ibandronic acid. She developed level II-IV lymph node metastases in her neck and her recent MRI of the spine show stable spinal metastatic disease.

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including:
   - De-identified demographic information (age, gender, ethnicity)

Authors present the case in anonymised fashion.

   - Main symptoms of the patient

Symptoms of the patient were not presented, but this can be extrapolated from the given information in the manuscript, for example, authors report that "the patient presented with cervical lymphadenopathy" and this could be understood that patient had symptoms of swelling in their neck. At the same time, it remains interesting to know whether the patient had any airway pressure symptoms. Because eventually MDT recommended thyroidectomy and it is interesting to know what was the cardinal point in recommending the palliative surgery instead of conservative palliation. What was the main reason of MDT opting for thyroidectomy with central neck dissection and latero-cervical lymph node biopsy?

The patient had no airway pressure symptoms (information added to the case description). The FNAC was misleading and there was no clear diagnosis; therefore the MDT recommended thyroidectomy with central neck dissection and latero-cervical lymph node biopsy.

   - Medical, family and psychosocial history

These details are not presented from the manuscript, however, I presume that if there would be relevant history authors could have mentioned. Despite this, in accordance with Journals policy mentioning relevant information would be preferable.

We believe that we mentioned all relevant information.

   - Relevant past interventions and their outcomes
b. The relevant physical examination findings

There were no mentioning of any physical signs related to case report, except some generalised information as mentioned above (cervical lymphadenopathy).

c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at \( T = 0 \), follow up at \( T = 1 \) month.

Authors quite frequently report months and years of events related to the case. It would be better to use alternative ways of indicating an event time, for example, disease relapsed in early 2014, or patient received 6 month of Al and bisphosphonates and due to disease progression capecitabine was commenced until after 6 cycles when it was discontinued due to capecitabine-related toxicity.

The case description has now been amended as per comments.

d. Diagnostic assessments, including:

- Diagnostic methods

Authors well presented their diagnostic methods.

- Challenges (e.g., financial, language/cultural)

no challenges were presented in the manuscript

- Reasoning and prognostic characteristics (e.g., staging), where applicable

Authors presented very nicely utilized diagnostic methods, however, diagnostic reasoning and importance of these tests were not discussed neither in the case presentation nor in the discussion.

Please note we do refer to reasoning (e.g. staging CT and MRI). In addition, we do describe that the patient developed cervical lymphadenopathy, which was further investigated with FNAC and then the decision was made to proceed to total thyroidectomy with central neck dissection and latero-cervical lymph node biopsy. The rest of the reviewers agree that this information is sufficient.
e. Types and mechanism of intervention
Outlined in the manuscript nicely.

f. A summary of the clinical course of all follow-up visits

Unfortunately, information about follow up remains unclear, it is interesting to know at least short term outcome of this case presentation, as a reader I would be very keen to know overall outcome, follow up results etc. And also it would be difficult to summarise the results of such an intervention should future researchers would seek for information.

New information regarding follow-up now included: The patient was reviewed 14 months following the thyroidectomy. Overall, she remains clinically stable and is currently on treatment with Fulvestrant and Ibandronic acid. She developed level II-IV lymph node metastases in her neck and her recent MRI of the spine show stable spinal metastatic disease.

Comments:

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Reference list style is not uniform (for example reference No-8 stands out). Please revise reference list accordingly and as per JMCR's submission guidance.

"All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission." - citation from JMCR's submission guidance.

All references have now been revised according to the style required by the journal.

Comments:

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes
7. Is the Abstract representative of the case presented?

Comments:

Authors briefly and clearly highlighted main points of the manuscript, but there is a minor discrepancy between two abstracts, on the title page and at the beginning of the article.

Abstract on the title page is missing the word "Afro-Caribbean".
This has now been amended.

8. Does the case represent a useful contribution to the medical literature?

Comments:

We believe so.

9. Additional comments for the author(s)?

Dear Authors,

It was a great honour and pleasure to read your manuscript as reviewer.

