

## Peer Review File

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### Reviewer Comments

This case reports a patient who was diagnosed with Cowden syndrome and mastocytosis after being diagnosed with breast cancer. However, the uniqueness of this case should be the relationship between mastocytosis and Cowden, breast cancer, and this part of the content is missing whether in the Introduction, Case presentation, or Discussion. When the relationship between them was separated, this article lost its value.

1. First, please start a detailed discussion on mastocytosis. What are the clinical manifestations and characteristics of mastocytosis and what treatment are needed. Are there any simultaneous cases of mastocytosis and breast cancer? How are these cases diagnosed and treated?

Reply:

Mastocytosis is often related to allergic disorders and can appear in tumours. Its clinical manifestations include hives, gastrointestinal symptoms such as nausea, vomiting and pain, bone and muscle pain and bleeding disorders. Treatment includes identification and avoidance of triggers, medications such as anti-histamines or corticosteroids to inhibit further release or chemotherapy or stem cell therapy in cases where systemic mastocytosis is associated with hematological malignancies. No previous reported cases of mastocytosis and breast cancer in patients with Cowden Syndrome.

Changes in text:

We have modified our text as advised (see Page 4, line 75-81, page 5 96-122)).

2. What are the possible connections between mastocytosis and Cowden? Are there any cases where the two occur simultaneously? This part of the content should be elaborated to determine whether mastocytosis happened by accident.

Reply:

Some case reports have documented the occurrence of mastocytosis in Cowden Syndrome, but only occurring in soft tissues. No case report has since discussed the presence of mast cells in Cowden Syndrome induced breast cancer. In our patient, this finding is purely incidental and only discovered on detailed pathological examination. Upon review of her preoperative and postoperative clinical condition and test results, there was no evidence of systemic mastocytosis.

Changes in text:

We have modified our text as advised (see Page 5-6)

3. In the case representation, there is no description of the diagnosis and treatment of mastocytosis. Has the patient been treated for mastocytosis? What is the outcome of treatment? What effect may mastocytosis have on breast cancer?

Reply:

The diagnosis of mastocytosis in this patient is purely incidental during the examination of the mastectomy specimen. As the patient did not display any symptoms suggestive of systemic mastocytosis, no treatment was needed. Mastocytosis have been suggested to result in development and progression in breast cancer. Some observations include higher grade tumour, lymph node metastasis and hormonal receptor positive tumours.

Changes in text:

We have modified our text as advised (see Page 4, line 75-81 & Page 5-6, line 102-140)

4. After supplementing the above content, it should be summarized again: what is the take-away lesson? Should Cowden patients be alert to the occurrence of mastocytosis?

Reply:

There appears to be an association between mast cells and the occurrence of non-hereditary breast cancer. Our case reflects that this association seems to exist even in hereditary mammary cancer syndrome such as Cowden Syndrome. However, in depth research can be considered to study if there are any differences in the relationship between mast cells and breast cancer among the hereditary (ie Cowden Syndrome) versus the non-hereditary conditions and in turn, affect clinical outcomes. As this is an isolated incidental finding with no systemic manifestation of mastocytosis, Cowden patients should not be alerted at the present moment. Moreover, there are no preceding similar cases prior to our patient.

Changes in text:

We have modified our text as advised (see Page 7-8 line 142-152)

Other concerns regarding checklist:

Comment:

1. Please change a title to highlight the uniqueness of this article.

Reply: Incidental mastocytosis in a lady with Cowden Syndrome: A case report

Changes in text:

We have modified our text as advised (see Page 1, title)

Comment:

2.Please provide the therapeutic interventions and outcomes regarding checklist 3c.

Reply:

As mastocytosis was an incidental finding in our patient with no systemic manifestation, no further treatment was required. She otherwise had undergone appropriate surgical treatment and adjuvant therapy for her cancer.

Changes in text:

We have modified the text as advised

Comment:

3.What is the main take-away lessons from this case? It should be provided in the Abstract regarding checklist 3d.

Reply:

As this is the first reported case of mastocytosis in patients afflicted with Cowden syndrome and synchronous breast cancer, more research needs to be done to evaluate this association and perhaps, to compare the differences in tumour biology and clinical outcomes as compared to non hereditary mammary tumours.

Changes in text:

We have modified our text as advised

Comment:

4.A timeline figure is suggested regarding checklist 7.

Reply: added

Changes to text:

Added timeline

See figure 6

Comment:

5.I fail to find prognosis such as staging in oncology in the Case presentation regarding checklist 8d.

Reply: This patient was found to have Stage 3 left breast cancer and Stage 0 right breast cancer.

Changes in text:

We have modified our text as advised see timeline and page 4 78-84

Comment:

6.Are patients followed-up? Please provide follow-up evidence and test results regarding checklist 10a~10d.

Reply: The patient has been followed up and there has been no relapse based on clinical findings and biochemical investigations.

Changes in text:

We have modified our text as advised(line 83-84 page 4)

Comment:

7.What is the limitations about this case? Is there something better that can be done in the diagnosis and treatment? Please add this content regarding checklist 11a.

Reply:

The limitation is that this is an isolated and incidental finding of mastocytosis in a single patient with a concomitant diagnosis of Cowden syndrome and bilateral synchronous breast cancer. In spite of the limited data linking mast cells with poor tumour features in breast cancer, the overall role of mast cells and its resultant effect on the prognosis in breast cancer still remain uncertain. No study has yet to document its role in Cowden syndrome induced breast cancer, its clinical effect on tumour biological features and to compare differences with those with non- Cowden Syndrome related mammary tumours. More research can be performed in this area. In the meantime, if mast cells are seen in the mastectomy specimens, clinicians should raise the suspicion and look out for systemic manifestations of mastocytosis.

Changes in text:

We have modified the text as advised (see page 7, line 142-150)