Author's response to reviews

Title: Late onset Li-Fraumeni syndrome with bilateral breast cancer and other malignancies: case report and review of the literature

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Version: 3 Date: 5 April 2012

Author's response to reviews: see over
April 5th, 2012

Subject: Cover Letter

Dear Mr. Danrolf de Jesus,

Thank you for your e-mails from February 22th, 2012 and March 22th, 2012. We hereby resubmit our revised manuscript entitled “Late onset Li-Fraumeni syndrome with bilateral breast cancer and other malignancies: case report and review of the literature” (MS: 1885776070645663), which was revised according to your and the referee’s comments:

1. David Malkin

Major Compulsory Revisions:

1. There are numerous grammatical errors - the manuscript would benefit from a careful read and editing to correct the english.

Response:
The manuscript was edited by Edanz as proposed.

2. In the introduction, a statement is made (and citation #5) that the increased lifetime risk in women compared to men, is related to the increased breast cancer incidence. This is only partially correct as recent publications by the Strong group suggest the increased risk in females is pervasive at all ages. This should be noted.

Response:
In order to reduce word count the statement for higher prevalence of malignancies in females was combined with information on earlier onset without speculation about breast cancer as a reason for gender differences. Literature was added as suggested.

3. Some clarification of the delay to biopsy of the ‘incidental tumor’ should be made. It is not clear why biopsies was delayed, or what is meant by ‘incidental tumor’.
Response:
The periadrenal tumour was first classified as most likely benign by radiologic criteria. On tumour growth a biopsy was taken, which could not prove malignity. This is now added in part “Case Presentation”.

4. It would be very important to know the TP53 status of the various tumors. Is there LOH? Is there no LOH? These findings are particularly important in light of the lengthy discussion of the mechanisms for tumor formation in TP53 mutation carriers.

Response:
LOH status was not analyzed because of the known germline mutation. Even with the wild type allele present in the tumour, no conclusion towards treatment response could be drawn since an epigenetic phenomenon might be relevant. Due to necessity for cutting down the word count, the discussion on mechanisms for tumour formation was omitted.

5. The Discussion, though interesting, is far too long. It really tries to cover everything from mechanisms of TP53 loss of function in tumors, to relevance to treatment options. While these questions are relevant to the case, without the somatic TP53 data on these tumors, the relevance of the discussion to the case becomes harder to correlate.

Response:
The discussion on adjuvant treatment options, somatic TP53 mutations and details on the specific missense germline mutation was cut down. The discussion now concentrates on treatment changes because of knowledge on the germline mutation.

6. In the section in the Discussion on Difference between somatic and germline, what is the meaning of the last sentence?

Response:
Tumours that arise on the basis of a germline TP53 mutation might behave different compared to tumours that are triggered by other mechanisms and only adopt a somatic TP53 mutation in the course of tumour formation. Information on treatment response on adjuvant systemic and radiation therapy was mainly gathered with tumours that displayed somatic mutations. Direct adoption of these insights to carriers of a germline mutation might not be correct. Due to lack of immediate importance to this case the discussion was cut down as mentioned earlier.

7. The point about the case discussion that the treating physicians decided to 'cancel' radiation of the breast cancers based on the TP53 finding is important, as this has not generally been specifically defined in the published literature, although much discussion about appropriate treatment decisions has been made (some of which is cited).

Response:
So far, there is no general recommendation to omit radiation therapy to prevent secondary cancers in patients with LFS. At the same time elevated risk for secondary tumours was discussed since the first description of the tumour predisposition syndrome, as it is noted in the discussion. The decision to offer intensified screening or preventive surgery instead of taking the risk of secondary cancers was made in the context of probably impaired effect of radiation therapy and unfavourable prognosis of the periadrenal liposarcoma.
Izilda Cardinalli

Major Compulsory Revisions:

1. The authors report a Li-Fraumeni-Syndrome (LFS) patient affected by four synchronous malignancies including a myxofibrosarcoma of the right upper arm, bilateral breast cancer and a periadrenal liposarcoma. The diagnosis of these tumors appears not to be in doubt when reading the text. However, histological images and microscopic descriptions were not provided. Photomicrographs of each neoplasm depicting the main histological findings would be helpful to support the evidence for multiple tumors of different histogenesis.