However, there are some opinions of mine humbly presented below for your kind consideration.

Case presentation:

Please, mention the type of immediate breast reconstruction (implant or flap). (page 3, line 74)

Implant, now amended.

Would it be possible to clarify the mode of biopsy of the lateral nodal disease (excisional, core, FNA etc.) (page 4, line 88).

Excision biopsy (now amended).
What was the rationale behind the MDT recommending thyroidectomy with central neck dissection and biopsy of the latero-cervical nodes? (page 4, lines 90, 91)

This has now been amended. The FNAC was misleading and there was no clear diagnosis; therefore the MDT recommended thyroidectomy with central neck dissection and latero-cervical lymph node biopsy.

Discussion:

Overall discussion is well written, but some paragraphs require paraphrasing or further development of the points authors intended to discuss. For example last paragraph of the discussion as presented:

"There are no prospective studies addressing the role of surgery in metastatic disease of the thyroid. Isolated thyroidectomy has been proposed in previous studies (Cichon 2006)(Chen 1999) as a local disease control option to palliate and prevent the potential morbidity of tumor extension related to the airway (Chen 1999). It has been also suggested that this may be beneficial for a selected group of patients with clinically significant and relatively isolated metastatic disease of the thyroid especially from a renal primary (Calzolari 2008) but this is at best speculative."

It would be nice to paraphrase and develop this paragraph further clarifying to the reader a point authors would like to make or paraphrase it to make authors point clearer.

This has now been amended: "There are no prospective studies addressing the role of surgery in metastatic disease of the thyroid. Isolated thyroidectomy has been proposed in previous studies (Cichon 2006)(Chen 1999) as a local disease control option to palliate and prevent the potential morbidity of tumor extension related to the airway (Chen 1999). It has been also suggested that this may be beneficial for a selected group of patients with clinically significant and relatively isolated metastatic disease of the thyroid especially from a renal primary (Calzolari 2008); however, in the absence of prospective trials this is at best speculative."

The following sentence (page 4, lines 109, 110, 111) is difficult to read

"Metastases to the thyroid gland from a breast primary are uncommon, representing between 3% and 34% of all metastases to the thyroid (Surov 2015) (HooKim2015) (Hegerova 2015) (Moghaddan 2013)( Saito 2014) whilst synchronous or metachronous respective primary breast and thyroid cancers are probably more common."
At the same time authors earlier already mentioned that metastases to the thyroid are very rare - 0.18 - 1.4% (same page, line 103) and repeating this with controversial statement probably not required.

Especially the last statement - "whilst synchronous or metachronous respective primary breast and thyroid cancers are probably more common" sounds a little trivial.

Paraphrasing the sentence to something like this:

"Some authors (…) suggest that breast cancer metastasises to the thyroid gland in 3% from all metastases to the thyroid, while others (…) suggest 34%.'"

Or

"From the available literature, it is difficult to understand true rate of metastases of breast cancer to the thyroid gland, since some authors (…) suggest that breast cancer metastasises to the thyroid gland in 3% from all metastases to the thyroid, while others (…) 34%.'"

This has now been amended: It is difficult to establish the true rate of metastases from breast cancer to the thyroid gland with a quoted range of prevalence from 3%, of all thyroid metastases (Surov 2015) to 34% (Saito 2014) (Table 1).

Also, the following sentence on page 5, lines 114, 115, 116 might require paraphrasing "Breast cancer is the most common malignant tumor among women (…) whilst thyroid cancer is uncommon but nevertheless the most common endocrine malignant tumor with an incidence that is increasing (…)"

To something like this: "Among women breast cancer reported to be most common cancer (…), whilst being uncommon, thyroid cancers are the most common endocrine malignancies and the incidence rising (…)"

This has now been amended: Breast cancer is the most common malignant tumor among women (Jemal 2008), whilst being uncommon, thyroid cancers are the most common endocrine malignancies and the incidence rising (Zamora 2015).

