Dr. Lian-Sheng Ma
Editor-in-chief
The World Journal of Clinical Oncology
December 9th, 2016

Dear Dr. Ma:

We are re-submitting a case report entitled "Intermittent facial spasms as the presenting sign of a recurrent pleomorphic adenoma" by Rosalie Machado and colleagues, for consideration by The World Journal of Clinical Oncology. (ID: 00570455) We followed the author guidelines in the preparation of this manuscript. This original work is not under consideration for publication elsewhere.

The intimate anatomical relationship of the facial nerve to the parotid parenchyma has a significant influence on the presenting signs and symptoms, diagnosis and treatment of parotid neoplasms. However, to our knowledge, hyperactivity of this nerve, presenting as facial spasm, has never been described as the presenting sign or symptom of a parotid malignancy. We report a malignant parotid tumor arising in a recurrent benign tumor that presented with hemifacial spasms. We outline the differential diagnosis of hemifacial spasm as well as a proposed pathophysiology.

All authors have approved the content of the manuscript and its resubmission to the World Journal of Clinical Oncology.

We have reviewed the comments and concerns of each of the reviewers which are addressed in a point by point fashion below:

Reviewer: 1

In this manuscript, the authors report an interesting case of carcinoma ex pleomorphic adenoma arising in the background of a recurrent pleomorphic adenoma with the astonishing clinical finding of facial spasms. Some questions and suggestions are below: - In abstract there are some repetitive information. It would be interesting to restructure this section. - In section "introduction", the authors state: "...We report a malignant parotid tumor arising in a recurrent benign tumor...". Malignant transformation has been reported in several types of benign salivary gland tumors besides pleomorphic adenoma, including Warthin tumor, basal cell adenoma and myoepithelioma. Thus, this statement seems generic and sounds good to rewrite this sentence as "We report a case of carcinoma arising in a recurrent pleomorphic adenoma (i.e., carcinoma ex pleomorphic adenoma)"... or something like this. - In "case report", it is stated that "Within the nodules, two foci of early non-invasive carcinoma were identified. Within one nodule a 4 mm focus of cytologically malignant cells surrounded by benign appearing epithelial elements was identified. In a separate nodule, an intraductal malignant neoplastic proliferation exhibiting an intact benign myoepithelial cell rim was noted. None of the malignant neoplastic foci showed invasion into adjacent fibroadipose tissue and nerves". This pathological description is

compatible with a non-invasive CXPA. Therefore, it is unlikely that facial spasms were secondary to carcinomatous invasion. How do the authors explain this curious clinical finding in the clinicopathological picture described? This discussion is not present in the text, but it would be very interesting. - In “conclusion” the authors use the term “dedifferentiation” to describe malignant transformation of pleomorphic adenoma. Dedifferentiation is a term firstly used to describe dedifferentiated chondrosarcoma, which histologically shows chondroid areas associated with high-grade sarcomatous areas (i.e., dedifferentiated areas). However, both high and low-grade malignancies may arise in pleomorphic adenoma, and this term may not be appropriated to this setting. - Figure 3 shows a multinodular neoplastic growth compatible with recurrent pleomorphic adenoma. The circled area highlights two peripheral nerves and not neoplastic nodules. Besides this, it is important to show in the photomicrographs the aspects of carcinomatous areas and its relationship with adjacent tissues.

Response to Reviewer 1:

- We have reviewed and restructured the abstract to delete repetitive sentences.
- We have edited the “introduction” section of the abstract as noted by the reviewer.
- The authors have now added a section that describes that facial spasms occurred at the same time as the malignant transformation. In the absence of perineural invasion we can attribute the hemifacial spasms to an inflammatory response causing neural stimulation. This has been incorporated into the discussion to explain the clinical presentation of the patient.
- The term “dedifferentiation” has been reviewed and replaced with “transformation.” We decided the word “transformation” was more appropriate and the change in reflected in the manuscript.
- Since the neurological symptoms were not related to the malignant transformation of the PA, we do not think that including a photomicrograph with the carcinomatous areas is necessary.

Reviewer 2:

Thank you for the opportunity to review this case report. It is a well written and clearly presented case report. Still, I think a few issues have to be clarified. -) Hemifacial spasms where already described in literature. What makes the authors believe that the malignant aspect of the tumor caused the spasm and so makes this case unique? -) Have other differential diagnoses as listed by the authors and e.g. prior ear surgery have been excluded? -) Has there been any paresis of palsy of the facial nerve concomitant with presentation of spasms? What are

the authors explanations or pathophysiological hypotheses for facial spasm in this tumor entitiy, especially if perineural invasion was not observed? Further issues: -) Page 8 line 5: Citation is unclear, please cite primary literature. -) When citing, sometimes authors write a blank between full stop and parentheses, sometimes not - unification recommended.

Response to Reviewer 2:

- The malignant transformation occurred with the start of the intense hemifacial spasms and in the absence of perineurial invasion, it is thought that the hemifacial spasm may have been caused by a peritumoral inflammatory response. This has been included in the discussion.
- The patient did not have prior ear surgery or any other known etiology that could have caused the hemifacial spasm. This has been included in the discussion
- The citation on page 8 line 5 has been fixed and all literature cited is the primary literature. Citation format is now uniform.

Reviewer 3

One additional piece of information that would be useful for the authors to add is the extent to which tumor size (or volume) affected the uptake and decrease of IV contrast. This would be valuable information to note particularly for the War-T and BCA subtypes. Minor editing to improve some awkward sentences and grammatical errors should also be undertaken.

Response to Reviewer 3:

- On page 7, in the paragraph that starts "Repeat CT scan showed" we wrote that the CT scan showed enlargement of avidly and uniformly enhancing solid tumor without areas of necrosis or extracapsular extension along with suspicious changes in enlarged (15mm) left level IV lymph node.

-We have edited the paper to improve awkward sentences and grammatical errors.

We thank you for considering our re-submission.

Sincerely,
Mark L. Urken, MD, FACS, FACE