Response: Images of the tumors are added.


Similarly, liposarcomas of the breast may eventually simulate carcinomas, particularly in small biopsies, with vacuolated lipoblasts mimicking signet ring cells (Üzüm N, et al. Journal of Breast Health 2010; 6(2): 87-90). Authors are encouraged to discuss the differential diagnosis between multiple primary tumors and metastatic lesions with more details.

Response: As mentioned above, the liposarcoma did not show any myxoid differentiation. The liposarcoma expressed the S100 protein as sign for a lipogenenic differentiation. The myxofibrosarcoma did not display any lipogenic morphology. The myxofibrosarcoma was relatively small (1,7x1,2x1,2cm) and was nearly complete embedded.

Both breast cancers were invasive ductal breast cancers with an intraductal component and expression estrogen receptor in a high percentage of tumor cells. The first diagnosis of breast cancers was made by sufficient biopsies and was confirmed by resection specimens.

A short description of histology is now included the parts “Case presentation” and “Discussion”.

3. Taking into account that myxofibrosarcomas and, more rarely, breast carcinomas, may be included in the differential diagnosis of liposarcomas, ancillary techniques

Response:
The diagnosis of liposarcoma was confirmed by immunohistochemistry (detection of S100 expression). The diagnostic procedure of invasive ductal breast carcinomas includes also the analysis of estrogen and progesterone receptor. Short information about immunohistochemistry is now included the parts “Case presentation” and “Discussion”.

Minor Essential Revisions:
1. In the Abstract, second paragraph, third line, the authors identified a heterozygous pathogenic TP53 germline mutation, and the analysis of both parents revealed that the mutation has arisen "de novo". However, in “Genetic counselling and molecular analysis”, first paragraph, it is noteworthy a frequent occurrence of cancer in multiple family members at an early age. Authors are encouraged to explore the topic in more detail.

Response:
Only one second degree family member was diagnosed with early cancer in this family. Still the Eeles criteria for TP53-testing were fulfilled, and also the wider updated Chompret criteria. This is explained in the section “Genetic counselling and molecular analysis” in part “Case Presentation”.

2. In Background section, third paragraph, second line, the authors describe that “The rare event of concomitant four primary malignancies led to delayed diagnosis of a periadrenal liposarcoma, which at first was classified as incidental tumor and is now crucial for the patient’s prognosis”. However, the periadrenal liposarcoma was the largest tumor at the moment of the diagnosis among the four concurrent neoplasms. Further down, in Case Presentation section, on Bilateral Breast Cancer topic, first paragraph, the authors comment that “Biopsy of the periadrenal tumor yielded an inconclusive histological result”. Why was the initial histological result inconclusive? Please provide further details and discuss as appropriate.

Response:
The first core biopsy of periadrenal tumor was very small and not really representative for a final diagnosis. Thus, the result of biopsy was only suspicious for a esenchymal tumor. More detailed information to the first biopsy of periadrenal tumor is now added in part “Case presentation”.

3. Steven Narod

Major Compulsory Revisions

1. This is an interesting case report. It is far too long. Length should be cut in half. Too much detail in cases and too much discussion. No one will ever finish it. Cut to 1000 words
Response: Manuscript was revised and shortened considerably.

2. Also need a more comprehensive review of testing for p53 mutations in early onset breast cancer.

Response: Numerous publications mention selected and non-selected testing of early onset breast cancer cases for TP53 mutations with low absolute numbers of cases. Whereas the NCCN guidelines recommend testing of singular cases without family history for LFS, others negate necessity because of low mutation rates of 0-7% and high psychological burden. As costs for testing is getting lower in future and screening with whole body MRI might be established, testing of patients with early onset breast cancer without family history of cancer will be more appropriate. This is added in the text now with more literature citations.

We are looking forward to hear from you soon.

With best regards,

Karin Kast, MD