In the conclusion section of the manuscript statements of authors doesn’t seem to be backed up in the discussion or case presentation.
For example;
"If confirmed on FNAB it is usually a poor prognostic sign and indicative of disease beyond cure."

This statement requires further clarification in the main sections of the manuscript allowing the reader logically reach this conclusion.

It brings up some questions, and one of them - "if lesion is not confirmed on FNAB, does this carry different prognostic value?"

This has now been amended and that statement deleted.

Another conclusion also requires further clarification as above:
"The empirical thyroidectomy should be considered in select patients for local disease control."

(Last paragraph of the discussion seems to cover this point, but as well as mentioning patient's symptoms or MRI/CT findings requiring local symptom control would further clarify this issue of why in this case report the empirical thyroidectomy was contemplated).

This has been now clarified in the case report and the rationale for the MDT’s decision to perform the thyroidectomy is now explained.

Best wishes

peer reviewer
Reviewer #2: About the paper "Breast cancer metastases to the thyroid gland: an uncommon sentinel for diffuse metastatic disease: a case report and literature review".

The authors presented a well detailed case report about a patient who developed thyroid gland metastases 12 years after the initial diagnosis of the primary breast cancer.

The reviewer would like to thank the authors for this article, and offer a few comments and questions.

IN GENERAL:

- References should be reported according to the Instructions for Authors guidelines (i.e. "All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission")
- Reference 12 (Lam 1998) is reported after Ref.13 (Chung 2012) and Ref.24 (Chen 2015) follows Ref.20 (Heffess 2002)
- There are few writing mistakes. Please, correct them

All references have now been amended.

ABSTRACT:

It is clear enough

INTRODUCTION:

Short and clear.


This has now been amended.
CASE DESCRIPTION:

- Please, report the TNM stage of the primary breast tumors Right – T2N0 (0/20)M0 multifocal Gr1+2 IDC ; left – T3N1(2/18)M0 Gr 1 IDC, now amended
- What kind of reconstruction technique did you perform? Implant (amended now)
- Why did you carry out axillary node dissection bilaterally? Not certain – I suspect LNs looked suspicious on imaging – certainly not standard practice now!
- How was the Ki67? Please, define the breast cancers according to St.Gallen classification. We did not do the ki67
- What kind of chemotherapy did you administer to the patient? FEC, amended now
- When did the patient develop metastases to the bones and lungs? Bone mets noted on bone scan April 2012, lung nodules date back to July 2008 – initially thought to be benign
- Please, define MRI and CT [Page 4 - Line 89] ["If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided"] This has now been amended.
- How was the postoperative period? Is the patient still alive?

New information regarding follow-up now included: The patient was reviewed 14 months following the thyroidectomy. Overall, she remains clinically stable and is currently on treatment with Fulvestrant and Ibandronic acid. She developed level II-IV lymph node metastases in her neck and her recent MRI of the spine show stable spinal metastatic disease.

DISCUSSION:

- "Fine needle aspiration is the investigation of choice in the work-up of thyroid nodules" [Page 5 - Line 137]. Did you mean FNA cytology or biopsy?
- "If confirmed on FNAB..." [Page 6 - Line 158]. Since you have written about FNAC in the entire paper I think you did a writing mistake here.
Reviewer #3: 1. Do you believe the case report is authentic?
Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.
Comments: No

3. Does the Introduction explain the relevance of the case to the medical literature?
Yes

4. Does the article report the following information? Where information is missing, please specify.
   a. The relevant patient information, including:
      - De-identified demographic information (age, gender, ethnicity) - yes
      - Main symptoms of the patient - yes
      - Medical, family and psychosocial history - yes
      - Relevant past interventions and their outcomes - yes
   b. The relevant physical examination findings - yes
   c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month. - yes
   d. Diagnostic assessments, including:
      - Diagnostic methods - yes
      - Challenges (e.g., financial, language/cultural) - not applicable
      - Reasoning and prognostic characteristics (e.g., staging), where applicable - yes
   e. Types and mechanism of intervention - yes
f. A summary of the clinical course of all follow-up visits -

