Author's response to reviews

Title: Challenging dedifferentiated liposarcoma identified by MDM2-amplification, a report of two cases

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Author's response to reviews: see over
Dear Ms Zapanta,

thank you for your e-mail concerning our report on two challenging cases of dedifferentiated liposarcoma. We appreciated the detailed reviewer comments and carefully revised the report accordingly. The revised report has been uploaded and below is a point-by-point response to each of the issues raised by the reviewers:

**Reviewer 1, Robert Canter:**
Reviewer 1 questions that the presented cases were of sufficient interest for publication in BMC Clinical Pathology. The authors agree that the article may be of limited interest for sarcoma experts. However, given that lipomatous tumours are the most frequent soft tissue malignancy the authors consider the two cases of importance for a broader audience. The report highlights challenges in diagnosing dedifferentiated liposarcoma and thus raises awareness for important pitfalls. Additionally the report exemplifies how molecular tests may supplement histopathology.

**Reviewer 2, Andrea Renda:**
Reviewer 2 has no major remarks. The Reviewer asks for follow-up information on the two patients. We contacted the responsible primary care physicians and discussed both cases. The additional information have been included in the manuscript:
Both patients are in good health one year after treatment. Patient #1 was readmitted soon after the initial procedure due to an ileus caused by abdominal adhesions. There were no signs of recurrent disease. Patient #2 was transferred to a medical centre specialised in abdominal surgery and re-operated. Tumour implants were found on the small intestine and could be removed locally in sano. The course of disease illustrates that scattered DDLPS tissue may easily spawn tumour implants.

**Reviewer 3, Jerad Gardner**
Reviewer 3 has 12 minor essential revisions:

1. page 2 "background" line 5: "[MDM2].. is characteristic for most liposarcoma with low differentiation AS WELL AS DEDIFFERENTIATION." both WDL and DDL are usually MDM2 amplified"
The term 'liposarcoma with low differentiation' was also addressed by reviewer 5 (Reviewer 5, revision 1) and has been changed throughout the manuscript.

2. page 2 "case presentation" line 8: "since LOW GRADE osteosarcoma may also harbour MDM2 amplification...""
The manuscript has been changed accordingly.

3. page 2 "conclusions" line 4: "...with low differentiation AND DEDIFFERENTIATION"
Cf. revision 1.

4. page 3 "background" line 5: . "WDLS are most frequently located in the RETROPERITONEUM, followed by the limbs, particularly the thighs..." WDLS is most frequent in the retroperitoneum followed by limbs, whereas DDLS is most frequent in retroperitoneum but uncommon in limbs. most frequent "
The authors would kindly like to refer the current WHO classification of soft tissue tumours (2013) which describes the sites of involvement in WDLS as "ALT occurs most frequently in deep soft tissue of the limbs, especially the thigh, followed by the retroperitoneum, the paratesticular area and the mediastinum [...]" (WHO Classification of Tumours of Soft Tissue and Bone; WHO 2013).

5. page 3 "background line 9: MFH is an old name. Should be called "undifferentiated pleomorphic sarcoma (WHO term). Can still add MFH in parenthesis though."
The manuscript has been changed accordingly.

"6. page 3 background line 12: "which" should be "and"
The manuscript has been changed accordingly.

"7. page 3 "histologic" line 5: "higher differentiation" should be "more well differentiated"
The manuscript has been changed accordingly.

"8. page 3 "histologic" line 6: "myoepithelial" should be "myofibroblastic"
The manuscript has been changed accordingly. The legend of figure 2 has also been changed accordingly.

"9. page 4 conclusions line 2: authors state both tumors showed osteoblastic areas, but in text only one of the cases showed that finding"
The sentence was imprecise and has been changed. The one case featured a heterologous component of myofibroblastic appearance, the other case featured a component of osteoblastic appearance.

"10. page 4: "dichotomicly" should be "dichotomously"
The manuscript has been changed accordingly.

"11. page 4 second to last line: ", only a fraction of pleomorphic liposarcoma has MDM2 amplification" Please provide a reference.
This point was also addressed by reviewer 5 (reviewer 5, revision 5). The authors are thankful this important point has been addressed; recent studies indicate pleomorphic liposarcoma to be MDM2 negative (e.g. Le Guellec et al, Am J Surg Pathol. 2014, 38:293-304). The current WHO classification of soft tissue tumours (2013) says "[Immunohistochemical] staining for MDM2 and CDK4 is typically negative (239)". While 'typically' might implicate that there were exceptions with positive MDM2 staining, the quoted study (Binh et al., Am J Surg Pathol. 2005 Oct;29(10):1340-7.) investigated 559 soft tissue tumors by arrayCGH and did not find a single case of pleomorphic liposarcoma with MDM2 amplification.
The manuscript has been changed accordingly.

"12. page 5: LOW GRADE osteosarcomas harbor MDM2 amplification. Please be sure to clarify that in the text (twice on page 5).
The manuscript has been changed accordingly.

Reviewer 4, Yoon-La Choi
Reviewer 4 questions the value of the information of the report. The criticism is similar to the arguments raised by Reviewer 1 and the authors would like to point out that we do consider the two cases of interest for broader audience. The possible differential diagnosis would go along with much worse prognosis. FISH testing for MDM2 supports the histomorphological diagnosis and the authors think these points are something every pathologist should keep in mind when challenged with similar cases.

Reviewer 5, Agnes Neuville
Reviewer 5 has six minor essential revisions:

"1. The use of term “liposarcoma with low differentiation” can be confusing. MDM2 amplification in undifferentiated sarcoma, correlated with location and clinical presentation, is characteristic for dedifferentiated liposarcoma (DDLPS). It will be more appropriate to use only the term DDLPS."
The manuscript has been changed accordingly.
"2. In the Table 1, complete the code 8851/3 for well differentiated liposarcoma/atypical lipomatous tumour by the code 8851/1, according to the last WHO Classification of Soft Tissue Tumours."
Table 1 has been adjusted accordingly.

"3. In the Table 1, suppress the term “mixed liposarcoma” which is not in the last WHO Classification of Soft Tissue Tumours (Fletcher CDM, et al. World Health Organization classification of tumours of soft tissue and bone. 2013)." ’Mixed liposarcoma’ has been removed from table 1.

"4. MDM2 amplification is observed in low grade osteosarcoma arising on the surface of bone, but not in osteosarcoma of soft tissue that is a complex genomic sarcoma without recurrent MDM2 amplification. In consequence, the authors should modify in the abstract and in the fourth paragraph of the chapter conclusion the discussion on the differential diagnosis between osteosarcoma of soft tissue and osseous heterologous component of DDLPS." The authors are thankful for this important remark and have changed the conclusions accordingly.

"5. In the third paragraph of the chapter conclusion: “only a fraction of pleomorphic liposarcoma has MDM2 amplification”. Pleomorphic liposarcoma is a complex genomic sarcoma with lipoblasts, but without MDM2 amplification. It has been recently demonstrated that even without a well-differentiated component, a peripheral undifferentiated sarcoma with MDM2 amplification corresponds to a dedifferentiated sarcoma (Le Guellec et al, Am J Surg Pathol. 2014, 38:293-304). I think that a clear message should be sent about the different types of liposarcoma: no MDM2 amplification in pleomorphic and myxoid liposarcoma." Again the authors are thankful this issue has been addressed. The point was also noticed by reviewer 3 (reviewer 3 revision 11). The manuscript has been changed accordingly.

"6. When the name of the gene is used, it should be italicized (MDM2)."
The manuscript has been changed accordingly.

With best regards,

Andreas Scheel
Suvi Lokka