Comments: Not included

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments:

Not adequate

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes

7. Is the Abstract representative of the case presented?

Comments: yes

8. Does the case represent a useful contribution to the medical literature?

Comments: yes

9. Additional comments for the author(s)?

This is a useful case report for both oncological and surgical audiences. I would suggest the following minor changes are made to the manuscript:

1. Please include the details of the follow up of this patient, if available.

New information regarding follow-up now included: The patient was reviewed 14 months following the thyroidectomy. Overall, she remains clinically stable and is currently on treatment with Fulvestrant and Ibandronic acid. She developed level II-IV lymph node metastases in her neck and her recent MRI of the spine show stable spinal metastatic disease.
2. Include the generic names of the drugs indicated in the manuscript - e.g Zoledronic acid. This has now been amended

3. Discussion does not make any reference to the patient mentioned in the case report.

It does, please refer to line 165

Reviewer #4: 1. Do you believe the case report is authentic?

Yes/No

Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Comments: No

3. Does the Introduction explain the relevance of the case to the medical literature?

Yes/No Yes
4. Does the article report the following information? Where information is missing, please specify. Yes

a. The relevant patient information, including:
   - De-identified demographic information (age, gender, ethnicity) Yes
   - Main symptoms of the patient No
   - Medical, family and psychosocial history No
   - Relevant past interventions and their outcomes Yes

b. The relevant physical examination findings No

c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month. Yes

d. Diagnostic assessments, including:
   - Diagnostic methods Yes
   - Challenges (e.g., financial, language/cultural) Yes
   - Reasoning and prognostic characteristics (e.g., staging), where applicable Yes

e. Types and mechanism of intervention Yes

f. A summary of the clinical course of all follow-up visits

Comments:

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments: Yes

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes/No Yes
7. Is the Abstract representative of the case presented?

Comments: Yes

8. Does the case represent a useful contribution to the medical literature?

Comments: No

9. Additional comments for the author(s)?

Reviewer #5: This is an important case report, but still need some additional revisions to improve its quality.

1- Please adapt the references to the style of the journal. This has now been amended
2- Add the CT scan and thorax MRI to the manuscript. This has now been amended: Staging investigations including magnetic resonance imaging (MRI) spine demonstrated stable deposits involving C2, C5, T4 and L1 without neural compromise computer tomomography (CT) of the thorax demonstrated no change in the lung nodules.
3- It is suitable to summarize all the available data etc about this rare presentation in a table (case reports, retrospective studies etc). Please find attached a new table added summarising the case series published so far. It is not suitable to summarise any more detailed data as most case series include cases of metastases from other organs to the thyroid and they do not include any more detailed information regarding cases with breast metastases to the thyroid.
4- Check the English of your manuscript. This has now been revised.
5- Please add all the changes with another color during the revision. Tracked and final versions both attached.
Reviewer #6: 1. Do you believe the case report is authentic?

Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Comments: NO

3. Does the Introduction explain the relevance of the case to the medical literature?

Yes

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including:
   - De-identified demographic information (age, gender, ethnicity)
   - Main symptoms of the patient
   - Medical, family and psychosocial history
   - Relevant past interventions and their outcomes

   YES

b. The relevant physical examination findings

   YES

c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at $T = 0$, follow up at $T = 1$ month.

   YES
d. Diagnostic assessments, including:
   - Diagnostic methods
   - Challenges (e.g., financial, language/cultural)
   - Reasoning and prognostic characteristics (e.g., staging), where applicable

YES

e. Types and mechanism of intervention

YES

f. A summary of the clinical course of all follow-up visits

YES

Comments:

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments:

YES

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes

7. Is the Abstract representative of the case presented?

Comments:

Yes
8. Does the case represent a useful contribution to the medical literature?

Comments:

yes

9. Additional comments for the author(s)?

Nicely written and well organized